Percutaneous coronary interventions in patients with mild to moderate chronic renal failure: to dilate or not to dilate?

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Introduction

Worldwide, the incidence of chronic kidney disease has risen relentlessly over recent years due to an increasing prevalence of diabetes mellitus and arteriosclerotic vascular disease [1–4]. A further increase in the number of patients with chronic renal failure has to be expected in the coming years [4,5]. Thus, adequate management of these patients will become a more and more pressing issue in clinical medicine.

It is well known from patients with end-stage renal failure that a large number will develop cardiovascular disease over time and that coronary heart disease (CHD), myocardial infarction and congestive heart failure represent major causes of morbidity and mortality in these patients [6]. Moreover, chronic renal failure not yet requiring renal replacement therapy has not been recognized—at least by many cardiologists—as an important cardiovascular risk factor. However, a few but very consistent recent studies provided good evidence that even mild to moderate chronic renal failure is associated with markedly impaired long-term survival.

Chronic renal failure and cardiovascular risk

Recent data from the ARIC (Atherosclerosis Risk in Communities) study [7] in 15 350 healthy subjects without known cardiovascular disease showed that a re-
duced glomerular filtration rate (GFR) was associated with a significant increase of major cardiovascular events over a follow-up period of 6.2 years (events defined as myocardial infarction, cardiac procedures, death and stroke). In brief, patients with calculated GFRs of 15–59 ml/min had a hazard ratio of 1.38, and those with a GFR of 60–89 ml/min had a hazard ratio of 1.16 for cardiovascular events, compared to patients with a normal GFR (90–150 ml/min). In brief, patients with calculated GFRs of 15–59 ml/min had a hazard ratio of 1.38, and those with a GFR of 60–89 ml/min had a hazard ratio of 1.16 for cardiovascular events, compared to patients with a normal GFR (90–150 ml/min). In comparison to healthy controls (5.0%), all-cause mortality was significantly higher only in the subgroup with a GFR of 15–59 ml/min (16.7%) but was identical in patients with moderately reduced GFR (4.4%). Thus, the higher rate of all events in the group with a moderately reduced GFR of 60–89 ml/min was almost exclusively due to cardiac procedures and non-fatal infarctions. However, since the subjects did not undergo cardiac evaluation before entering the study, those with chronic renal failure might have already had asymptomatic cardiovascular disease at the time of inclusion. Therefore, it remains unclear whether chronic renal failure represents an independent cardiovascular risk factor per se, or whether it is only a marker of (probably not yet diagnosed) general or coronary arteriosclerosis.

In addition to these epidemiological data, observations regarding the impact of chronic renal failure in patients with manifest CHD are limited to outcome analyses of patients who underwent coronary revascularization: end-stage renal disease [8–10] and chronic renal failure [10,11] have both been identified as important risk factors for impaired acute and long-term outcome after bypass surgery a number of years ago. These experiences have been implemented in special preoperative scoring systems which aim to identify patients at risk [10,12]. In contrast, data about the outcome of patients undergoing percutaneous coronary intervention (PCI) are limited and derived from only a few studies.

**PCI in chronic renal failure**

First reports addressing the impact of chronic renal failure on the outcome after PCI appeared in 2000 and were based on a small case-control study with 66 patients [13] and on a large cross-sectional study of 362 patients by Rubenstein et al. [14]. Both trials assessed in-hospital complications and long-term survival in patients with serum creatinine levels of >1.5 mg/dl without previous history of haemodialysis. They found a markedly higher in-hospital and long-term mortality in these patients, with an overall survival of only 60% after 3–4 years. However, in these two studies the patients were not separated according to the degree of renal impairment.

Three subsequent studies also focused on the impact of the degree of renal failure on outcome after PCI. In a subgroup analysis of their previous study, Rubenstein et al. [15] compared patients with a serum creatinine level of 1.6–2.0 mg/dl to those with a level of >2.0 mg/dl. They found a significantly higher mortality after 2 years in those with the higher serum creatinine levels (55 vs 75%) but also noted that the outcome of those with less severe renal failure was worse than that of patients with normal renal function. Best et al. [16] analysed the outcome after PCI as a function of the calculated creatinine clearance in subgroups with clearances of ≥70, 50–69, 30–49 and <30 ml/min, respectively. They found a significantly higher mortality for each of the three latter subgroups compared to that with a clearance of ≥70 ml/min (Figure 1, lower). Finally, a recent analysis from our institution [17] focused on PCI patients with marginally reduced renal function. We observed an increment in mortality with each stepwise increase in the serum creatinine level of 0.1 mg/dl above 1.0 mg/dl, with differences in survival becoming significant at a level of ≥1.3 mg/dl (Figure 1, upper).

Even though the approaches of all these studies were different, the mortality rates observed were similar and consistently indicated a reduced outcome of chronic renal failure patients after PCI. From these reports the issue arose of whether a threshold in terms of GFR could be defined above which no negative impact on...

![Fig. 1.](https://academic.oup.com/ndt/article-fig/18/Suppl_1/2219)
mortality might be expected. The implication from our analysis, which showed that even patients with serum creatinine levels of 1.1 and 1.2 mg/dl had a non-significant trend towards higher mortality (Figure 1, upper), is that the possible threshold may be lower than previously expected and that the number of patients at risk may therefore be higher. One has to bear in mind that in many subjects a serum creatinine level of 1.3 mg/dl signifies a reduction in renal function by 50%, which obviously impacts on the clinical outcome of PCI in those patients. Thus, the terms ‘mild’ or ‘moderate’ renal failure will have to be redefined, as they appear to be too imprecise. The new Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend a more rigorous definition of various stages of chronic kidney disease [18]. A wide application of these new definitions will improve comparisons between clinical studies.

It is of note that, in all of the five studies mentioned above, the mortality curves after PCI separated very early, and at 1 year cumulative survival was already significantly lower in renal failure patients. Therefore, it is debatable whether PCI is effective and acceptable in patients with reduced GFRs, since 25–40% of patients with serum creatinine levels of ≥1.6 mg/dl will have died within the next 3–4 years [13–17].

**PCI vs bypass surgery: and the winner is . . .**

‘Are patients with renal failure good candidates for percutaneous coronary revascularization in the new device era?’ This question was asked in the above-mentioned landmark study by Rubenstein et al. [14]. When considering only patients with end-stage renal failure, the situation appears to be clear. In their analysis of >10,000 patients from the US Renal Data System database, Herzog et al. [19] showed that coronary bypass grafting was associated with a significantly higher 2 year survival than PCI (56% vs 48%). In addition, other studies demonstrated that the risk for recurring revascularization and the efficacy to reduce angina were also clearly in favour of bypass surgery [20–22]. However, there are not enough data available presently to decide whether these results can be extrapolated from end-stage kidney disease to less advanced stages of chronic renal failure.

Moreover, all PCI studies, as well as the analyses of bypass surgery trials, were retrospective in nature. Apart from general limitations inherent in this approach, one major caveat has to be taken into consideration. PCI, but not bypass surgery, is feasible in patients with advanced cardiovascular disease and in those with a markedly reduced general condition or with acute myocardial infarction, and it has even marked benefits in patients with cardiogenic shock [23]. Such high-risk patients have actually been included in the above-mentioned trials. In contrast, bypass surgery is almost exclusively limited to patients who are considered to be ‘fit for surgery’. Patients with acute infarction and cardiogenic shock are usually excluded or only treated in rare instances. Thus, always a substantial bias will remain between patients selected for bypass surgery and those submitted to PCI. This bias has most likely affected patients’ outcome in the above-mentioned trials. However, since most patients with renal failure undergo elective coronary revascularization in an acceptable general condition, randomized prospective trials seem to be feasible.

Finally, the increasing use of coated coronary stents (e.g. with sirolimus) will influence acute and long-term outcome of PCI patients with or without chronic renal failure. Even in the above-mentioned PCI in chronic renal failure trials, the implantation of conventional coronary stents (used in only ~50% of cases) was associated with a significantly better survival [17,24]. Moreover, coated stents were found to have very low rates of restenosis (0–3% of cases), myocardial infarction or mortality [25]. Accordingly, benefits have also been observed in high-risk patients, e.g. those with unfavourable coronary anatomy or diabetes mellitus [26,27]. Taking into account the dismal outcome of PCI in renal failure patients, one may speculate that this is due to coronary restenosis with subsequent fatal or non-fatal infarctions, which may be prevented by these new coronary devices.

**Conclusions**

Of late, it has been recognized that even patients with mild chronic renal failure and CHD have an unfavourable outcome after PCI. The main contributing factors remain unclear, and the question of ‘why chronic kidney disease is the spoiler for cardiovascular outcomes’ [28] has to be discussed further. In the absence of randomized prospective trials, the revascularization procedure of choice for these patients still has to be determined. However, in patients with acute coronary syndromes or high surgical risk, PCI does represent an effective and eligible therapy. Future trials formally comparing surgical and interventional revascularization procedures and evaluating the use of adjunctive pharmacological therapy, e.g. by blockade of the renin–angiotensin system, are needed to make evidence-based treatment decisions possible in this particularly vulnerable set of patients.

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