Percutaneous coronary interventions in patients with renal failure: overcoming in-stent restenosis?

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Keywords: end-stage renal disease

Introduction

Patients with end-stage renal disease (ESRD) have a 20- to 40-fold higher cardiovascular mortality than patients without renal disease [1]; 52% of dialysis patients surviving an acute myocardial infarction die from a cardiac cause within the following 2 years [2]. This very unfavourable prognosis of ischaemic heart disease in dialysis patients is not only due to the severity of coronary artery disease, but may also reflect the underutilization of modern treatment measures for acute myocardial infarction [1,2].

One of the reasons for the underutilization of coronary revascularization procedures in the ESRD population may be the perception that patients with chronic renal failure (CRF) benefit less from coronary angiography, as they often have diffusely calcified coronary artery disease, which is neither suited to percutaneous nor to surgical revascularization. Nevertheless, several studies have shown that surgical revascularization has a better long-term outcome in dialysis patients than percutaneous coronary interventions [3,4]. This has been corroborated and refined by a recent analysis of data from the US Renal Data System, which shows that the survival advantage of patients treated surgically is attributable to grafting of the internal mammary artery [5].

Despite results favouring surgical treatment, many patients with ESRD are poor surgical candidates making alternative treatment options, including percutaneous revascularization, desirable. In patients without renal failure, considerable progress has recently been made in the interventional treatment of coronary artery disease, especially in the setting of acute coronary syndromes due to the advent of highly effective anti-platelet regimens. Although the benefits of these advances have not been well documented in patients with renal failure, there is reason for optimism that the progress of interventional treatment for coronary artery disease in patients with normal renal function also pertains to patients with renal failure.

There are three main causes of the improved outcome of modern percutaneous coronary interventions: (i) the widespread use of coronary stents (in some centres up to 80% of all angioplasties); (ii) the inhibition of platelet function with multiple agents; and (iii) the effective treatment of in-stent restenosis. Recent results have generated considerable enthusiasm as they suggest that the latter problem may even be preventable.

Stenting

The widespread use of coronary stents has improved the outcome of coronary angioplasty [6]. This also pertains to patients with renal disease. Le Feuvre et al. [7] have reported data from a large case-control study of 1428 consecutive patients, in which patients on haemodialysis had a procedural success rate for percutaneous coronary interventions similar to non-dialysis patients. The stenting rate was 40%, which is lower than the present rate in most centres. Importantly, ESRD did not increase the risk of clinical in-stent restenosis after provisional stenting [7]. In contrast, another study using quantitative coronary angiography showed that despite an initial similar angiographic success rate, target lesion revascularization was twice as common in ESRD patients compared with matched controls during a 9-month follow-up. According to this study, restenosis is more frequent in dialysis patients, but the authors conclude that the overall risk of restenosis after stent placement is still low enough in dialysis patients to make coronary stenting a valuable treatment option [8]. In both studies, however, the 1-year survival of patients on dialysis was significantly reduced despite the efficacy and safety of coronary stenting, reflecting the overall morbidity of this patient population. An increased mortality rate despite successful coronary intervention has also been shown for patients with CRF who are not on dialysis, although stenting has improved...
the immediate and long-term outcomes of coronary revascularization in this group [9].

**Inhibition of platelet function**

Platelets play a key role in coronary thrombosis both after stent implantation and in acute coronary syndromes. The inhibition of platelet function with aspirin and the thienopyridine clopidogrel is current standard clinical practice after coronary stent implantation [10]. In the setting of unstable angina or myocardial infarction, additional platelet inhibition can be achieved with glycoprotein IIb/IIIa antagonists [11]. The clinically used compounds abciximab, eptifibatide and tirofiban must be administered intravenously. Orally active glycoprotein IIb/IIIa antagonists are not in clinical use as they have been associated with an increased mortality [12]. The recently published PCI-CURE study has shown that the orally administered thienopyridine clopidogrel can significantly improve the outcome of percutaneous coronary interventions in patients with acute coronary syndromes compared with placebo, even in addition to intravenous glycoprotein IIb/IIIa antagonists, without increasing the risk of major bleeding complications [13].

It is unclear if the aggressive inhibition of platelet function is similarly beneficial in patients with renal failure, since platelet function is already inhibited in uraemia. This raises the concern that the aggressive inhibition of platelet function in acute coronary syndromes may increase the risk of bleeding complications in patients with renal failure. Careful studies of the effect of platelet inhibition with multiple drugs in patients with renal failure are warranted.

**Management of restenosis**

The long-term success of coronary stenting is limited by in-stent restenosis, which occurs in 20–30% of patients. This problem occurs within the first 6 months after stent implantation. In-stent restenosis is a specific inflammatory/proliferative response of the vascular wall to the trauma of angioplasty and stent implantation. The treatment of the exaggerated neointima formation within the stent that causes the restenosis has been frustrating. Repeat angioplasty within the stent is possible and requires transient aggressive platelet inhibition with aspirin and clopidogrel, as the repeat angioplasty causes de-endothelialization of the stent struts. However, the repeat angioplasty often results in a new proliferative response of the vessel wall with consequent rapid restenosis. Thus, the direct mechanical treatment of in-stent restenosis is often unsuccessful.

The treatment of restenosis by pharmacological means has been unsatisfactory, as the neointimal proliferation induced by the vessel injury is refractory to systemically administered drugs. Intracoronary radiation has therefore been used to eliminate neointimal proliferation. One such approach has been the use of radioactive stents [14]. Although the neointima proliferation is indeed reduced within such stents, there is considerable neointimal proliferation at the stent edges, regardless of whether they emit β- or γ-radiation (the so-called ‘candy wrapper’ phenomenon [15,16]). The problem of edge restenosis seriously limits the clinical usefulness of radioactive stents.

More recently, the management of in-stent restenosis with radioactivity has consisted of the temporary radiation of the stented vessel wall from an endoluminal radiation source. Both γ- and β-radiation are being used for the treatment of recurrent in-stent restenosis. This so-called brachytherapy can reduce the incidence of recurrent in-stent restenosis, but does not eliminate the problem. A recent study comparing the results of intracoronary radiation in 118 patients with CRF and 481 consecutive patients with normal renal function showed a restenosis rate in patients with renal failure and brachytherapy of 22.6% (compared with 53.8% in non-irradiated patients), which was similar to that found in patients without renal failure. However, because of the general morbidity of the patients with renal failure their mortality was significantly higher (7.6% compared with 1.9% in patients without CRF) [17].

Current brachytherapy protocols are designed for recurrent in-stent restenosis, i.e. after in-stent restenosis has already occurred. Recently, new coated stents eluting antiproliferative drugs have generated considerable excitement in that in-stent restenosis could be prevented altogether [18]. Rapamycin is one of the first antiproliferative agents and the one with the most published clinical data. Rapamycin was initially evaluated as an antibiotic, which turned out to be clinically unsuitable because of its antiproliferative and immunosuppressive actions. More recently, this drug has generated considerable interest precisely because of these properties [19]. Rapamycin exerts its cellular actions after binding to the FK506 binding protein, which is upregulated in the human stent-induced neointima [20]. Rapamycin-coated stents seem to eliminate the problem of neointimal proliferation after coronary stent implantation, at least up to a follow-up of 1 year [21]. These favourable initial results have been corroborated by a larger, multi-centre, double-blind RAVEL study [22] on 238 patients, the results of which were presented at this year’s European Heart Meeting: at repeat coronary angiography 6 months after stent implantation, the restenosis rate was 0% in patients treated with rapamycin-coated stents vs 26% in the control group receiving the same stent without the rapamycin-eluting coating. The results of the RAVEL study, which are currently available only in abstract form, are very encouraging indeed. It remains to be seen whether these impressive results pass the test of clinical routine application in unselected patients and if these benefits extend to patients with renal failure.
References