Nephrol Dial Transplant (1999) 14: 828–833

Nephrology
Dialysis
Transplantation

Invited Comment

Cardiovascular disease in chronic renal disease

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Introduction

Cardiovascular disease (CVD) is the major cause of death in patients with end-stage renal disease (ESRD). In the general population, CVD morbidity and mortality have declined substantially over the past three decades through risk factor identification and reduction and more effective treatment of coronary artery disease. In 1997, the National Kidney Foundation convened a Task Force*, consisting of experts in CVD epidemiology, clinical trials, clinical cardiology and nephrology, to consider whether strategies for prevention and treatment of CVD in the general population are applicable to patients with chronic renal disease (CRD). The Task Force found that definitive studies to guide clinical care in CRD are lacking, and there is still much to be learned. Nonetheless, based on extrapolation from the general population, the Task Force concluded that many of these same strategies could and should be implemented in the care of patients with CRD. Its recommendations were circulated for review by a large number of professional organizations and societies and, after appropriate revisions, were approved and adopted by the National Kidney Foundation in August 1998. This invited comment contains an outline of the process used by the Task Force, a summary of the clinical recommendations, and a discussion of the next steps required for implementation. It is based on the final report of the Task Force published in the *American Journal of Kidney Disease* (38: 853–906, 1998 and Supplement 3: 1–199), portions of which are presented here. For more complete discussion of the rationale, clinical and research recommendations, and references, readers are encouraged to review the original Task Force report.

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The process

Definitions

Work began by defining the target conditions and populations, the methods for assembly and review of evidence, and the criteria for extrapolating results from the general population to patients with CRD. Two target conditions and four target populations were considered. The two target conditions, coronary artery disease (CAD) and left ventricular hypertrophy (LVH), were selected because of their high prevalence in patients with CRD and their association with a high risk of death. The four target populations comprise the entire population of patients with CRD, including patients with chronic renal insufficiency (CRI), patients with ESRD treated by haemodialysis (HD), patients with ESRD treated by peritoneal dialysis (PD) and renal transplant recipients (RTR). CRI traditionally is defined as a reduction in glomerular filtration rate (GFR), manifested by an elevation in serum creatinine concentration above the normal range. For the purpose of this report, CRI also includes patients with increased excretion of total urine protein or albumin (including diabetic patients with microalbuminuria), even if the serum creatinine is not elevated, because albuminuria usually precedes the decline in GFR in CRD, and because of the strong association of albuminuria and CVD.

The interventions that were selected include risk factor reduction for CAD and LVH, screening for preclinical manifestations (inducible ischaemia and increased left ventricular mass), antiplatelet therapy and coronary revascularization for CAD, and treatment of hypertension and correction of anaemia for LVH. The effect of these interventions on CRD outcomes, such as proteinuria, the decline in renal function and onset of ESRD, were also considered.

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Table 1. CVD mortality by gender, race and target population (annual mortality, %)

Target population	All	Men	Women	White	Black	Diabetic	Non-diabetic
General population	0.28	0.28	0.27	0.29	0.23	0.80	0.26
Haemodialysis	9.12	9.38	8.83	11.18	6.68	11.09	7.78
Peritoneal dialysis	9.24	10.27	8.14	10.76	6.07	13.22	7.09
Renal transplant recipients	0.54	0.59	0.43	0.53	0.56	1.11	0.39

Assessment of risk

The Task Force conducted a comparison of CVD prevalence and outcomes in CRD with the general population to characterize the risk status of patients with CRD. This comparison was performed by secondary analysis of data from the United States Renal Data System (USRDS) and the US National Center for Health Statistics (NCHS), supplemented by additional sources of data. Altogether, mortality from CVD in dialysis patients is ~9% per year, which is ~30 times the risk in the general population (Table 1). Even after stratification for age, CVD mortality remains 10–20 times higher than in the general population (Figure 1). The excess mortality is related, in part, to the higher prevalence of CVD in patients with CRD as compared with the general population (Table 2) and, in part, to the higher case-fatality rate. These data document the high risk of CVD in patients with CRD and justify consideration of patients with CRD as a 'highest risk' group for prevention and treatment of CVD. Current guidelines suggest intensive therapy for 'highest risk' patients in the general population, including life-long drug therapy for risk factor reduction and invasive procedures to detect and revascularize coronary stenosis.

Rationale for extrapolation from the general population to patients with chronic renal disease

Few patients with CRD have been included in population-based epidemiologic studies of CVD or long-term randomized clinical trials. Therefore, the available studies of CVD in CRD are principally non-randomized trials and observational studies of non-representative cohorts. The Task Force considered three general criteria for extrapolation. First, the mechanisms and expressions of CVD in CRD should be similar to those observed in the general population. Second, therapies in patients with CRD should be as safe, or nearly so, as in the general population. Third, the duration of therapy required to improve CVD outcomes in the general population should not exceed the life expectancy of patients with CRD.

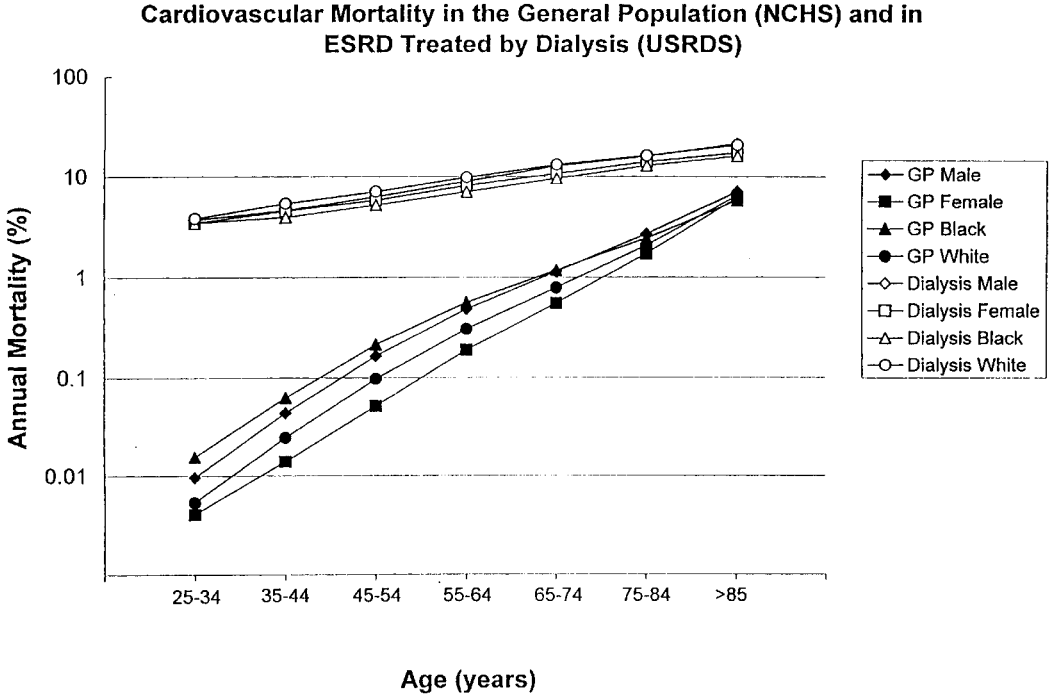

Fig. 1. CVD mortality by age, race and gender in the general population and in dialysis patients. Cardiovascular mortality is defined as death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease and pulmonary oedema. Data from the general population are from the National Center for Health Statistics (NCHS) multiple cause of mortality files 1993 (ICD 9 codes 402, 404, 410–414 and 425–429). Data from dialysis patients includes HD and PD combined, from United States Renal Data System 1994–1996 (USRDS special data request, Health Care Financing Administration form 2746 nos 23, 26–29 and 31).

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Table 2. Approximate prevalence (%) of cardiovascular disease in the general population and in chronic renal disease target populations

Target population	CAD (clinical)	LVH (echo)	CHF (clinical)
General population	5–12	20	5
Chronic renal insufficiency	NA	25–50 (varies with renal function)	NA
Haemodialysis	40	75	40
Peritoneal dialysis	40	75	40
Renal transplant recipients	15	50	NA

CAD, coronary artery disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; NA, not available.

Literature review and evaluation

Two methods were used to gather evidence from the medical literature, a MEDLINE search supplemented by addition of relevant articles by Task Force members. Altogether 938 articles were included in the Task Force review of the literature (Table 3). Critical review of the final list of articles reveals that it is incomplete. Studies show that even the most comprehensive electronic searches reveal only about one-half of the relevant articles. Methods to increase the yield of articles included in comprehensive reviews include cross-checking of references in retrieved articles and reviews. Although a comprehensive search is necessary for systematic reviews and for development of clinical practice guidelines, the Task Force considered the selective but systematic search described above to be appropriate for its purposes.

A review form and database were developed to abstract and store results from the retrieved articles. Of the 938 articles, review forms were completed based on the full-length article in 363 (38%) and the abstract alone in 578 (62%). Altogether, there were 1245 results in the database (Table 4). There were 396 results from clinical trials, 456 results from observational studies and eight results from studies of diagnostic testing, all extracted from primary data published in peer-reviewed journals. There were 240 results from review articles without primary data, 28 results from articles from journals that are not peer reviewed, 22 results about incidence and prevalence and 95 results that were not classified by Task Force members.

Evidence synthesis

Information in the database was grouped into evidence tables to answer questions posed about risk factor reduction, treatment and screening for CAD and LVH. For some topics, the evidence tables contain considerable information and provide a solid basis for clinical recommendations. However, for many topics, there were few studies, and fewer still with a high level of evidence. Overall, the evidence tables revealed the limited data that are available to guide clinical decisions.

When possible, evidence synthesis was based on the evidence tables and, in the absence of evidence tables, on the Task Force's interpretation of the available results. An important limitation to the evidence synthesis is that it is not quantitative. Thus, it relies considerably on the reviewer's interpretation of the strength of the results. In principle, a systematic review including a meta-analysis would provide a more precise estimate of the effect size and a more generalizable conclusion by expressing the results of each study

Table 3. Evidence retrieval for the NKF Task Force on cardiovascular disease in chronic renal disease

Number of titles retrieved from electronic search	3703
Number of titles discarded by Task Force member BEC	1760
Number of abstracts distributed to Task Force members	1943
Number of abstracts discarded by Task Force members	1555
Number of abstracts retrieved from the electronic search with relevant data	388
Number of abstracts added by Task Force members	550
Total number of abstracts identified with relevant data	938
Data extraction from article (number, %)	360 (38%)
Data extraction from abstract (number, %)	578 (62%)

Table 4. Classification of results in the NKF cardiovascular disease Task Force database

Clinical trials from peer-review journals	396 (32%)
Observational studies from peer-review journals	456 (37%)
Studies of diagnostic testing from peer-review journals	8 (<1%)
Review articles without primary data	240 (19%)
Articles from journals that are not peer reviewed	28 (2%)
Results about incidence and prevalence	22 (2%)
Not classified	95 (8%)
Total results in the database	1245

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Table 5. Risk factor reduction for primary and secondary prevention of cardiovascular disease in chronic renal disease

Risk factor	Evidence (observational studies)		Types of interventons	Evidence (intervention studies)			
	High prev in CRD	Assoc with CVD events in CRD		Effect on risk factor in CRD	Safety in CRD	Effect within 2–5 years in GP	Effect on CVD events in CRD
Hypertension	+++	++	Antihypertensive therapy	+++	+++	+++	–
Total of LDL cholesterol	++	++	Lipid-lowering diets	++	+++	+	–
			Lipid-lowering drugs	+++	+++	+++	–
Triglycerides	+++	+	Lipid-lowering diets	++	+++	+	–
			Lipid-lowering drugs	+++	++	+++	–
Hyperglycaemia (in diabetics)	++	–	Diet[a]	++	+++	–	–
			Insulin	+++	+++	–	–
			Oral agents[a]	++	++	–	–
			Pancreas transplantation	+++	+	–	–
Smoking (tobacco use)	+	+	Counselling	–	+++	+++	–
			Nicotine replacement	–	+	–	–
Physical inactivity	+++	–	Exercise	+	++	+++	–
Menopause	+++	–	Oestrogen replacement	+++	++	–	–
Homocysteine	+++	++	B-vitamins	++	+++	–	–
Thrombogenic factors	+	–	Anti-platelet agents	+++	++	+++	–

Screening for cardiovascular disease and treatment (other than risk factor reduction) in chronic renal disease

CVD	Evidence (observational studies)		Types of interventions	Evidence (intervention studies)			
	High prev in CRD	Assoc with CVD events in CRD		Effect on CVD in CRD	Safety in CRD	Effect within 2–5 years in GP	Effect on CVD events in CRD
CAD	+++	+++	Stress testing	++	++	+++	++
			Coronary revascularization	+++	++	+++	++
LVH	+++	+++	Echocardiography	–	–	–	–
			Antihypertensive therapy	+++	+++	+++	–
			Correction of anaemia	+++	+++	–	–

[a]Type 2 diabetes only.
CVD, cardiovascular disease; CRD, chronic renal disease; Prev, prevalence; Assoc, association; GP, general population; LDL, low density lipoprotein.
Key: + = weak, somewhat consistent evidence; ++ = moderately strong, rather consistent evidence; +++ = very strong, consistent evidence; – = poor or nonexistent evidence.
Format adapted from Pearson TA, Fuster V. Executive Summary. 27th Bethesda Conference: Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14–15, 1995. *J Am Coll Cardiol* 1995; 27:961–962.

according to a common measurement scale and pooling the results.

A summary of evidence, based on the Task Force's consensus, is presented in Table 5. As shown in the far right column, strong and consistent data from intervention trials are not available for any of the treatments considered by the Task Force. However, there are data to provide sufficient evidence to extrapolate from the general population. These data form the basis of the Task Force's clinical recommendations. The principal limitation to this summary, and to the clinical recommendations that derive from it, is the limited number of studies with a high level of evidence in patients with CRD. Conceivably, a more exhaustive search of the literature, coupled with a quantitative review of the retrieved articles could provide a more precise estimate of the results. Nonetheless, the evidence synthesis and recommendations represent a useful starting point for clinical decisions and for future research.

Clinical recommendations

Epidemiology of CVD

Patients with CRD should be considered in the highest risk group for subsequent CVD events. They have a high prevalence of CAD and LVH, which are precursors of CVD mortality and morbidity. They also have a high prevalence of congestive heart failure, which is an independent predictor of death in CRD. Treatment recommendations based on CVD risk stratification should take into account the 'highest risk' status of patients with CRD.

Risk factors

The excess risk of CVD in CRD is caused, in part, by a higher prevalence of conditions that are recognized as risk factors for CVD in the general population, such

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as older age, hypertension, hyperlipidaemia, diabetes and physical inactivity. The excess risk may also be caused, in part, by haemodynamic and metabolic factors characteristic of CRD, including proteinuria, increased extracellular fluid volume, electrolyte imbalance, anaemia and higher levels of thrombogenic factors and homocysteine than in the general population. Strategies for risk factor identification and reduction should target both the 'traditional' coronary risk factors as well as specific risk factors related to CRD.

Hypertension

Patients with CRD have a high prevalence of hypertension, and hypertension in CRD is associated with adverse outcomes of both CVD and CRD. The preferred therapy is control of extracellular fluid volume and maintenance of 'dry weight' through dietary salt reduction in all target populations, diuretics in patients with CRI and RTR, and reduction in fluid intake and ultrafiltration in HD and PD patients. In HD and PD patients, it is reasonable to use the guidelines of the Sixth Joint National Committee for Prevention, Detection, Evaluation and Treatment of High Blood Pressure to define the optimal and target blood pressure for antihypertensive therapy to reduce the risk of CVD outcomes. Optimal blood pressure is defined as $\leqslant$120/80 mmHg. Target blood pressure for antihypertensive therapy is defined as $<$140/90 mmHg. All classes of antihypertensive agents are effective, with the exception of diuretics. Low blood pressure may indicate the presence of undetected cardiovascular disease. In CRI and probably in RTR, target blood pressure should be $<$125/75 mmHg in patients with proteinuria, and $<$130/85 mmHg in patients without proteinuria, to reduce the risk of CRD outcomes. In CRI, treatment with angiotensin-converting enzyme (ACE) inhibitors is suggested. In RTR, ACE inhibitors or calcium channel blockers may be preferred.

Hyperlipidaemia

Patients with CRD have a high prevalence of lipid abnormalities. Elevated levels of total and low density lipoprotein (LDL) cholesterol are associated with CVD in CRD, but the relationship of elevated levels of triglycerides or low levels of high density lipoprotein (HDL) cholesterol to CVD, in the absence of elevated total or LDL cholesterol, is not known. It is reasonable to use the guidelines of the National Cholesterol Education Program Adult Treatment Panel II for initial classification, treatment initiation and target cholesterol levels for diet or drug therapy. In the highest risk group, target LDL cholesterol level is defined as $\leqslant$100 mg/dl for both diet and drug therapy. The 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors ('statins') are the most effective drugs to lower LDL cholesterol in CRD and are generally safe. They should be agents of first choice in CRD, but dosage reduction and additional monitoring may be required to avoid side effects, especially in RTR receiving cyclosporin or tacrolimus.

Hyperglycaemia

Diabetes is a risk factor for CVD in CRD, and diabetic patients with CRD have a high prevalence of CVD. It is not known, however, whether hyperglycemia *per se* causes CVD in the general population or in patients with CRD. The American Diabetes Association recommends lowering blood glucose levels to normal or near normal in most patients with type 1 and type 2 diabetes. Achieving strict glycaemic control is more difficult in patients with CRD, the risk of hypoglycaemia is greater, and the consequences may be more serious. It appears most reasonable to recommend intensive glycaemic control to patients with CRI or RTR to reduce the risk of adverse outcomes of CRD. The feasibility and importance of achieving intensive glycaemic control in HD and PD patients should be determined on an individual basis.

Tobacco use

As in the general population, tobacco use is associated with a higher risk of CVD in CRD. Based on general population guidelines, it is reasonable to recommend counselling and nicotine replacement therapy in patients with CRD.

Physical inactivity

Physical activity is reduced among patients with CRD, but can be increased by counselling and exercise. The American Heart Association recommends a moderate level of physical activity for 30 min per day on most days of the week for the general population. This level of activity is feasible in many patients with CRD, and should be actively encouraged.

Menopause

The majority of women with CRD are post-menopausal. As in the general population, the relationship between menopause and CVD in CRD is poorly understood. Hormone replacement therapy can overcome post-menopausal hormone deficiency in CRD, but the effect on serum lipids and CVD is unknown. Individual decision making is recommended.

Homocysteine

Homocysteine levels are elevated in CRD and elevated homocysteine levels are associated with CVD. The effect of dietary fortification with folic acid on homocysteine levels in CRD is unknown. The effect of lowering homocysteine levels on CVD risk is also not known.

Thrombogenic factors

Patients with CRD have decreased platelet function, and elevated procoagulant activity. Although aspirin may worsen platelet dysfunction in CRD, it is reasonable to prescribe aspirin (75–325 mg/day) to reduce

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the risk of subsequent CVD events in patients with CAD or in those at high risk of developing CAD.

Treatment of CAD by coronary revascularization

The medical management of CAD in patients with CRD is similar to that in the general population. In addition, control of extracellular fluid volume and partial correction of anaemia are important therapeutic adjuncts. Initial technical success of coronary revascularization and relief of symptoms in patients with CRD are similar to those in the general population. Coronary revascularization may improve survival in high risk patients with CRD. As in the general population, patients should be considered for coronary revascularization if they are at high risk of acute myocardial infarction or death, or if they remain symptomatic despite medical therapy. Coronary artery bypass grafting appears to be preferable to percutaneous transluminal angioplasty in CRD; however, angioplasty with intravascular coronary stenting is playing an increasing role in the management of CAD in CRD.

Treatment of LVH with antihypertensive agents and correction of anaemia

Both hypertension and anaemia are associated with LVH in CRD. Treatment of each condition causes regression of LVH, but the effect on clinical CVD events is not yet known. Until further information is available, the recommended target blood pressure for treatment of hypertension in patients with CRD complicated by LVH is the same as for patients without LVH, as specified in this report. The suggested target haematocrit for treatment of anaemia in CRD complicated by LVH is the same as for patients without LVH (33–36%), as specified in the clinical practice guideline of the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI).

Screening for CAD

Routine stress testing for inducible ischaemia is not recommended in patients with CRD who do not have clinical manifestations of CVD. It is reasonable to use the general population guidelines for screening prior to non-cardiac surgery in patients with CRD. The guidelines of the American Society of Transplant Physicians recommend screening all renal transplant candidates except those at lowest risk.

Screening for LVH

At the present time, there is not sufficient evidence to recommend for or against routine echocardiography for detection of increased left ventricular mass in patients with CRD who do not have clinical manifestations of CVD.

Discussion

In summary, the proposed recommendations of the NKF Task Force are based on published recommendations for the general population, a systematic review of the nephrology literature and a consensus of the members of the Task Force. They are based on what we already know, and represent a more focused, structured and perhaps more intensive approach to the prevention and treatment of CVD in CRD than currently is practiced.

Several features of the Task Force report deserve further comment. First, the Task Force considered patients with CRD across a continuum of stages, beginning with CRI (including the late phase, sometimes referred to as 'pre-ESRD'), through ESRD treated by HD and PD, and after renal transplantation. We believe this approach will facilitate development of comprehensive, patient-oriented strategies to prevent and treat CVD in CRD. Second, we caution against premature closure of discussion of the various clinical recommendations. Unlike the recommendations of the NKF-DOQI, the clinical recommendations of the Task Force on CVD are not clinical practice guidelines but, like them, are not meant to be standards of care. Instead, the Task Force anticipates that these recommendations will provide general direction to clinicians caring for patients with CRD, and serve as a catalyst for clinical research. Third, implementation of the Task Force's recommendations will require concerted effort by nephrology organizations world-wide. Further research is necessary to increase the database of results from clinical studies with high levels of evidence. For interventions in which substantial data are already available, systematic reviews are needed to develop quantitative estimates of efficacy. For interventions that are judged to be efficacious, development of practice guidelines should be encouraged. Education of providers and patients alike is necessary to implement guidelines, and continuous monitoring of patient outcomes is necessary to determine the effectiveness and efficiency of implementation. It will be necessary to encourage more efficient organization of health care services for CRD target populations to identify and overcome barriers to implementation of preventive strategies for CVD. Ultimately, it will be necessary to identify patients with CRD at an earlier stage in the course of their disease, to allow fuller implementation of strategies to prevent CVD.

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