How Does Minor Renal Dysfunction Influence Cardiovascular Risk and the Management of Cardiovascular Disease?

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Abstract. This review focuses on the association between mild renal insufficiency (stage 2 and 3 of chronic kidney disease) and cardiovascular disease and discusses therapeutic options. Although the association of chronic renal insufficiency and cardiovascular risk was first shown in patients with end-stage renal disease, even minor renal dysfunction is now established as an independent risk factor for atherosclerotic cardiovascular disease. The association has been established in patients with a high cardiovascular risk but also in the general population. Treatment with angiotensin-converting enzyme inhibitors and statins can reduce cardiovascular morbidity and mortality in patients with renal insufficiency. Coronary revascularization improves the prognosis in patients with minor renal dysfunction, but there is still an underutilization of coronary revascularization procedures in people with renal insufficiency. The use of coronary stenting has now reduced the incidence of restenosis in these patients, and there is hope that the development of new devices will improve the prognosis in patients with renal insufficiency as well. Nevertheless, people with cardiovascular disease and renal insufficiency die significantly more often than people without renal insufficiency independent of prior successful treatment. Further investigations should focus on the causes of and possible preventive interventions for the staggering cardiovascular risk in the ever-increasing number of people with minor renal dysfunction.

Cardiovascular disease is common in patients with renal insufficiency. The association between renal insufficiency and cardiovascular disease was first shown in patients with end-stage renal disease, whose cardiovascular mortality exceeds that of patients without renal disease by a factor of 20 to 40. Even in adolescents with end-stage renal disease, there is a staggering cardiovascular risk (1). However, the impact of renal insufficiency on the development of atherosclerotic cardiovascular disease probably begins with minor renal dysfunction (2). Until recently, there was little evidence linking minor renal dysfunction (stage 2 and 3 of chronic kidney disease) to an increased cardiovascular risk. Here, we review the evidence and therapeutic options.

Renal Insufficiency in People Not Selected for Cardiovascular Risk Factors

Patients with varying degrees of renal insufficiency have a predisposition to accelerated atherosclerosis and its consequences even in the absence of traditional cardiovascular risk factors (3). One of the first studies to assess minor renal dysfunction as a predictor of cardiovascular risk in a general population was the Framingham Heart Study (4); 6233 individuals with a mean age of 54 yr were followed for a mean of 15 yr. Minor renal dysfunction was present in 8% of women and 9% of men at baseline and was associated with a 40% greater all-cause mortality in men but not in women. However, there were only trends but no significant association between mild renal insufficiency and future cardiovascular morbidity and mortality. The cohort with minor renal dysfunction may have been too small for adequate statistical power (4). In the National Health and Nutrition Examination Survey II, with >6000 participants followed for 16 yr, mild to moderate renal insufficiency was independently associated with increased cardiovascular and all-cause mortality (5). Compared with subjects with an estimated GFR of ≥90 ml/min, those with <70 ml/min exhibited higher relative risks of death from cardiovascular disease (1.68; 95% confidence interval 1.33 to 2.13) and all-cause death (1.51; 95% confidence interval 1.19 to 1.91). This multivariate analysis included proteinuria, which also proved to be a kidney-related cardiovascular risk factor.

The suggestion that minor renal dysfunction can predict a substantial cardiovascular risk in the general population is further supported by the Atherosclerosis Risk in Communities study of 15,350 randomly chosen subjects aged 45 to 64 yr (6). Data were stratified according to the level of kidney function defined by GFR (GFR by Modified Diet in Renal Disease [MDRD] formula). As much as 50% of this sample exhibited minor renal dysfunction, and 2.8% exhibited more severe dysfunction. Only 5% and 4.8% of the subjects had coronary heart...
Table 1. Association of level of kidney function on ASCVD, de novo ASCVD, and recurrent ASCVD

<table>
<thead>
<tr>
<th>GFR Stratified into Three Groups and as a Continuous Variable</th>
<th>Unadjusted Hazard Ratio (95% CI), P Value</th>
<th>Adjusted Hazard Ratio (95% CI), P Value</th>
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<tbody>
<tr>
<td><strong>ASCVD</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>15 to 59 ml/min per 1.73 m²</td>
<td>2.89 (2.22 to 3.77), &lt;0.001</td>
<td>1.38 (1.02 to 1.87), 0.038</td>
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<td>60 to 89 ml/min per 1.73 m²</td>
<td>1.22 (1.07 to 1.40), 0.003</td>
<td>1.16 (1.00 to 1.34), 0.045</td>
</tr>
<tr>
<td>90 to 150 ml/min per 1.73 m²</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td><strong>De novo ASCVD</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 to 59 ml/min per 1.73 m²</td>
<td>2.55 (1.69 to 3.84), &lt;0.001</td>
<td>1.58 (1.01 to 2.47), 0.047</td>
</tr>
<tr>
<td>60 to 89 ml/min per 1.73 m²</td>
<td>1.24 (1.03 to 1.50), 0.023</td>
<td>1.25 (1.02 to 1.52), 0.031</td>
</tr>
<tr>
<td>90 to 150 ml/min per 1.73 m²</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<tr>
<td><strong>Recurrent ASCVD</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>15 to 59 ml/min per 1.73 m²</td>
<td>1.88 (1.20 to 2.96), 0.006</td>
<td>1.53 (0.95 to 2.47), 0.079</td>
</tr>
<tr>
<td>60 to 89 ml/min per 1.73 m²</td>
<td>1.18 (0.92 to 1.52), 0.201</td>
<td>1.12 (0.85 to 1.48), 0.409</td>
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<tr>
<td>90 to 150 ml/min per 1.73 m²</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<td><strong>Continuous variable</strong></td>
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<tr>
<td>ASCVD&lt;sup&gt;b&lt;/sup&gt; (per 10 ml/min per 1.73 m² lower GFR)</td>
<td>1.14 (1.10 to 1.18), &lt;0.001</td>
<td>1.05 (1.02 to 1.09), 0.006</td>
</tr>
<tr>
<td>De novo ASCVD&lt;sup&gt;c&lt;/sup&gt; (per 10 ml/min per 1.73 m² lower GFR)</td>
<td>1.11 (1.06 to 1.17), &lt;0.001</td>
<td>1.07 (1.01 to 1.12), 0.015</td>
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<sup>a</sup> ASCVD, atherosclerotic cardiovascular disease; de novo ASCVD, events in subjects without baseline ASCVD; recurrent ASCVD, events in subjects with baseline ASCVD; CI, confidence interval. (Reproduced from reference 6, with permission.

<sup>b</sup> Adjusted model with age, gender, race, baseline coronary heart disease, baseline stroke/transient ischemic attack, hypertension, diabetes mellitus, left ventricular hypertrophy by electrocardiogram (ECG), smoking status, pack years, body mass index, waist/hip ratio, activity level, systolic blood pressure, total cholesterol, HDL cholesterol, albumin, fibrinogen, and vasodilating agents.

<sup>c</sup> Adjusted model with age, gender, race, hypertension, diabetes mellitus, left ventricular hypertrophy by ECG, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, albumin, fibrinogen, cardiac agents, and vasodilating agents.

<sup>d</sup> Adjusted model with age, gender, race, diabetes mellitus, left ventricular hypertrophy by ECG, smoking status, systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, albumin, cardiac agents, and vasodilating agents.
disease and cerebrovascular disease, respectively, at baseline. In multivariate analysis, even minor renal dysfunction was a substantial risk factor for subsequent cardiovascular events and death (Table 1). A 10 ml/min per 1.73 m² lower GFR was associated with a 5% higher adjusted cardiovascular risk, and an increase in serum creatinine by 0.1 mg/dl was associated with a 4% risk increase.

**Renal Insufficiency in People with Other Cardiovascular Risk Factors**

The earliest evidence that minor renal dysfunction may be an independent predictor of future cardiovascular disease came from the Hypertension Detection and Follow-up Program (7). This study was a community-based, randomized, controlled trial of 10,940 people with hypertension. Included were 630 people with serum creatinine >1.4 mg/dl and only 72 people with creatinine >2.5 mg/dl at baseline. A linear relation was found between serum creatinine levels and cardiovascular mortality over the 5-yr follow-up, with a fivefold difference in cardiovascular mortality between the lowest and highest serum creatinine strata. Of note, this linear association started within “normal” limits of serum creatinine, and GFR was not calculated in that early publication. The risk associated with renal insufficiency was independent from other classic cardiovascular risk factors such as diabetes mellitus, smoking, or dyslipidemia.

Another megatrial in hypertensive patients, the Hypertension Optimal Treatment (HOT) study, including 18,790 hypertensive patients followed for 4 yr, confirmed the Hypertension Detection and Follow-up Program data (8). Most patients (approximately 90%) did not have evidence of atherosclerotic vascular disease at inclusion, and people with a baseline serum creatinine >265 μmol/L were excluded. There was a significantly increased (twofold) adjusted relative risk for major cardiovascular outcomes and for all-cause mortality in patients with a baseline serum creatinine level >133 μmol/L compared with patients with a baseline serum creatinine level <133 μmol/L (10% versus 3.5%). In a much smaller observational study, 1829 hypertensive patients lacking evidence of atherosclerotic disease and with normal pretreatment creatinine levels were followed for 4 yr (9). The number of cardiovascular events (total 175) increased progressively from the first to the fourth quartiles of serum creatinine (1.5, 2.3, 2.3, and 3.5 events per 100 patient-years; P = 0.003). Serum creatinine remained an independent predictor of cardiovascular events (P = 0.01) even after adjustment for age, sex, diabetes mellitus, cholesterol, smoking, and left ventricular hypertrophy as well as for 24-h pulse and mean BP. In the Multiple Risk Factor Intervention Trial, 5524 patients with hypertension and without evidence of atherosclerotic disease were followed for 16 yr (10). There was an association of higher cardiovascular risk with increasing serum creatinine levels during the trial but not with baseline serum creatinine.

Evidence for minor renal dysfunction as an independent cardiovascular risk factor is not restricted to hypertensive populations. The Heart Outcomes Prevention Evaluation (HOPE) study focused on 9297 people with evidence of previous atherosclerotic vascular disease, mostly coronary, or diabetes mellitus plus at least one other cardiovascular risk factor. The trial included 980 participants with a serum creatinine level between 125 and 200 μmol/L and 3394 participants with a calculated creatinine clearance <65 ml/min (11). Study participants with minor renal dysfunction defined by either serum creatinine or creatinine clearance had a 40% higher adjusted risk for major cardiovascular outcomes and for death (Figure 1). The primary outcome measure, the composite of myocardial infarction, stroke, and cardiovascular death, occurred in 22.2% of those with minor renal dysfunction and in 15.1% of the remaining trial population (P < 0.001); especially striking was the difference in cardiovascular and total mortality (11.4% versus 6.6% and 17.8 versus 10.6%; P < 0.001 each). Moreover, there was a significant trend for more primary outcomes with increasing levels of serum creatinine or decreasing GFR. The impact of minor renal dysfunction on the primary outcome was not affected by the presence of either diabetes mellitus or hypertension. It was also not affected by albuminuria, another substantial renal-related predictor of cardiovascular risk in individuals with and without diabetes mellitus (12). The data from the HOPE study were supported by Hemmelgarn et al. (2001), who showed in a prospective 3-yr follow-up of all people undergoing coronary angiography in Alberta (Canada) that patients with mild to moderate renal insufficiency (serum creatinine concentration > 2.3 mg/dl, 262 of 16,989 patients) had an impaired 4-yr survival (unadjusted hazard ratio 2.51, 2.02 to 3.12) (13).

Minor renal insufficiency is a risk factor also in patients with heart disease. Hillege et al. (2000) followed 1906 patients with severe congestive heart failure (New York Heart Association class III or IV) for a median of 277 d, during which 343 patients died (14). After stratification for baseline GFR (Cock-
roft-Gault formula), patients in the lowest GFR quartile (<44 ml/min) had a 2.85-fold risk of death compared with those in the highest GFR quartile (>76 ml/min). This increased risk was not related to left ventricular function (14). Is minor renal dysfunction also a cardiovascular risk factor in patients with less severe cardiac disease? The Atherosclerosis Risk in Communities study (see above) suggests that this may be the case: in subjects with left ventricular hypertrophy, a 10 ml/min per 1.73 m² lower GFR was associated with a 19% increase in risk for atherosclerotic vascular disease (6).

Renal Insufficiency in People with Acute Coronary Syndromes and Coronary Interventions

A large meta-analysis of 37,894 participants of the GUSTO-IIb, GUSTO-III, PURSUIT, and PARAGON-A trials with acute coronary syndromes (15) evaluated the impact of a calculated creatinine clearance <70 ml/min on mortality and reinfarction at 30 and 180 d. The number of outcomes at 180 d was inversely and significantly related to tertiles of creatinine clearance. After adjusting for baseline differences in comorbidities, low creatinine clearance remained independently associated with increased all-cause mortality in all single trials except in PARAGON-A.

Quite consistent reports indicate that when patients are sent for coronary interventions, i.e., percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting, those with minor renal dysfunction fare worse than those with normal renal function. Brooks and colleagues found minor renal dysfunction to be a potent, independent predictor of mortality among 3610 people in the Bypass Angioplasty Revascularization Investigation Randomized Trial and Registry (16). Their conclusions were supported by several studies. Best and colleagues analyzed cardiac mortality and all-cause mortality of 5327 patients undergoing PTCA between 1994 and 1999 (17). Again, minor renal dysfunction proved to be a strong and independent predictor of death and subsequent cardiac events after PTCA.

In a large series of 4157 consecutive patients after PTCA (with stenting in the vast majority), we compared the 650 patients with minor renal dysfunction (serum creatinine ≥ 1.4 mg/dl) with the rest (T. Pinkau et al., submitted). Although no significant difference was found for urgent target lesion revascularization or the incidence of restenosis at 6-mo follow-up angiography, the composite end point of death and myocardial infarction was more frequently observed in patients with minor renal dysfunction (11.4% versus 4.0%; P < 0.001, multivariate odds ratio 2.3, 95% confidence interval 1.67 to 3.07) (Figure 2).

Therapeutic Options for Patients with Renal Insufficiency and Cardiovascular Disease

Medical Therapy. It is obvious from the above that people with minor renal dysfunction should be regarded as individuals at increased cardiovascular risk even in the absence of classic risk factors. Prospective treatment studies of cardiovascular outcomes in samples with minor renal dysfunction are lacking. However, based on post hoc analysis of several studies, we suggest the following targets for therapy: BP < 130/80 mmHg, plasma LDL level < 2.5 mmol/L, cessation of smoking, regular physical exercise, and metabolic control in patients with diabetes mellitus. Furthermore, the HOPE study indicated that angiotensin-converting enzyme (ACE) inhibition with ramipril is beneficial because it reduced the high cardiovascular risk associated with minor renal dysfunction (11,18,19). The composite primary event rate was reduced from 40 to 32 and from 64 to 46 events per 1000 patient-years in people without and with minor renal dysfunction, respectively. For cardiovascular mortality, all-cause mortality, and heart failure hospitalization, the risk reduction was significantly smaller in those without than with minor renal dysfunction (11,20). Thus, the frequent practice of withholding ACE inhibitors in patients with renal insufficiency is unwarranted. New data from the HOPE study further suggest that hyperkalemia (<6.5 mmol/L) does not increase the risk of cardiovascular events, whereas hypokalemia (<3.5 mmol/L), which is mitigated by ACE inhibitors, is harmful (21).

The results of several recent reports indicate that treatment with statins can reduce cardiovascular morbidity and mortality in patients with minor renal dysfunction. In the ALERT trial, patients who had received a kidney transplant and displayed a mean serum creatinine of 145 μmol/L and a mean total cholesterol of 6.4 mmol/L were treated with fluvastatin or placebo for 5 to 6 yr (22). Fluvastatin reduced the odds ratio for cardiac death (0.83) and myocardial infarction (0.65). The lipid-lowering arm of the ASCOT megatrial, which included 10,305 patients with hypertension and additional risk factors but total cholesterol <6.5 mmol/L, demonstrated a profound reduction of myocardial infarction and cardiovascular death by atorvastatin (odds ratio 0.64) (23). The drug was also effective (odds ratio 0.61) in patients (n = 651) classified as suffering from renal dysfunction, a definition that included abnormalities in the urinalysis. A post hoc subgroup analysis of those participants of the CARE study with mild renal impairment (GFR < 75 ml/min but serum creatinine <1.5 times the upper normal

Figure 2. Cumulative rates of death and myocardial infarction during a 1-yr follow-up after coronary intervention, usually with stenting, in people with and without renal insufficiency. The composite end point of death and myocardial infarction was more frequently observed in patients with than without renal insufficiency (11.4% versus 4.0%; P < 0.001).
Coronary revascularization strategies: Bypass grafting versus percutaneous angioplasty. Coronary revascularization can improve prognosis in patients with end-stage renal disease (25,26); similar prospective data are lacking for people with less severe renal insufficiency. There is underutilization of coronary revascularization in people with renal insufficiency, probably because of the assumption that they benefit less from intervention and experience more complications than people without renal insufficiency (27). Several interventional trials showed a lower short-term and long-term success rate of balloon angioplasty and a lower long-term event-free survival in patients with than without renal insufficiency (28–36). In a retrospective study, Herzog and colleagues compared the survival of chronic dialysis patients after PTCA or coronary artery bypass surgery and found better long-term survival after coronary artery bypass surgery compared with PTCA (37). Another study showed similar data (36). A recent retrospective study of 3902 patients after coronary surgery demonstrated that even minor renal dysfunction was an independent risk factor for 30-d mortality (7% versus 3%; \( P < 0.001 \)), a prolonged mechanical ventilation time (15% versus 8%; \( P = 0.001 \)), more stroke events (7% versus 2%; \( P < 0.001 \)), and more bleeding complications (8% versus 3%; \( P < 0.001 \)) (38). Although the currently available data appear to be more favorable for artery bypass grafting, it is important to bear in mind that most of these studies were performed before the widespread use of new anti-platelet regimens and of coronary stenting.

Coronary artery revascularization strategies: newer options for percutaneous angioplasty. A high risk of restenosis after balloon angioplasty was documented in patients with end-stage renal disease (29,39,40). However, the use of coronary stents has improved the outcome of coronary angioplasty in patients without renal failure. Azar and colleagues showed that despite an initial similar angiographic success of coronary stenting, repeat target lesion revascularization was twice as frequent in patients with end-stage renal disease compared with those without renal insufficiency during a follow-up of 9 mo (35% versus 16%; \( P < 0.05 \)) (41). In contrast, Le Feuvre and colleagues showed in 1428 PTCA patients enrolled in a case-control study with a stenting rate of 40% that the procedural success rate was identical in the 100 patients with end-stage renal disease and in controls (42). End-stage renal disease did not increase the risk of restenosis after provisional stenting in this series. Coronary stenting also reduced the incidence of major adverse cardiac events as well as the restenosis rate in hemodialysis patients (43). In a retrospective analysis of 3334 patients, Rubenstein and colleagues found that the increase of stent utilization between 1994 and 1997 was associated with an increase in procedural success and a reduction in in-hospital major coronary events, especially in people with minor renal dysfunction (31). In our own series of 4157 PTCA patients treated mostly by stenting, target lesion revascularization was required in 16.9% of patients with minor renal dysfunction and 18.8% of those with normal serum creatinine values (\( P = 0.26 \)). There was no increase in the incidence of restenosis in the renal insufficiency group; late lumen loss and diameter stenosis at follow-up were also comparable (Figure 3) (T. Pinkau et al., submitted).

Gruberg and colleagues compared the results of brachytherapy in 118 patients with renal insufficiency and 481 patients without renal insufficiency (44). At 6-mo follow-up, restenosis, target lesion revascularization, and target vessel revascularization rates were similar in the two groups. In patients with renal insufficiency, radiation therapy compared with placebo reduced restenosis (53.8% versus 22.6%; \( P = 0.04 \)). New coated stents eluting antiproliferative drugs have now raised the hope that they will improve outcomes for people with minor renal dysfunction (45).

Conclusions

A substantial amount of data that have accumulated in recent years suggest that even minor renal impairment is an important and independent cardiovascular risk factor that should be more vigorously addressed in the care of an aging population. It is important to note that in many studies, patients with only minor renal dysfunction had worse baseline characteristics than patients without minor renal dysfunction. They are usually older and more likely to have diabetes mellitus, hypertension, congestive heart failure, and more severe coronary heart disease (6,11,15,17,31,36,44,46). Although these factors may play a role, they cannot fully explain the cardiovascular risk associated with minor renal dysfunction. Cardiovascular sequelae of impaired renal function have been clearly demonstrated in experimental animals and in young (20 to 30 yr old) patients in whom the “traditional” risk factors for cardiovascular disease

<table>
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<th>Incidence (%)</th>
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<td>patients with renal insufficiency</td>
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Figure 3. Incidence of angiographic (left) and clinical (right) restenosis in patients with and without renal insufficiency. There was no significant difference between the two groups.
could be largely excluded (47). Therapeutic options at present include strategies such as ACE inhibition and statins, which may be underused in patients with renal disease. Nevertheless, a better understanding of the pathophysiology of cardiovascular disease in the setting of minor renal dysfunction and more rigorous prospective treatment trials will be required to establish future guidelines for therapy of a growing yet underestimated population of people at risk.

References


43.アクセスto UpToDate on-line is available for additional clinical information at http://www.jasn.org/