

# Overview: Increased Cardiovascular Risk in Patients with Minor Renal Dysfunction: An Emerging Issue with Far-Reaching Consequences

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It has been known since the 1970s (1) that the cardiovascular (CV) risk is dramatically increased in patients who are on renal replacement therapy. The magnitude of the risk has been more clearly quantified in recent studies (2). What is new, however, is the recognition that even minor renal dysfunction as reflected by an increase in serum creatinine (or, more precise, by estimated GFR) on the one hand and/or albuminuria or trace proteinuria on the other hand has a major impact on the CV risk. Although a higher CV risk in patients with proteinuria had been recognized two decades ago (3), both the consistency and the magnitude of the CV risk, which is associated with minor renal dysfunction, have been fully appreciated only in the recent past (4, 5). The following series of “Frontiers in Nephrology” is designed to address several problems related to this issue.

First, what is the magnitude of the risk? As is outlined by Mann, an increase of the CV risk by a factor of 2 to 4 with elevated creatinine or microalbuminuria retrospectively has been recognized in multiple populations (6–16), including (1) in the general population, *i.e.*, the Framingham study (14) and confirmed in the prospective Hoorn study (17); (2) in individuals with hypertension (18); and (3) in individuals at high CV risk (19) as well as (4) in patients with heart failure (20). Furthermore, recent studies in patients with acute myocardial infarction (7, 8) documented a substantial increase of in-hospital and postdischarge mortality in individuals with acute myocardial infarction. This was explained only in part by iatrogenic factors, particularly withholding therapeutic options such as thrombolysis and interventional measures (coronary artery bypass graft and percutaneous transluminal coronary angioplasty) or cardioprotective medication (platelet inhibitors,  $\beta$  blockers, angiotensin-converting enzyme inhibitors). These results have been confirmed in a large international prospective observational study (21). These findings are further complemented by a recent analysis (22) indicating that the mortality



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after percutaneous transluminal coronary angioplasty increased progressively with increasing serum creatinine concentrations in the high-normal to slightly elevated range, so the evidence is overwhelming (1) that in the individual with even slightly reduced renal function, the risk of a CV event is dramatically increased, comparable in magnitude to that conferred by diabetes (19, 23); and (2) that slight renal dysfunction exposes the patient with a cardiac event to an excessive cardiac mortality.

This raises the second question: Through which mechanisms does impaired renal function have an impact on the CV risk? It would be naive to assume that there is one single cause. One important factor is early activation of the sympathetic nervous system as a result of excitation of intrarenal chemoreceptors and mechanoreceptors that send activating signals into the hypothalamus, where catecholamine turnover is increased, leading to increased efferent sympathetic nerve traffic, as shown in experimental (24) and clinical (25) studies. This may occur even when GFR is still normal (26). Increased sympathetic activity is of course the last thing you want to have in a patient with CV problems. This issue is addressed by Koomans. There are several other pathogenetic pathways. First, the concept of Lindner of accelerated atherogenesis (1) was re-

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Table 1. Prevalence estimates of CKD among populations with CVD<sup>a</sup>

Author	Study	Year	CVD Patients	Study Condition	Definition of CKD	% CKD
Matts <i>et al.</i> (6)	POSCH	1993	417	Post-MI	S <sub>cr</sub> >1.4 mg/dl	3.2
Wright <i>et al.</i> (7)	—	2002	3062 <sup>b</sup>	MI	Cr <sub>cr</sub> ≤75 ml/min	43.2
Shlipak <i>et al.</i> (8)	CCP	2002	13,009	Post-MI	S <sub>cr</sub> ≥1.5 mg/dl	36.7
Reis <i>et al.</i> (10)	—	2002	1309 <sup>c</sup>	Angiogram	S <sub>cr</sub> 1.2–1.9 mg/dl	56.1
Best <i>et al.</i> (11)	—	2002	5277 <sup>b</sup>	PCI	Cr <sub>cr</sub> <70 ml/min	49.1
Anderson <i>et al.</i> (12)	—	1999	3954	Post-CABG	S <sub>cr</sub> ≥1.5 mg/dl	17.3
Szzech <i>et al.</i> (13)	BARI	2001	3608	CAD	S <sub>cr</sub> >1.5 mg/dl	2.1
Mann <i>et al.</i> (19)	HOPE	2001	9287	High risk CVD	S <sub>cr</sub> ≥1.4 mg/dl	10.6
Tonelli <i>et al.</i> (37)	CARE	2003	4156	Post-MI	Cr <sub>cr</sub> ≤75 ml/min	41.1
Culleton <i>et al.</i> (14)	FHS	1999	749 <sup>d</sup>	Population-based	Men: S <sub>cr</sub> >135 μmol/L Women: S <sub>cr</sub> >120 μmol/L	10.9 15.9
Shlipak <i>et al.</i> (9)	CHS	2002	2449 <sup>e</sup>	Population-based	Men: S <sub>cr</sub> ≥1.5 mg/dl Women: S <sub>cr</sub> ≥1.3 mg/dl	15.1
Muntner (33)	NHANES	2002	351 <sup>d</sup>	Population-based	GFR <70 ml/min	63.5
Manjunath <i>et al.</i> (16)	ARIC	2003	1382 <sup>d</sup>	Population-based	GFR <60 ml/min per 1.73 m <sup>2</sup>	6.2

<sup>a</sup> CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease.

<sup>b</sup> Excludes patients with ESRD.

<sup>c</sup> Reported to angiographically mild and severe coronary artery disease.

<sup>d</sup> Estimated from data in Table 1 in report.

<sup>e</sup> Estimated from data in Table 2 in report.

cently confirmed in an experimental study (27). As a cause or consequence of increased atherogenesis, evidence of oxidative stress and a state of microinflammation is usually found, and this is true in early renal failure as well, as recently found by Shlipak *et al.* (9). This issue is dealt with in depth by Kaysen.

These are not the only abnormalities of potential pathogenetic relevance. Abnormal apolipoprotein patterns with increased Lp(a) (28) as well as increased concentrations of an inhibitor of nitric oxide synthase, asymmetric dimethyl-L-arginine (ADMA), possibly secondary to impaired ADMA breakdown (29), have been found in patients with renal disease even when inulin clearance was still normal (30). In addition, increased BP and left ventricular dysfunction were documented in patients with biopsy-confirmed glomerulonephritis and normal inulin by Stefanski *et al.* (31). These and other pathomechanistically interesting abnormalities are fertile areas for future research. In this context, we point particularly to the fallacy of equating a normal whole-kidney GFR with normal renal parenchymal function, because nephron loss leads to increased single-nephron GFR, which may mask loss of nephrons and the associated loss in renal metabolic function.

What are the practical implications? First, recent epidemiologic data illustrated the magnitude of the problem. Although terminal renal failure is found only in a small proportion (0.1%) of the general population, it has recently been reported (32) that 3.0% of the population have estimated GFR of 60 to 69 ml/min and 3.4% have estimated GFR of 30 to 59 ml/min. It is interesting that a recent report by Muntner and colleagues (15, 33) found that the rate of ESRD attributable to individuals with prevalent CV disease (CVD) in the general population is

comparable in magnitude (1463 per 1 million people per year) to that estimated for individuals with diabetes (2567 per 1 million people per year), rates much higher than those estimated for individuals with neither condition (153 per 1 million people per year). The high rate of ESRD among patients with CVD and the association of modest impairment of renal function with increased risk of CVD underscore the importance of sorting out the mechanisms that are responsible (Table 1).

There is also evidence for a high frequency of microalbuminuria in the general population (34), and this concerns particularly the population of elderly, hypertensive, and diabetic individuals. This issue is also dealt with in depth in this contribution to “Frontiers in Nephrology.”

The committee of the Kidney Disease Outcomes Quality Initiative guidelines recommended not to rely on serum creatinine measurements only, which are easily confounded by muscle mass, dietary intake, and alterations of tubular creatinine transport, but to estimate GFR with an appropriate formula (35), although none of the current formulas is completely satisfactory (36). As nephrologists, we look forward to the day when chemical laboratories not only report accurately calibrated serum creatinine concentrations but also, based on information on age, gender, and body mass submitted to the laboratory, will be able to report an estimated GFR to identify early renal dysfunction as a novel and so far underappreciated CV risk factor. It has been argued that—analogue to what has been postulated for diabetes—renal dysfunction should be considered a CV risk factor of the first order. Correspondingly, prevention should be regarded as “secondary prevention.” We hope that the following contributions help to increase aware-

ness and understanding of this problem, which has repercussions far beyond the nephrologic community.

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