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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, β 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 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[a]

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

[a] CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease.
[b] Excludes patients with ESRD.
[c] Reported to angiographically mild and severe coronary artery disease.
[d] Estimated from data in Table 1 in report.
[e] 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—analogous 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.

References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290: 697–701, 1974
2. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE: Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int* 54: 1720–1725, 1998
3. Samuelsson O, Wilhelmsen L, Pennert K, Berglund G: Prognostic factors in treated hypertension. *J Hypertens Suppl* 3[Suppl 3]: S497–S500, 1985
4. Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF: Renal function: the Cinderella of cardiovascular risk profile. *J Am Coll Cardiol* 38: 1782–1787, 2001
5. Ritz E: Minor renal dysfunction: An emerging independent cardiovascular risk factor. *Heart* 89: 963–964, 2003
6. Matts JP, Karnegis JN, Campos CT, Fitch LL, Johnson JW, Buchwald H: Serum creatinine as an independent predictor of coronary heart disease mortality in normotensive survivors of myocardial infarction. POSCH Group. *J Fam Pract* 36: 497–503, 1993
7. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, Miller WL, Murphy JG, Kopecky SL, Jaffe AS: Acute myocardial infarction and renal dysfunction: A high-risk combination. *Ann Intern Med* 137: 563–570, 2002
8. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137: 555–562, 2002
9. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int* 62: 997–1004, 2002
10. Reis SE, Olson MB, Fried L, Reeser V, Mankad S, Pepine CJ, Kerensky R, Merz CN, Sharaf BL, Sopko G, Rogers WJ, Holubkov R: Mild renal insufficiency is associated with angiographic coronary artery disease in women. *Circulation* 105: 2826–2829, 2002
11. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB: The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 39: 1113–1119, 2002
12. Anderson RJ, O'Brien M, MaWhinney S, VillaNueva CB, Moritz TE, Sethi GK, Henderson WG, Hammermeister KE, Grover FL, Shroyer AL: Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. *Kidney Int* 55: 1057–1062, 1999
13. Szczech LA, Best PJ, Crowley E, Brooks MM, Berger PB, Bittner V, Gersh BJ, Jones R, Califf RM, Ting HH, Whitlow PJ, Detre KM, Holmes D: Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. *Circulation* 105: 2253–2258, 2002
14. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56: 2214–2219, 1999
15. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 13: 745–753, 2002
16. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, Sarnak MJ: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 63: 1121–1129, 2003
17. Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD: Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney Int* 62: 1402–1407, 2002
18. Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, Zanchetti A: Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 12: 218–225, 2001
19. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001
20. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 102: 203–210, 2000
21. Santopinto JJ, Fox KA, Goldberg RJ, Budaj A, Pinero G, Avezum A, Gulba D, Esteban J, Gore JM, Johnson J, Gurfinkel EP: Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: Findings from the global registry of acute coronary events (GRACE). *Heart* 89: 1003–1008, 2003
22. Reinecke H, Trey T, Matzkies F, Fobker M, Breithardt G, Schaefer RM: Grade of chronic renal failure, and acute and long-term outcome after percutaneous coronary interventions. *Kidney Int* 63: 696–701, 2003
23. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339: 229–234, 1998
24. Campese VM, Kogosov E: Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension* 25: 878–882, 1995
25. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG: Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 327: 1912–1918, 1992
26. Klein IH, Ligtenberg G, Oey PL, Koomans HA, Blankestijn PJ: Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. *J Am Soc Nephrol* 12: 2427–2433, 2001
27. Buzello M, Tornig J, Faulhaber J, Ehmke H, Ritz E, Amann K: The apolipoprotein e knockout mouse: A model documenting accelerated atherogenesis in uremia. *J Am Soc Nephrol* 14: 311–316, 2003
28. Kronenberg F, Kuen E, Ritz E, Junker R, Konig P, Kraatz G, Lhotta K, Mann JF, Muller GA, Neyer U, Riegel W, Reigler P, Schwenger V, Von Eckardstein A: Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. *J Am Soc Nephrol* 11: 105–115, 2000
29. Ito A, Tsao PS, Adimoolam S, Kimoto M, Ogawa T, Cooke JP: Novel mechanism for endothelial dysfunction: Dysregulation of dimethylarginine dimethylaminohydrolase. *Circulation* 99: 3092–3095, 1999
30. Kielstein JT, Boger RH, Bode-Boger SM, Frolich JC, Haller H, Ritz E, Fliser D: Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol* 13: 170–176, 2002

31. Stefanski A, Schmidt KG, Waldherr R, Ritz E: Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. *Kidney Int* 50: 1321–1326, 1996
32. Levey AS, Coresh J: Should the K/DOQI definition of chronic kidney disease be changed? *Am J Kidney Dis* 42: 626–630, 2003
33. Muntner P, Coresh J, Powe NR, Klag MJ: The contribution of increased diabetes prevalence and improved myocardial infarction and stroke survival to the increase in treated end-stage renal disease. *J Am Soc Nephrol* 14: 1568–1577, 2003
34. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE: Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 249: 519–526, 2001
35. Bostom AG, Kronenberg F, Ritz E: Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 13: 2140–2144, 2002
36. Couser WG: Chronic kidney disease—How many have it? *J Am Soc Nephrol* 13: 2810, 2002
37. Tonelli M, Moye L, Jacks FM, Kiberd B, Curhan G, Cholesterol and Recurrent Events (CARE) Trial Investigators: Pravastation for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med Sci* 138: I28, 2003