PERCUTANEOUS CORONARY REVASCULARISATION – THE CURRENT STATE OF THE ART

PA MacCarthy and W Wijns, Cardiovascular Center, OLV Ziekenhuis, Aalst, Belgium

Since their introduction by A Gruentzig in 1977, percutaneous coronary interventions (PCI) have undergone numerous technological advances and gained widespread clinical application. Following the availability of miniature and highly steerable guidewires, which have permitted access to virtually any patent branch of the epicardial coronary tree, the next decisive improvement resulted from the application of metallic endovascular stents (Figure I).

1. CONTEMPORARY RESULTS OF PCI

Stents are presently used in 60–80% of all PCI procedures. Stents are superior to balloons for several reasons: plaque fractures and arterial dissection caused by balloon angioplasty often result in what initially appears to be a successful procedure whilst in fact only limited luminal enlargement is obtained; the treated lesion shows greater stability after stenting, whereas abrupt vessel closure is not uncommon within 48 hours of balloon treatment (up to 15% of cases in the presence of severe residual dissection); the angiographic results that are obtained with stenting are predictable, irrespective of the complexity of the stenosis; and stent implantation results in fewer vessel re-occlusions and lower rates of clinical restenosis. Several randomised clinical trials (RCTs) support these statements, particularly the ‘Benestent’ series of RCTs, which represents the foundations of the practice of PCI, at least in Europe. For instance, Benestent II tested the hypothesis that use of the heparin-coated Palmaz-Schatz stent (plus systemic aspirin and ticlopidine) would result in a better event-free survival than standard balloon angioplasty. After stenting, 87.2% and 84.3% of patients were event-free at six and 12 months respectively, as opposed to 80.7% and 77.6% after balloon angioplasty. Despite allocation to balloon treatment, ‘bailout’ stenting was unavoidable in 13% of patients. The rates of stent thrombosis were as low as 0.2%. The best outcome (89.3% event-free rate at six months) was observed in patients randomised to clinical follow-up (in whom repeat angiography was only performed on clinical grounds). Other trials have shown that this benefit was maintained up to five years after the initial procedure.

The efficacy of PCI has greatly improved over the last few years due to a number of factors acting in synergy. Plain balloon angioplasty has yielded better results by adequate balloon sizing and conditional stenting in the face of inadequate angioplasty results (which are usually due to recoil or flow-limiting dissection). The stent implantation technique has improved by proper stent expansion and apposition, having taken into account and learned from intravascular ultrasound imaging. The safety of PCI has also benefited from major advances in adjuvant therapy, in particular the accompanying anticoagulation and antiplatelet regimens. Several RCTs (including CAPTUREI, EPLOG, EPISTENT, IMPACT II), have shown the added value of using Glycoprotein (GP) IIB/IIIa blockers during PCI. A pooled analysis by

![Image of angiograms](image)

**FIGURE 1**
Bifurcation stenosis in the mid-left anterior descending artery ((a) arrow), treated with the ‘Frontier™’ device, a stent specifically designed for bifurcation lesions, which is mounted on a balloon which allows access to the side branch with a second guide wire (b), giving a good final angiographic result (c).
Kereakes (Figure 2) showed an impressive reduction in the incidence of death/infection/urgent intervention at 30 days from 20.8% after placebo to 8.1% after the use of GP IIB/IIIa blockade. Although these potent antiplatelet drugs do not reduce angiographic restenosis per se, the peri-procedural benefit is maintained at six months.

The use of orally administered antiplatelet agents, in addition to aspirin, have also represented a significant advance. Early attempts to prevent stent thrombosis with aggressive anticoagulation were associated with a high haemorrhagic complication rate and were superseded by the implementation of oral antiplatelet agents to aspirin. The first of these drugs was ticlopidine, a thienopyridone adenosine diphosphatase-receptor antagonist, which was effective at preventing stent thrombosis but was associated with significant side-effects. A second-generation agent, clopidogrel, has been shown to be safer and at least as effective as ticlopidine. Moreover, recent RCTs have demonstrated a mortality reduction in patients with an acute coronary syndrome treated with clopidogrel, both in the setting of medical management and PCI.

Additional benefit has been derived from a more careful anticoagulation strategy using weight-based heparin dosage and intra-procedural monitoring of clotting times. Together with the systematic use of smaller size femoral sheaths, the excess of bleeding and vascular complications is now greatly reduced.

Another recent development is the increasingly frequent use of direct stenting, i.e. stent implantation without balloon pre-dilatation. Animal experiments suggest that direct stenting reduces endothelial and other vessel wall damage, and produces less neointimal proliferation. Protagonists of this approach claim that clinical restenosis rates (RR) below 10% will be achieved. Controlled data from several RCTs have not confirmed the superiority of direct stenting over stent implantation after prior balloon dilatation, except for the shorter procedural time, the reduced radiation exposure and the cost.

In practice, PCI can now be considered as the preferential mode of revascularisation in almost every lesion subset and patient condition, with four exceptions: diabetes, left main stem stenosis, multi-vessel disease and chronic total occlusion. Although a formal RCT evaluating the value of PCI in diabetics has not yet been performed, every analysis has shown that the outcome of diabetics was worse following PCI than after bypass surgery. Even in the most recent Arterial Revascularisation Therapy Study (ARTS) trial comparing PCI with surgery in patients with multi-vessel disease, the outcome of diabetics was poor in both treatment arms but even more so following PCI. For instance, mortality was 6.3% after PCI versus 3.1% after bypass surgery and the major adverse cardiac event (MACE) rate was 38.4% versus 13.5%, respectively. Until proven otherwise, PCI should therefore be used with a certain reservation in diabetics, particularly if more than one artery is involved. The same recommendation can be made for patients with left main stenosis and multivessel disease in whom the prognostic benefit of surgery has
been established for many years. Although several reports indicate the feasibility of PCI, surgery should remain the preferred approach, particularly in significant left main arterial stem stenosis (>60%) and multi-vessel disease to compound left ventricular function. Lastly, chronic total occlusions still represent the most frequent mode of failure of PCI. When the occlusion can be crossed with a guide-wire and the distal lumen is reached, satisfactory results are obtainable with stent implantation, as shown by several RCTs (SICCO, GISSOC, TOSCA), albeit at the expense of high RR ranging from 32–55%. However, in the majority of patients presenting with chronic total occlusion(s), the obstruction cannot be successfully crossed and bypass surgery remains the only alternative.

II. ADVANCES IN THE PREVENTION AND TREATMENT OF RESTENOSIS

From the early days of PCI until now, restenosis has been the Achilles' heel of PCI. Prior to the stent era, both mechanical and pharmacological approaches to the prevention of restenosis failed. This is because restenosis after balloon angioplasty (or other mechanical PCI procedures) is a complex process involving the onset of the healing process which results in neointimal proliferation as well as constrictive remodelling of the vessel due to contraction of newly formed scar tissue. Implantation of a cage of a metallic stent virtually eliminates vessel shrinkage and thereby significantly reduces restenosis. In patients with restenosis after balloon angioplasty, stenting lowers the restenosis rate from 32–18%, which is similar to the restenosis rate after primary stent implantation. Thus, restenosis after balloon angioplasty has now virtually disappeared and has been replaced by in-stent restenosis, which occurs less frequently but has proved to be a difficult management problem. In addition, a number of lesion subsets are associated with a higher restenosis rate even after stent implantation, in particular if there is involvement of small vessels (RR 30%), long arterial lesions (RR 32%), saphenous vein graft disease (RR 34%) and ostial lesions (RR 40%).

When present, in-stent restenosis can be difficult to treat because of recurrence rates ranging from 19–83% after any new intervention, whether this is a plain balloon angioplasty or a combined procedure involving plaque debulking. This is particularly the case when diffuse or proliferative in-stent restenosis is present. In-stent restenosis has been shown to be almost exclusively due to neo-intimal proliferation, and therefore adjuvant intracoronary irradiation (brachytherapy) has been successfully applied, initially with γ-radiation, and more recently with β-radiation.

In view of the excellent results obtained for the treatment of in-stent restenosis, the value of β-irradiation for the primary prevention of restenosis at the time of the initial balloon angioplasty or stent implantation was recently evaluated. At the dose of 18 Gy (at 1 mm tissue depth), very encouraging results were obtained with brachytherapy following plain balloon angioplasty since RR as low as 4.7% were obtained. Brachytherapy at the time of new stent implantation was plagued by unacceptably high rates of stent thrombosis and late vessel occlusion, presumably due to delayed re-endothelialisation. Prolonged antiplatelet treatment did not resolve this problem entirely and brachytherapy is no longer used for prevention of restenosis.

The next decisive advance in the clinical efficacy of PCI came with the introduction of drug-eluting stents. With the use of a sirolimus-eluting device, a durable result of PCI could be obtained at first attempt, as indicated by the two-year follow-up results of the First-in-Man registry and the one-year results of the RAVEL RCT. This has been confirmed in the recently presented SIRIUS study (Transcatheter Cardiovascular Therapeutics meeting, 2002) which involved more complex lesions in 1,058 patients and demonstrated a reduction in restenosis from 35.4% with standard stents to 3.2% in sirolimus-coated stents. Nearly equivalent results have been obtained using paclitaxel-eluting stents in two small RCTs (ELUTES, presented at the American Heart Association Scientific Sessions, 2001 and ASPECT, presented at Transcatheter Cardiovascular Therapeutics, 2001). Although these studies performed in selected patients have demonstrated that the concept of a ‘restenosis-free’ stent is viable, implementation in daily practice has been slow. The current price of a single device challenges even the most generous of healthcare budgets to an unprecedented extent. Use of the sirolimus device in less favourable patient subsets in the SIRIUS trial has revealed restenotic problems at the edges of the stent in nearly 10% of the patients. Further trials in specific patient/lesion subsets are underway or planned but results will not be available before 2004. At this stage, it is not known whether drug-eluting stents should be used in all patients nor whether all patients/lesions respond equally well to the same compound (‘one size fits all’). Due to financial considerations, however, interventional cardiologists may be restricted in their use of these ‘restenosis-free’ stents (at least for the foreseeable future) and will have to limit the implantation of such devices to high-risk cases.

III. INDICATIONS FOR PCI BY CLINICAL SUBSETS

The evidence supporting the use of PCI in various clinical syndromes is briefly reviewed, assuming that the culprit lesions are technically suited for dilatation and stenting.
IIIa. Acute Coronary Syndromes

Acute ST segment elevation myocardial infarction

A meta-analysis of all studies comparing direct PCI with thrombolytic treatment clearly indicates a reduced mortality and re-infarction rate following PCI, when PCI can be performed by experienced teams within six hours after onset of symptoms. This should be the preferred approach, particularly in high-risk patients, after failed thrombolysis or in the presence of cardiogenic shock. The main limitation remains the poor applicability of the invasive approach due to the restricted availability of the required technical facilities and human resources. Recent studies suggest that acute transfer of the patient to the nearest tertiary cardiac centre for primary PCI may confer mortality benefits over local administration of thrombolysis (DANAMI 2 and PRAGUE 2 trials, awaiting publication).

Reperfused infarction after thrombolysis

The DANAMI I RCT showed that PCI should be performed in the presence of spontaneous or inducible ischaemia following myocardial infarction initially treated with thrombolysis. The relative risk of death, re-infarction or unstable angina was 0.67 (confidence interval (CI) 0.56–0.80) in favour of the invasive approach. However, there is no evidence supporting the systematic use of angiography in all patients recovering from acute infarction, although this strategy is widely applied in some (but not all) Western countries. The recently presented GRACIA trial (European Society of Cardiology Congress, 2002) compared cardiac catheterisation and stenting within 24 hours of thrombolysis versus the ischaemia-guided approach to thrombolysed acute myocardial infarction with ST-segment elevation. This study showed a reduction in adverse cardiac events at 30 days in the interventional group, with a decreased hospital stay and no excess complications.

Unstable angina pectoris

The publication of the FRISC II RCT and the recent disclosure of the RITA 3 RCT have settled the long-standing controversy about the best approach to be used in patients with unstable angina (with ST-T changes on the ECG) or non-Q wave infarction (with abnormal CKMB or troponin T values): early conservative or early invasive management. Both studies clearly indicate benefit for the invasive approach, the relative risk of death and non-fatal infarction in FRISC II being 0.78 (CI 0.62–0.98) in favour of the early invasive strategy.

IIIb. Stable Coronary Artery Disease

The obvious goal of PCI in patients with stable coronary artery disease is to relieve angina, improve quality of life and abolish signs of inducible ischaemia. In patients with severe ischaemia, such as those included in the ACIP RCT (patients had both stress-inducible ischaemia and at least one episode of silent ischaemia on 48-hour Holter monitoring), revascularisation significantly reduced death and infarction rates at two-years follow-up when compared with medical treatment. However, in the vast majority of patients with stable angina, prognosis is excellent and unlikely to be improved by PCI. Instead, the AVERT trial in which patients were randomised to PCI or medical care, including high-dose atorvastatin (80 mg daily), strongly challenged the idea that every epicardial stenosis should be ‘fixed’. In fact, outcome was better in patients treated medically confirming the potentially powerful anti-ischaemic effect of statins. At 1-5 years, the incidence of any ischaemic event was 13.4% after atorvastatin versus 20.9% after PCI. This observation, along with others showing the additional benefit of ACE inhibitors in patients with known coronary disease undergoing revascularisation, has shifted the attention from the epicardial vasculature to a more physiological approach, which incorporates the microcirculatory compartment and its decisive impact on myocardial perfusion.

The limitations of the angiogram, a two-dimensional ‘lumenogram’ giving little physiological information, are now recognised. Coronary pressure measurements (from a micromanometer-tipped, intracoronary guidewire) and calculation of the fractional flow reserve can be used to guide PCI. This technique is now well established and a fractional flow reserve ‘cut-off value’ of 0.75 has been well validated as indicating a stenosis capable of causing myocardial ischaemia. When the fractional flow reserve is greater than 0.75, PCI confers no long-term benefit, either in terms of morbidity or mortality. The pressure wire is also a useful tool periprocedurally, when, for example, serial stenoses and diffusely diseased arteries can be interrogated to establish the most important point of flow limitation or the functional result of PCI can be assessed after stent deployment. Indeed, studies with the pressure wire have shown that there may be an important pressure drop along the course of a diffusely diseased but angiographically ‘normal’ coronary artery, emphasising the limitations of the coronary angiogram for assessing myocardial ischaemia.

Within this framework, it is critical to be able to assess functionality of stenoses and discern whether ischaemia is due to epicardial or microvascular disease, in order to identify which patients with stable angina should receive revascularisation, medical treatment or both. These are the challenging questions that non-invasive imaging techniques and invasive functional tests in particular should attempt to address.

IV. A GLIMPSE INTO THE FUTURE

Methods of imaging the coronary arteries are continually evolving and whilst the ultimate goal of accurate, high-resolution, non-invasive imaging of the epicardial circulation is some way off, there have been
many exciting recent developments. Contrast-enhanced electron beam CT is effective in quantifying coronary calcification and visualising proximal coronary arteries and saphenous vein grafts. High-resolution MRI scanning has also shown promise in this regard and this technique may have the ability to characterise the composition of atherosclerotic plaques.

The truly innovative techniques are those that do not merely give anatomical information, but indicate pathophysiology and the risk of future coronary events. The plaque rupture which underlies acute coronary syndromes and myocardial infarction often occurs at a site in the coronary tree where there is only a minor angiographic stenosis, and one of the major challenges to interventional cardiology is the accurate identification of the plaque which is vulnerable to such a process. Techniques such as intravascular ultrasound and angioscopy characterise certain features which indicate that a plaque is more liable to rupture, such as a 'yellow' appearance or the presence of a lipid-rich core or a thin cap. Recent studies have shown that an inflammatory process underlies coronary atherosclerosis; and this is also the case with remodelling and plaque rupture. Accordingly, the temperature of the vessel wall has been used as a marker of inflammation and 'thermography' catheters have been developed which are capable of detecting small changes in temperature along the length of an epicardial vessel. Consistent with increased inflammation and plaque rupture, a heterogeneity in vessel temperature recorded in this way is greater in patients presenting with acute coronary syndromes.

However, the inflammation associated with active (i.e. vulnerable) coronary artery disease appears to be a systemic and generalised process with all coronary arteries equally affected and thus vulnerable plaques may be found at multiple sites throughout the coronary tree. This raises the challenging question of how these lesions should be treated when identified. Although the answer is likely to be largely via a systemic, pharmacological approach (with statins and similar 'plaque-stabilising' agents), focal plaque sealing with interventional, intracoronary techniques has been advocated as a prophylactic measure. This may be more feasible in the era of drug-eluting stents when in-stent restenosis is less of a factor in the risk–benefit equation.

There is no doubt that such 'restenosis-free' stents will dramatically change interventional cardiology practice, not only by altering the threshold at which stents are used, but also expanding the use of PCI into areas such as prophylaxis and other patients with complex coronary arterial anatomy currently reserved for surgical intervention. With these challenges and the prospect of vulnerable plaques being accurately identified and safely treated with minimal restenosis, we can look with great optimism to a beneficial future of interventional cardiology.

ACKNOWLEDGEMENTS
Dr MacCarthy is the recipient of a British Heart Foundation Advanced Training Scholarship.


REFERENCES

13 Kereiakes D. Preferential benefit of platelet glycoprotein IIb/IIIa receptor blockade: specific considerations by device and state. Am J Cardiol 1998; 81:49E–54E.


