likely to help mobilize the considerable investment required from both governments and private industry. Indeed, given the level of investment required to develop gene therapy protocols, it is perhaps clinical problems of this prevalence which will attract the necessary backing and be among the first to reach the desired objective. Second, the target tissue most often in question (the arterial wall) is relatively easily accessible with current technology (using balloon catheter or stent) allowing direct local targeting of DNA. The review by Lafont et al. concludes that, in spite of its apparent straightforward nature, implementation of gene therapy will require a coordinated development of technologies and interaction of many disciplines in medical and basic science. I would echo this sentiment. We should also exercise caution and not over-sell gene therapy (particularly to the public at large) at this early stage. These are exciting times but it will take a considerable effort before gene therapy makes any real impact in the clinic.

References


Is anticoagulation for intracoronary stenting justified?

See page 1373 for the article to which this Editorial refers

It is now 10 years since the first coronary stents were implanted to treat abrupt closure and restenosis after balloon angioplasty. But the rapid discovery of stent thrombosis in 18% of patients in the early series led to aggressive anticoagulation with coumadins. When this failed to eliminate the problem, heparin, low molecular weight dextran, aspirin, dipyridamole and even thrombolytic agents were added in increasing and somewhat desperate attempts to improve the situation.

The significant reductions in restenosis with the use of Palmaz-Schatz stents in the Benestent and Stress trials (relative reduction of 33% and 25% respectively) were remarkable since a world-wide research effort to reduce restenosis had until then produced entirely negative results. Stents were relatively easy to use and produced attractive and reliable angiographic results, so the trials led to increased intracoronary stenting despite the attendant problems. The anticoagulant regimens used in both these trials had reduced the rate of subacute thrombosis — in the hands of the experienced operators involved — to 3.5% but the vascular and bleeding complications were unacceptably high (13.5%) and very costly in terms of morbidity, staff time and length of hospital stay (7-8 days).

It took a remarkable leap of faith to challenge the accepted wisdom of anticoagulation but, employing intravascular ultrasound and balloons inflated to high pressures to deploy the stents, Antonio Colombo reported thrombosis rates of 1.6% and vascular complications of only 0.6% without anticoagulation in patients treated with the antiplatelet agents ticlopidine and aspirin, or aspirin alone. More recently, a multicentre French registry reported a subacute thrombosis rate of 1.2% in unselected patients treated with ticlopidine, aspirin and low molecular weight heparin for one month, using high pressure balloon inflation to deploy the stents but without ultrasound guidance. Preliminary results of the MUST trial (stenting without intravascular ultrasound control) and MUSIC trial (with intravascular ultrasound) also indicate low rates of thrombosis without routine anticoagulation.

In the current issue, Lablanche and co-workers report the results of a prospective, observational study of 529 patients stented predominantly

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with Palmaz–Schatz or Wiktor stents who were managed with ticlopidine 500 mg and aspirin 200 mg daily but given no anticoagulation after the sheaths were removed. Overall, the stent thrombosis rate was 2.3% and serious bleeding complications occurred in 2.1%. The incidence of both bleeding and thrombosis was strongly related to the indication for stenting: 5.4% of the patients stented as a bailout procedure had events thought to be related to stent thrombosis and the same number had bleeding complications; none of the patients stented electively, who were equivalent to the patients in the Benestent trial, had complications. A recent similar trial of antiplatelet therapy following successful implantation of Gianturco–Roubin stents in 216 patients reported 0.9% stent thrombosis and 3.8% vascular and bleeding complications, although this trial excluded from study patients with suboptimal final angiographic results[8]. It is particularly noteworthy that in this latter series 57% of the vessels stented were between 2.0 and 3.0 mm in diameter.

These observational studies, suggesting that antiplatelet therapy is at least as effective and considerably safer than anticoagulation, are supported by the randomized study recently reported from Schomig et al[9] who compared conventional therapy using intravenous heparin, phenprocumon and aspirin with ticlopidine and aspirin alone in a randomized trial of 517 patients stented both electively and for bailout. Only two patients (0.8%) of the antiplatelet group had occlusion of the stented vessel compared to 14 (5.4%) of the anticoagulated group; both occlusions with antiplatelet agents were thought to be due to dissection while all but one in the anticoagulant group were considered thrombotic. Haemorrhagic complications were confined to the anticoagulant group (6.5%).

So, is anticoagulation after intracoronary stenting needed at all? In the French registry the use of low molecular weight heparin was progressively decreased in four phases and finally omitted altogether; with each phase the vascular complications fell but there was no significant increase in the rate of stent thrombosis. The pilot study of Benestent II using heparin-coated Palmaz–Schatz stents reported no stent thrombosis and a progressive reduction in bleeding complications from 7.9% in phase I, where patients were treated early with heparin and coumadin, to 0% in phase IV where ticlopidine and aspirin were used alone[10]. And in the current paper by Lablanche et al.[7] patients who had sheath removal delayed overnight and were given additional heparin had significantly more peripheral complications (P<0.001) than those in whom the sheaths were pulled the same day.

From all the available data, it must be concluded that routine use of anticoagulation is not justified to prevent stent thrombosis and is a potent cause of vascular and bleeding complications. In certain circumstances, such as low cardiac output, reduced coronary flow or residual dissection after stenting, many operators may still suggest anticoagulation for a limited period but there is no evidence that such a strategy reduces the risk/benefit ratio in any of these cases.

What will be the impact of these changes in technique and post-implant therapy? Firstly, the low incidence of stent thrombosis and the fact that it tends to present earlier than was seen with anticoagulants is leading to a marked reduction in the length of hospital stay. Only one stent thrombosis occurred after 48 h in the trial by Lablanche et al.[7] and there was a progressive reduction in the length of stay from 6.2 to 4.2 days. Twenty-two percent of patients in the trial with Gianturco–Roubin stents were discharged from hospital the day after the procedure and the average stay was only 2.5 days post stenting[8]. It is already routine practice in many centres to discharge uncomplicated stent patients with good angiographic results the day after the procedure; same-day discharge for these patients may well be feasible. The lack of groin and other bleeding complications reduces staffing requirements and follow-up is cheaper and easier without the need to monitor anticoagulation. These factors should help to reduce procedural costs.

But, the reduction in complications and high success rate has made operators more comfortable with stenting both electively and for suboptimal results and there has been a dramatic increase in the rate of stenting. Lablanche et al. in this issue found a progressive increase from 4% to 25% of angioplasties performed as the trial progressed and rates above 50% are seen in some institutions in routine practice. Since stents are currently extremely expensive, this may negate the savings in procedural costs unless the use of stents is targeted to those patients who are most at risk. The final cost-benefit analysis will depend on the long-term clinical outcome and the need for reintervention in the new stenting era.

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References

This condition is closely associated with silent astole which may amplify any ischaemic event. Myocardial perfusion time due to shortened diastole decreases myocardial oxygen demand and reduces demonstration of the autonomic system with myocardial sympathetic dysregulation and may therefore involve loss of sensor function. Exercise testing is also more frequent among diabetics in addition to loss of vagal reflexes. As a result, diabetic patients with coronary heart disease are more prone to develop myocardial heart failure, and the propensity for atherosclerotic disease. Patients with insulin-resistant non-insulin dependent diabetes mellitus (NIDDM) have a strong degree of coronary vascular involvement more extensive in diabetics than non-diabetics with more widespread and peripheral location, which is reflected in the frequent occurrence of small and silent infarcts. The Framingham study observed 39% silent infarcts among diabetics compared to 22% among non-diabetics. Silent ischaemia during exercise testing is also more frequent among diabetics and may therefore involve loss of sensor function. Diabetic patients with coronary heart disease demonstrate marked dysfunction of the autonomic system with myocardial sympathetic dysregulation in addition to loss of vagal reflexes. As a result, resting heart rate is increased with loss of diurnal variation in heart rate. Elevation of heart rate increases myocardial oxygen demand and reduces myocardial perfusion time due to shortened diastole which may amplify any ischaemic event. This condition is closely associated with silent ischaemia, increased risk of myocardial infarction and cardiovascular death, especially sudden death.

Hyperglycaemia may increase the risk of coronary heart disease as a result of dyslipoproteinemia, increased oxidative stress, non-enzymatic glycosylation and endothelial dysfunction, and by causing a prothrombotic state. In addition microvascular complications develop in many patients with insulin-dependent diabetes (IDDM) which is independent of the occurrence of coronary heart disease. Patients with insulin-resistant non-insulin dependent diabetes mellitus (NIDDM) have a strong propensity for atherosclerotic disease.

**Long-term treatment**

Beta-blocker treatment can be used to reduce the resting heart rate in diabetic patients with autonomic dysfunction, and several clinical trials have demonstrated their marked effect on the risk of cardiovascular death after myocardial infarction. In long-term studies, mortality is reduced by 33% in non-diabetic patients treated with beta-blockers compared to 48% in similarly treated patients with diabetes. Risk reduction appears proportional to heart rate reduction. However, the risk of prolonged hypoglycaemia and masking of symptoms in diabetic patients treated with beta-blockers is real, but its occurrence is rare and beta-blocker treatment should not be withheld because of the possibility of hypoglycaemia.