Renal Disease in Cardiovascular Disorders: An Underrecognized Problem

Alain Baumelou^a Eric Bruckert^b Corinne Bagnis^a Gilbert Deray^aDepartments of ^aNephrology and ^bEndocrinology, Hôpital Pitié-Salpêtrière, Paris, France

Key Words

Cardiovascular mortality · Renal disease · Chronic kidney disease · Cholesterol · Diabetic nephropathy

Abstract

Chronic renal disease is generally appreciated as a major and rapidly growing health problem. In the United States alone, as many as 19.5 million people may have markers of early renal disease, and more than 660,000 people are expected to require renal replacement therapy by the year 2010. By contrast, the presence and pathological role of renal disease in patients with cardiovascular disease are somewhat underrecognized. Evidence now shows that even minor impairments in renal function, as indicated by measures including glomerular filtration rate and microalbuminuria, are common in cardiovascular disease states and predictive of cardiovascular events. Indeed, microalbuminuria may be a marker of systemic vascular disease rather than kidney dysfunction alone. In patients with hypertension, diabetes, metabolic syndrome, acute coronary syndromes, and stroke, markers of renal disease have proved to be at least as predictive of morbidity and mortality as conventional risk factors. Yet, chart reviews in a variety of clinical settings reflect poor recognition and management of renal disease in at-risk patients. Models for renal protection are based on

the control of risk factors, particularly blood pressure, that are associated with renal and cardiovascular outcomes. Screening protocols for markers of renal disease should recognize the potential inaccuracy of serum creatinine concentrations and the preferability of glomerular filtration rate estimates that take age and gender into account. Pilot programs for screening high-risk populations have shown efficacy in detecting renal disease.

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Introduction

The concept that chronic renal disease and cardiovascular disease go hand in hand is not new; nevertheless, many aspects of this relationship are still poorly understood. There is no question that cardiovascular disease is much more prevalent in patients with renal disease than in those without and that it is the most common cause of death in patients with end-stage renal disease (ESRD) [1]. That renal disease is common and prognostic of adverse events in many cardiovascular disease states is less well known, as is evidence that even minor impairments in renal function can be correlated with the cardiovascular risk status [2]. As a result, renal insufficiency in cardiovascular disease patients frequently goes undetected in clinical settings. Such underrecognition appears to extend

Fig. 1. Data from NHANES III on the incidence of impaired GFR (<60 ml/min/1.73m²) in the general population by age. From Coresh et al. [10], with permission.

even to patients with hypertension or diabetes [3–5], diseases that are strongly associated with both progressive renal failure and cardiovascular complications. This situation demands remedy, since early recognition paves the way for treatments that can delay or prevent deterioration of the renal function as well as control the cardiovascular risk. Accordingly, the primary goal of this paper is to raise the awareness of chronic renal disease as a common and prognostic comorbidity in the context of cardiovascular disease. In addition, we have limited our scope predominantly to patients with stage 1–3 chronic kidney disease (CKD).

Overall Prevalence of Renal Disease

CKD is a growing problem worldwide. Prevalence and incidence rates are typically based on markers of early dysfunction (discussed below) and by indices of ESRD. Striking prevalence figures have been documented in renal replacement therapy programs, in which ESRD patients receive life-extending dialysis. In the United Kingdom, the rate of acceptance of patients into such programs doubled in the 1990s and continues to increase steadily [3]. In the United States, the number of patients in Medicare-funded dialysis programs increased from about 10,000 in 1973 to more than 340,000 in 1999 [6, 7] and is predicted to exceed 660,000 by 2010 [8]. These data can partially be explained by longer survival of

ESRD patients; however, the majority of the increase is due to new patients whose renal disease has progressed as a complication of diabetes, hypertension, or heart failure [9].

According to data extrapolated from the Third National Health and Nutrition Examination Survey (NHANES III) [10], about 10 million people in the USA had serum creatinine concentrations ≥ 1.5 mg/dl in 1990 [13]. In a separate analysis of NHANES III [10] data, 8.3 million Americans were estimated to have a glomerular filtration rate (GFR) <60 ml/min/1.73 m², and an additional 11.2 million were estimated to have microalbuminuria, but a normal GFR, yielding an even higher total of 19.5 million with evidence of CKD [6, 14].

Age is a major determinant of incidence and prevalence of CKD, as it is for cardiovascular disease. Data from NHANES III [10] indicate that a decreased GFR is present in 0.2% of the general population aged 15–29 years, in 4.3% of the segment aged 30–59 years, and 31.2% in the segment aged 60–89 years (fig. 1). The incidence of ESRD rises rapidly in the last decades of life, due largely to increased rates of diabetes and hypertension [3]. Race and ethnicity also influence renal disease rates [13]. In the London area, in the early 1990s, the rates of participation in renal replacement therapy were roughly threefold higher for blacks and Asians than for Caucasians [14]. In the USA, in 1999, 10% of all new ESRD cases were Hispanic, and the incidence rates ranged from 237 per million population among Caucasians to 652 per million among American-Indians and to 953 per million among African-Americans. African-Americans and Hispanics reach ESRD at an earlier age than Caucasians, and African-Americans have disproportionately higher rates of hypertension and diabetes as the primary causes of ESRD [6, 7].

Measures of the Renal Function

Renal damage is detectable in its early stages through the use of laboratory tests. The GFR is considered the gold standard; however, the serum creatinine concentration may be used as a measure of GFR in the clinical setting, obviating the need for 24-hour urine collections. Mild renal insufficiency is defined as a serum creatinine concentration >1.5 mg/dl (132 μ mol/l) in men and >1.4 mg/dl (123 μ mol/l) in women [12, 15]. The gender difference in this definition reflects the fact that creatinine is produced in skeletal muscle; hence, women as well as elderly patients with less muscle mass may have decep-

tively low levels of serum creatinine even in the presence of a decreased GFR [15, 16]. Gender-based algorithms, such as the Cockcroft-Gault formula, have been applied to improve the accuracy of serum creatinine measures. If the GFR is assessed by estimated creatinine clearance (CrCl) using this formula, values <60 ml/min are considered to represent mild renal insufficiency for both men and women [17, 18].

Proteinuria

The diagnosis of CKD can also be based on findings of proteinuria, measured as total protein or albumin [19] and regardless of the level of renal function. Elevated urinary excretion of albumin reflects impairment of the glomerular filtration barrier rather than the filtration rate [15], and it appears prior to other detectable changes in renal function [20]. Microalbuminuria is defined by albumin excretion rates of between 30 and 300 mg/24 h and is measured by specific dipsticks or antibody assays. An albumin excretion >300 mg/24 h, detected with routine urinalysis dipstick, is considered proteinuria. The albumin-to-creatinine ratio can also be analyzed in spot urine samples to determine microalbuminuria, with a ratio >17 mg/g in men or >25 mg/g in women considered abnormal [19].

The urinary albumin concentration may be temporarily elevated in conditions such as sleep apnea or fever. However, persistent elevation not only suggests chronic renal disease, but is also a highly sensitive, independent predictor of cardiovascular events, particularly in high-risk individuals, including hypertensive patients, and as outlined in the last JNC 7 [15, 20, 21]. Microalbuminuria may, in fact, indicate endothelial cell dysfunction and increased permeability not just in the kidney but throughout the vascular system [22]. If such damage to the vascular endothelium is implicated in the promotion of atherosclerotic plaque or other mechanisms of vascular pathophysiology, this phenomenon might help explain the link between CKD and increased heart attack and stroke rates in cardiovascular disease states, including hypertension and diabetes mellitus [20, 22, 23]. It is important to note that the current parameters for defining microalbuminuria and excess serum creatinine are based on the ability to predict progressive renal disease. As suggested by studies discussed below, however, many individuals with renal disease markers in the 'normal' range have been found to be at increased risk of cardiovascular events.

Prevalence and Prognostic Significance of Renal Disease in Cardiovascular Disease States

Hypertension

Renal dysfunction and essential hypertension are closely linked. Before antihypertensive drugs became widely available, renal complications in hypertensive patients were extremely common. A 1955 study of 500 untreated patients with hypertension (diastolic blood pressure >90 mm Hg) [24], for example, found that 42% had proteinuria. Nitrogen retention was present in 18% and was a major predictor of death; many patients with renal involvement lived only 4 or 5 years [24].

Studies beginning with the Hypertension Detection and Follow-Up Program (HDFP) in 1989 have helped to clarify prevalence and prognostic significance of renal dysfunction in treated hypertensive patients. The HDFP trial enrolled 10,940 patients in a 5-year program of antihypertensive therapy in stepped or referred care models. Renal dysfunction, defined as a serum creatinine concentration ≥ 1.7 mg/dl, was present in 2.76% of the patients at baseline (5.79% had creatinine levels ≥ 1.5 mg/dl, the current cutoff point for men). Over 8 years, the mortality for this high-risk subgroup was more than three times that of all others in the trial; the cause of death was usually cardiovascular – the relative risk of mortality was 2.2 after adjusting for other cardiovascular risk factors. However, the mortality risk was shown to increase at creatinine levels as low as 0.80–0.99 mg/dl [25]. More recently, the Hypertension Optimal Treatment study [26] detected a CrCl <60 ml/min in $\geq 13\%$ of the hypertensive patients. For patients with serum creatinine levels >1.5 mg/dl, the relative risk of all-cause mortality was 2.86 after adjustment for other cardiovascular risk factors. Both CrCl and elevated serum creatinine concentration predicted elevated cardiovascular risk – even when the blood pressure was well controlled.

In the NHANES 3 study [27], the prevalence of renal insufficiency (all stages, but predominantly mild, i.e., CrCl 60–90 ml/min) was 51.5 and 64.3% in hypertensive patients without and with medications, respectively.

Proteinuria and microalbuminuria are also common and predictive of cardiovascular events in association with hypertension. Proteinuria was three times more common in hypertensive individuals than in nonhypertensives in the population-based Framingham Heart Study; among men (but not women), it predicted cardiovascular mortality even when other risk factors were adjusted for [30]. The prevalence of microalbuminuria in

Table 1. Incidence and risk of cardiovascular events in the HOPE study participants with diabetes by microalbuminuria status at baseline [adapted from ref. 33, with permission]^a

Variables	With micro-albuminuria, %	Without micro-albuminuria, %	Crude risk (95% CI) ^b	Adjusted risk (95% CI) ^b
MI, stroke, or cardiovascular death	25.0	13.9	1.80 (1.56–2.07)	1.97 (1.68–2.31)
All-cause mortality	18.6	9.3	2.01 (1.69–2.39)	2.15 (1.78–2.60)
CHF hospitalization	8.5	2.5	3.34 (2.49–4.50)	3.70 (2.64–5.17)

^a Time-to-event analyses using Cox regression were performed to calculate the risk for cardiac events and total mortality.

^b Adjusted for randomization to receive ramipril. All are $p < 0.001$.

hypertensive individuals ranges from 7 to 40% [22]. In the Hoorn study [31], based in Amsterdam, microalbuminuria was more strongly predictive of all-cause and cardiovascular mortality in hypertensive individuals than in normotensives. The relative risk of all-cause mortality associated with microalbuminuria, after adjustment for age, sex, impaired glucose tolerance, and diabetes, was about five times higher in hypertensive as compared with normotensive individuals (2.48 vs. 0.44, respectively).

Diabetes

Persons with diabetes, like those with hypertension, are at high risk of both renal disease and cardiovascular disease. In the NHANES 3 study [27], the prevalence of renal insufficiency (all stages, but predominantly mild, i.e., CrCl 60–90 ml/min) was 55.5% in diabetic patients.

Beyond reflecting underlying glomerular injury, microalbuminuria is a well-recognized marker of cardiovascular morbidity and mortality in those with type 1 or type 2 diabetes [30–32]. Its prevalence in diabetes patients is approximately 30–40% [20] as compared with roughly 15% in those without diabetes [33]. Although microalbuminuria often clusters with multiple other risk factors in diabetes, including dyslipidemia, hypertension, insulin resistance, and abnormalities of coagulation, it has been shown to be an independent predictor of cardiovascular events [30].

Data from the HOPE study [33] expanded our understanding of the link between microalbuminuria and cardiovascular risk in persons with diabetes. A cohort of 3,498 diabetic patients with at least one cardiovascular risk factor was evaluated for baseline microalbuminuria and the following three end points over a median of 4.5 years: cardiovascular events – acute myocardial infarction (MI), stroke, or cardiovascular death –, all-cause

mortality and hospitalization for congestive heart failure (CHF). Microalbuminuria, assessed as albumin-to-creatinine ratio, was defined as ≥ 2.0 mg/mmol (17.6 mg/g). In patients with microalbuminuria, the relative risks were 1.97 for a cardiovascular event, 2.15 for all-cause mortality, and 3.70 for CHF hospitalization (table 1). The predictive strength of microalbuminuria held even with adjustment for other cardiovascular risk factors, including smoking, hypertension, and dyslipidemia. Moreover, it held continuously for albumin-to-creatinine ratios beginning as low as 0.5 mg/mmol (4.4 mg/g) – well below the threshold for microalbuminuria. This study also included a cohort of nondiabetic patients whose relative risks for the study end points were similarly increased by the presence of microalbuminuria.

The LIFE study [34] strongly supports a relationship between microalbuminuria and mortality. In those patients, a continuous increase in mortality risk in submicroalbuminuria strata was observed.

An analysis from the Wisconsin Epidemiological Study of Diabetic Retinopathy [35] looked at both microalbuminuria and gross proteinuria in a cohort of 840 patients with diabetes. At baseline, 24.8% of the group had microalbuminuria, and 20.5% had proteinuria. During the course of 12 years, the relative risk of cardiovascular death was 1.84 for those with microalbuminuria and 2.61 for those with proteinuria. These rates were independent of cardiovascular and diabetes risk factors, including age, sex, glycemic control, insulin use, alcohol intake, physical activity, use of antihypertensive drug therapy, and history of cardiovascular disease.

Metabolic Syndrome

The metabolic syndrome, a condition characterized by abdominal obesity, hypertriglyceridemia, low high-den-

sity lipoprotein cholesterol (HDL-C) levels, high blood pressure, and high fasting glucose levels [36], is now considered an independent risk factor for cardiovascular disease [37]. As is the case with diabetes, microalbuminuria and other indications of renal dysfunction, while not directly associated with insulin resistance, are more common in patients with the metabolic syndrome than in those without [38, 39]. Several studies have reported a correspondence between the number of components of the metabolic syndrome present in a given patient and the prevalence of microalbuminuria [36, 40–42]. The largest of these [36], using data collected from over 6,000 adults in the USA participating in the NHANES III study, found that patients with three, four, or five components of the metabolic syndrome listed above had increased odds ratios of 1.62, 2.45, and 3.19, respectively, for microalbuminuria, as compared with those with either none or one component [36].

As a result of increasing evidence of an independent association between microalbuminuria and the metabolic syndrome, a 1998 World Health Organization (WHO) proposal [43] expanded its definition of metabolic syndrome to include microalbuminuria as 1 of 4 components, along with hypertension, dyslipidemia, and obesity. The inclusion of microalbuminuria as a separate component of the metabolic syndrome remains in dispute, but renal markers are gaining greater recognition for their ability to predict cardiovascular outcomes in patients with metabolic syndrome [44]. In one study of the predictive value of individual components of the syndrome, as defined by the revised WHO definition [44], microalbuminuria was associated with the strongest risk of cardiovascular death (relative risk 2.80; $p < 0.001$), highlighting the significance of renal disease in cardiovascular complications.

Dyslipidemia

Dyslipidemia, with well-established links to cardiovascular disease, metabolic syndrome, and diabetes, is independently associated with markers of renal disease. Specifically, high levels of triglycerides (TG) and low levels of HDL-C have been shown to be significantly predictive of renal dysfunction, although the levels of total cholesterol and low-density lipoprotein cholesterol have not [45, 46]. In the Atherosclerosis Risk in Communities (ARIC) study of 12,728 patients with baseline serum creatinine levels <2.0 mg/dl (men) or <1.8 mg/dl (women) [46], individuals with high TG and low HDL-C levels were found to be at increased risk of creatinine elevations ($p \leq 0.02$). Similarly, in a separate study involving Japa-

nese patients [45], a post hoc analysis of 4,326 patients free from proteinuria at baseline showed that high levels of TG were significantly predictive of the development of proteinuria during a 3-year follow-up period – relative risk 1.007 for men ($p = 0.04$) and 1.032 for women ($p = 0.02$). The increased incidence of markers for renal impairment in patients with high TG and low HDL-C levels suggests that proteinuria and elevated serum creatinine level may, in turn, help predict cardiovascular risk and outcomes, but to date no clinical evidence has demonstrated their utility in this regard.

Acute Coronary Syndromes (ACS)

Patients enrolled in four major cardiovascular intervention trials were the focus of a recent study on prevalence and prognostic significance of renal dysfunction in ACS [47]. The trials, all of which took place in the 1990s, were the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I Ib and III [48, 49]; Platelet Glycoprotein I Ib/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) [50], and Platelet I Ib/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-A) [51]. The patients in these trials had experienced chest pain with or without ST segment elevation on electrocardiography, and their renal function had been assessed by serum creatinine and CrCl data at trial enrollment. Renal impairment, defined as CrCl <70 ml/min, was documented in 41% of the 18,621 patients with ST segment elevation and in 42% of the 19,304 patients without ST elevation; it was more likely to be present in older patients, women, and in those with more baseline comorbidities. Regardless of their ST status, the patients with renal dysfunction were found to have significantly higher all-cause mortality and combined mortality/reinfarction at 30-day follow-up. After 180 days, the incidence of these end points increased, as the CrCl values decreased (table 2). For example, GUSTO-I Ib patients in the 33rd CrCl tertile had more than sixfold greater all-cause mortality (16.2%) than patients with the highest clearance rates (100th tertile; 2.5% mortality) and 2.5-fold greater mortality/reinfarction (22.1 vs. 8.5%, respectively). Renal dysfunction remained an independent predictor of mortality in the majority of the patients, even after adjustment for baseline comorbidities.

Several smaller studies support the potent influence of renal insufficiency on outcomes in ACS patients. Investigators from GRACE (Global Registry of Acute Coronary Events) [52], based in Argentina, found that stage 3 CKD (CrCl 30–60 ml/min) and stage 4 CKD (CrCl <30 ml/

Table 2. All-cause mortality at 180 days for patients with ACS [from ref. 47, with permission]

	No ST segment elevation			ST segment elevation	
	PURSUIT	GUSTO-IIb	PARAGON-A	GUSTO-IIb	GUSTO-III
Renal function					
Abnormalities	10.7	10.6	9.7	14.3	16.7
Normal	3.5	3.3	3.3	3.5	4.3
Tertiles of CrCl					
33rd	11.3	12.8	10.6	16.2	19.0
66th	5.0	4.5	5.6	5.1	6.0
100th	2.5	2.5	2.2	2.5	3.2
Unadjusted hazard ratio	0.72	0.70	0.74	0.64	0.67
95% CI ^a	0.69–0.75	0.64–0.74	0.67–0.81	0.61–0.69	0.65–0.69
p	<0.001	<0.001	<0.001	<0.001	<0.001
Adjusted hazard ratio	0.80	0.81	0.83	0.79	0.79
95% CI ^a	0.65–0.97	0.66–0.99	0.50–1.38	0.72–0.88	0.76–0.83
p	0.026	0.039	0.481	<0.001	<0.001

PARAGON: Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; GUSTO: Global Use of Strategies to Open Occluded Arteries; PURSUIT: Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy.

^a Increase of 10 ml/min.

min) independently predicted hospital death among 11,774 patients with acute MI or unstable angina (odds ratios 2.09 and 3.71 and 95% CI 1.55–2.81 and 2.57–5.37, respectively, for moderate impairment). The risk of major bleeding episodes also increased with worsening renal function. Again, older patients, women, and those with greater baseline comorbidities were more likely to have renal impairment. Thrombolysis in Myocardial Infarction (TIMI) investigators [53] evaluated creatinine data from 2,180 ST segment elevation MI patients in past intervention trials and found that elevated serum creatinine, impaired CrCl, or both predicted a higher 30-day mortality, regardless of other risk factors, including CHF. In addition, a study of 2,503 patients with acute MI and unstable angina in London hospitals found that the risk of left ventricular failure and cardiac death increased in direct accord with decreasing CrCl values, with odds ratios of 0.34 (95% CI 0.16–0.72) and 0.14 (95% CI 0.03–0.74), respectively, for patients in the highest CrCl quartile as compared with those in the lowest quartile. No threshold for this adverse relationship was noted; it held even in patients with well-preserved clearance [53].

An investigation of microalbuminuria in patients undergoing elective coronary angiography provided another perspective on renal function and cardiovascular risk [21]. Urinary albumin excretion and creatinine were

measured on the day of angiography in 308 patients; microalbuminuria was defined as an albumin-to-creatinine ratio of ≥ 30 mg/g. The prevalence of microalbuminuria was 20% in patients with confirmed coronary artery disease (CAD) versus just 3% in patients without CAD ($p < 0.001$). Moreover, the albumin-to-creatinine ratio increased in direct proportion to the severity of CAD. In parallel with creatinine findings in other studies of ACS, even albumin levels below the diagnostic threshold for microalbuminuria were predictive of CAD severity in this study. Fasting serum insulin was also measured in the study, and, although insulin levels were related to urinary albumin excretion ($r = 0.256$, $p < 0.001$), multiple regression analysis demonstrated that the two measures independently predicted CAD and its severity.

Interestingly, several studies [55, 56] have shown that standards of care medications are less likely to be used after MI in patients with higher levels of CKD. Therefore, unwarranted less aggressive treatment may play a role beyond lack of recognition of kidney disease.

Stroke

The relationship among renal disease markers and stroke has not been widely investigated. In a New Zealand study [57], multivariate proportional hazards models showed that the serum creatinine concentration indepen-

dently predicted mortality over 18 months in 492 stroke patients ($p = 0.0001$). A separate study of risk factors for stroke tested for urinary albumin in 186 patients and found that microalbuminuria was present in 29% of the patients with recent stroke and in 10% of those with remote stroke or transient ischemic attacks (TIA), whereas it was undetectable in healthy elderly controls ($p < 0.001$). During a mean of 1.5 years of follow-up, 20% of the patients with recent stroke, 14% of those with remote stroke/TIA, and 0% of the healthy controls experienced a recurrent stroke, MI, or vascular death ($p < 0.004$).

Microalbuminuria significantly predicted a future stroke in the combined recent stroke and remote stroke/TIA group, even when other major risk factors were considered (Cox proportional hazard ratio 4.9; 95% CI 1.4–17.6; $p < 0.01$) [58].

More recent data from a prospective study performed in Scotland [59] suggest that several measures of the renal function predict both short- and long-term mortality in stroke patients. The study cohort consisted of 2,042 stroke patients with a mean age of 73 years. Serum creatinine concentration, calculated CrCl, urea, and ratio of urea to creatinine were measured on hospital admission. During 7 years of follow-up, all of the renal measures significantly predicted all-cause mortality, even when the effects of age, neurological status, ischemic heart disease, treated hypertension, smoking, and diuretic use were accounted for. A CrCl ≤ 51.27 ml/min significantly and independently predicted mortality, and elevations of urea and creatinine were predictive, even if they were within normal reference intervals. Similarly, creatinine ≥ 119 $\mu\text{mol/l}$ (relative risk 1.59; 95% CI 1.32–1.92), urea 6.8–8.9 mmol/l (relative risk 1.34; 95% CI 1.09–1.65) or ≥ 9 mmol/l (relative risk 1.74; 95% CI 1.42–2.13), and urea:creatinine ratio ≥ 0.08573 mmol/ μmol (relative risk 1.24; 95% CI 1.03–1.50) remained significant predictors of mortality after adjustment for confounding variables. The predictive strength of these measures held for both short- and long-term mortality and in subgroups with ischemic versus hemorrhagic stroke or initial versus recurrent stroke.

CKD in More Representative Community-Based Populations

Weiner et al. [60] have recently analyzed data from four pooled publicly available, community-based studies: ARIC, CHS, FHS, and OFFSPRING. They found that the presence of CKD is an independent risk factor for adverse outcome (hazard ratio 1.19, CI 1.07–1.32 for composite outcome) in this large ($n = 22,364$), pooled

community-based cohort without cardiovascular disease. Furthermore, CKD was a more pronounced risk factor in black than in white patients.

Underrecognition of Renal Disease and Disease Markers

The studies cited above indicate that markers of early renal dysfunction in the context of cardiovascular disease can reveal a wealth of information regarding morbidity and mortality, yielding prognostic information at least as powerful as that offered by traditional cardiovascular risk factors. Many doctors may be unaware of the importance of early renal disease in cardiovascular patients or may be working under the assumption that renal markers apply only to renal function or signify little unless they are clearly abnormal. There is evidence that early renal disease is often underrecognized, even in settings, where its risks are documented and guidelines for its detection and management are well established.

In the UK, a chart audit of screening for renal dysfunction in twelve general practices in the London area [3] revealed a low testing rate in patients known to be at high risk of renal disease (individuals aged 50–75 years and either from ethnic minorities or having diabetes or hypertension or a family history of these diseases). The audit found that little more than half the patients with hypertension or diabetes had had their serum creatinine measured in the previous 2 years. Urine tests for proteinuria had been performed in only 29%. Of the 11% of the patients found to have a creatinine concentration >125 $\mu\text{mol/l}$ (signifying renal insufficiency), only 25% had been referred to a nephrologist. In the USA, a 1994 chart review of hospitalized Medicare patients with hypertension or diabetes [4] revealed numerous shortcomings in the recognition and management of renal dysfunction. The 587 patients were younger than 75 years and, in the diabetes group, more likely to be African-Americans. Admission notes rarely cited the presence or absence of a history of renal disease, and discharge plans generally failed to reflect renal dysfunction detected during the hospital stay. The serum creatinine level was measured in 90–97% of the patients, but only 4 diabetic patients and 2 hypertensive patients were tested for microalbuminuria. Proteinuria was tested for in fewer than 70% of the diabetic patients and in only 59% of the hypertensive patients. In France, a chart review [5] found that only 30% of 5,518 diabetic patients were tested for proteinuria during a 1-year period and that only 36% were

Table 3. Renoprotective strategy in patients with hypertension [adapted from ref. 62, with permission]

Lifestyle changes
Salt intake
Body weight
Smoking
Strict blood pressure control
<130/80 mm Hg; combination therapy required in most cases
<125/75 mm Hg, if proteinuria >1 g/day
Blockade of angiotensin II effects required
Control of associated risk factors
Lipids
Insulin resistance
Platelet aggregation
Control of nontraditional risk factors
Anemia
Disturbed mineral metabolism
Excess homocysteine
Excess parathyroid hormone

tested for microalbuminuria. The blood pressure was >140 mm Hg systolic and/or >80 mm Hg diastolic in 82% of the patients receiving antihypertensive therapy.

The reasons for this apparently widespread underrecognition of renal disease are unclear, especially in situations where a framework for detection and management is already in place. Lack of awareness regarding the associated risks, as well as skepticism surrounding the accuracy and prognostic strengths of laboratory tests may be involved. Furthermore, many practitioners are not aware that prevention of cardiovascular disease through optimal management of classical risk factors also decreases the risk to display renal insufficiency. In any case, it is reasonable to assume that underrecognition is even greater in cardiovascular patients, such as those with ACS or stroke, whose renal-related risks are newly evident. A greater appreciation of the importance of renal disease should be promoted, along with a heightened awareness regarding the types of patients now considered to be at substantial risk.

Renal Protection in Cardiovascular Disease Patients

Renal protection in cardiovascular disease patients has the goals of preventing or slowing the progression of renal disease and reducing the cardiovascular risk. Protection programs specific to subtypes of cardiovascular patients are evolving, but would appropriately be mod-

eled, at a fundamental level, on approaches currently employed in patients with hypertension and diabetes (table 3). Blood pressure control is a cornerstone of renal disease prevention and management: a goal of <130/80 mm Hg should be targeted, with the understanding that even mild elevations from this target are associated with an increased risk for both cardiovascular and renal diseases. The target blood pressure for cardiovascular disease risk reduction in CKD should be <130/80 mm Hg [61].

Body weight, salt intake, and smoking can directly affect renal function and blood pressure and should also be controlled. Antihypertensive drug regimens should include an angiotensin-converting enzyme inhibitor; drugs of this class have been shown to provide both renal and cardiovascular benefits through a variety of mechanisms, including the reduction of proteinuria. More than one antihypertensive drug will be necessary in most cases to achieve and maintain blood pressure goals [8, 62].

Control of traditional cardiovascular risk factors is also integral to renal protection in cardiovascular disease. These include dyslipidemia, insulin resistance, and platelet dysfunction [62].

Among patients on lipid-lowering therapy, preclinical evidence and a limited body of clinical data suggest that those receiving HMG-CoA reductase inhibitors (statins) may receive renoprotective benefits from these agents (e.g., decreased proteinuria and slowing of progression of renal disease), although the precise mechanisms for such effects have yet to be established [63–66]. A study performed by Tonelli et al. [64], for example, examined the impact of pravastatin on the renal function in patients participating in the Cholesterol and Recurrent Events (CARE) trial who were determined to have renal insufficiency at baseline (defined as GFR <60 ml/min/1.73 m²). Among 3,384 CARE patients for whom the renal function could be calculated, 703 (20.8%) were found to have renal insufficiency. The investigators found a significantly slower decline in annualized GFR in pravastatin recipients as compared with patients receiving placebo among those with a baseline GFR <50 ml/min/1.73 m²/year (0.6 ml/min/1.73 m²/year slower; *p* = 0.07; 95% CI –0.1 to 1.2) and GFR <40 ml/min/1.73 m²/year (2.5 ml/min/1.73 m²/year slower; *p* = 0.0001; 95% CI 1.4–3.6).

Nontraditional risk factors associated with renal disease and cardiovascular disease, such as anemia, disturbed mineral metabolism, and excess levels of homocysteine and parathyroid hormone, should also be addressed as part of a comprehensive approach to renal

protection [1]. Further research is warranted to confirm potential links between renal protection and cardiovascular risk reduction, particularly those that may revolve around control of proteinuria and microalbuminuria.

Finally, the use of potential nephrotoxic drugs should be avoided. Better awareness for contrast media induced nephropathy for patients with cardiovascular disease and renal insufficiency is needed. Vigilance with the risk of CHF exacerbation associated with thiazolidinediones, which otherwise would be antidiabetic agents of choice in CKD, as well as the potential risk of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs should be exercised. Aspirin use itself may also exacerbate heart failure in patients with CKD [4].

Screening Recommendations

National guidelines recommend screening of high-risk populations for renal and cardiovascular risk factors during routine health care visits. Specific recommendations recognize the prognostic significance of microalbuminuria. Patients with diabetes, for example, should be screened yearly with a spot urine albumin-to-creatinine ratio [67]. Any patient in whom proteinuria or microalbuminuria is present in two tests over a 3-month period should have further evaluation, including referral to a nephrologist [20]. An elevated serum creatinine level, as noted, is an important indicator of renal dysfunction and provides a practical alternative to the 'gold standard' GFR. However, the deficiencies of serum creatinine measurements should be kept in mind: low levels can be misleading in older patients and in those (typically women) with less muscle mass. Serum creatinine based estimates of the GFR should preferably utilize equations that account for age, gender, race, and body size [19]. Finally, in addition to such traditional cardiovascular risk factors as hypertension, hyperlipidemia, and physical inactivity, renal risk factors such as electrolyte imbalance and anemia should be considered in screenings [68].

Some innovative models for screening high-risk individuals have proven successful. A program for microalbuminuria testing, for example, was launched by the National Kidney Foundation in 1997 to target those with diabetes or hypertension and first-degree relatives of individuals with diabetes, hypertension, or renal disease. Blood pressure, weight, hematuria, pyuria, blood glucose, and serum creatinine were also measured. Among 1,935 participants in the pilot program, 75% had at least one abnormal result, and 30% had microalbuminuria [69]. In

a practice-based model employed in Germany, patients with hypertension were taught to test for microalbuminuria at home using an inexpensive reagent strip. Thirty percent of the patients detected microalbuminuria; the rates of CAD, left ventricular hypertrophy, stroke, and peripheral vascular disease were significantly higher in this group than in patients who detected no microalbuminuria [70].

Summary and Conclusions

Chronic renal disease is widespread and increasing in prevalence. Individuals with ESRD come largely from the ranks of hypertensive and diabetic patients with progressive renal dysfunction. It is now apparent that renal disease is highly prevalent but underrecognized, not only in hypertension and diabetes, but also in acute coronary syndromes, and stroke, where it predicts cardiovascular outcomes independently of traditional risk factors, even in cases where renal parameters reflect only mild renal disease. New treatment guidelines modeled on, but expanded, from current approaches to cardiovascular patients would also be desirable, especially as research improves our understanding of the pathophysiological links between renal and cardiovascular diseases and the collective benefits of lifestyle and pharmacological therapies.

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