Stent coatings and local drug delivery

State of the art

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Why we need coatings and drugs

The new enemy of percutaneous intervention is in-stent restenosis. He joins the old enemy, restenosis after balloon angioplasty, who, after 21 years of resistance, refuses to capitulate. Unlike restenosis after balloon angioplasty, in-stent restenosis is a consequence almost entirely of tissue hyperplasia, occurring principally around the points where the stent struts impinge upon the artery wall[1]. Less common, but troublesome when it occurs, is subacute thrombosis, a complication not quite eliminated by modern stent deployment techniques and anti-platelet agents. These two factors are particularly limiting in diffuse disease, small vessels and arteries with poor run-off. Stenting, therefore, presents both the need and the opportunity for local drug delivery. Whilst the struts may create the problem, they may also present the solution, by carrying a coating or drug targeted at the thrombotic or hyperplastic responses occurring locally.

Methods of drug delivery

How may drugs be delivered in the context of stent implantation? There are three basic routes. First, drug may be absorbed into a suitable stent material itself, which is intended to act rather like a sponge. Release of the drug is dependent upon diffusion down a concentration gradient, or upon biodegradation of the stent material. Second, drug may be chemically bonded onto the surface of the stent struts and released after further chemical or biological action of the surrounding milieu or tissue. A coating on the stent may, of course, be regarded as a drug (in the loosest sense); albeit one which is intended to remain attached to the stent and confer desirable properties of haemocompatibility or biocompatibility (‘presentation’ of drug on a coating). A combination of this and the last approach may be attempted with a coating, for example a polymer with the necessary tertiary structure, which may be used as a depot for a drug to be held and released, the characteristics of uptake and release being controllable by the composition of the coating (‘elution’ of drug from a coating. Third, stent implantation and drug delivery can be treated as separate procedures. A dedicated local drug delivery catheter may be deployed to deliver drug intramurally, either before or after stent placement. This is termed adjuvant local drug delivery. The three methods may be combined. In this review, we will sub-divide stent-related local drug delivery into these three categories.

Drug delivery, not brachytherapy

It is appropriate to recall that therapeutic modalities other than drugs and coatings, for example local radiotherapy, may be applicable to stenting. Local radiotherapy is undergoing clinical trials at present, using the approach of either implanting a stent incorporating a suitable isotope with a short radioactive half-life into the stent struts, or treatment of the lesion site with a dose of radioactivity from a temporarily placed endoluminal wire. Both β and γ emitters are being studied, and at the time of writing it is unclear which is superior. It is also the case that, however remarkable the reduction in neointimal growth after such treatment in animal models, there remain doubts about both the long-term efficacy and safety of endoluminal radiotherapy. Discussion of this large topic is beyond the scope of this paper.

Development of drug delivery systems

Local drug delivery in association with stenting is currently active at three stages of development. First are the
coatings and drugs which are sufficiently advanced to be the subject of clinical trials. These include surface-presentation of agents such as heparin, selected polymeric and inorganic coatings and adjunctive local delivery, via ‘leaky’ balloon, of anti-proliferative agents such as antisense oligonucleotide to the transcription factor c-myc. Second, more numerous and innovative but less proven in efficacy, are the coatings and drugs which are the subject of animal studies. There are, currently, dozens of these. Third, and highly novel and speculative, are the concepts which are still at the stage of laboratory bench testing, many of which will never achieve success in the clinical arena. Development of viable local drug delivery systems in the context of stenting requires the development of two (or even three) technologies together: stent design and manufacture, coating technology and drug pharmacology. Expertise in these areas has, heretofore, traditionally been concentrated in separate companies. Yet the regulatory bodies demand that a device with a drug constitute a combined therapeutic ‘entity’. This is difficult for both the regulatory body and the companies. To stay at the cutting edge in a competitive market, either mergers or deals must take place between organizations with the relevant experience and the regulatory bodies must provide a streamlined path for overseeing safety in a fast-moving field.

**Polymer stents**

Questions of stent strength, effect on flow and efficiency and duration of delivery wholly from non-metallic substances have been addressed using in vitro flow models of various kinds. Stents entirely constructed from Type I collagen in a compliant, self-expanding form revealed insignificant resistance to flow in vitro[16], but in vivo studies warned of a severe tissue reaction with some polymers. A polyethylene terephthalate braided-mesh stent produced an inflammatory reaction, although the polypolymers. A polyethylene terephthalate led to frequent thrombosis and early report of its use in such a group suggests that it is safe and feasible[17,18]. Its bulky profile but less proven in efficacy, are the coatings and drugs which are the subject of animal studies. There are, currently, dozens of these. Third, and highly novel and speculative, are the concepts which are still at the stage of laboratory bench testing, many of which will never achieve success in the clinical arena. Development of viable local drug delivery systems in the context of stenting requires the development of two (or even three) technologies together: stent design and manufacture, coating technology and drug pharmacology. Expertise in these areas has, heretofore, traditionally been concentrated in separate companies. Yet the regulatory bodies demand that a device with a drug constitute a combined therapeutic ‘entity’. This is difficult for both the regulatory body and the companies. To stay at the cutting edge in a competitive market, either mergers or deals must take place between organizations with the relevant experience and the regulatory bodies must provide a streamlined path for overseeing safety in a fast-moving field.

**Polymer-coated stents**

Polylactic acid, polycaprolactone and ethylvinylacetate, when presented on a metal backbone, stimulate the growth of an unacceptably thick neointima in porcine coronary arteries[14]. Yet it appears that not all polymers are detrimental. Polyorganophosphazene coating led to an average 81% arterial stenosis compared with 32% for polyurethane and 39% for bare metal[17]. Polyurethane-coated nitinol stents exhibited no excess reaction over uncoated stents in rabbit carotid arteries[18], and polytetrafluoroethylene was associated with a reduction in neointima[19]. More recently, biological mimicry has been introduced into the design of synthetic polymers, with interesting results. An example of this novel approach is phosphorylcholine. Phosphorylcholine is a Zwitterionic (neutral, but with balanced charges), hydrophilic phospholipid and a normal constituent of the cell membrane. Manufacture of clinically useful, stable phosphorylcholine is by mixture of it with methacrylate, triggering a thermal reaction in which the co-polymer methacrylo-phosphorylcholine-lauryl-methacrylate is produced. Phosphorylcholine polymer may then be physically adsorbed onto stent steel and exposed to γ radiation which both cross-links the polymer and sterilizes the stent. The average thickness of phosphorylcholine polymer on a stent is 50 nm and its weight 20 μg. Elastic and friction studies show that phosphorylcholine adheres well, even after balloon expansion of a stent. In vivo baboon and porcine studies have demonstrated its safety, thrombo-resistance and long-term biological neutrality[10–13]. The vascular response reaction to implanting uncoated and phosphorylcholine-coated stainless steel, balloon-expandable stents of up-to-date design in the porcine coronary artery at modest oversize showed minimal and equal neointima formation in both groups[14]. The cross-linking process allows the phosphorylcholine to contain domains where drugs can bind; a fertile area for future research. It can also be applied in single or multiple layers. Phosphorylcholine has been applied to the BiodivYsio stent (Biocompatibles). In the BiodivYsio registry, with open inclusion criteria, 270 unselected patients had a 30 day rate of major adverse cardiac events of 4.4%. The equivalent value for the heparin-coated Palmaz-Schatz stent (Codis) in Benestent-II was 3.9%[15–16].

**Membrane-covered stents**

A complete polymer membrane has been applied as a sandwich between two Jostents (JoMed). This system is designed for repair of vessel rupture and coverage of thrombotic and degenerate plaques in old aortic-coronary vein grafts, aneurysms and arterio-venous malformations. Early reports of its use in such a group suggest that it is safe and feasible[17,19]. Its bulky profile and relative stiffness are constraints to widespread use, however, though the concept of complete plaque coverage is intriguing.

**Drug-eluting stents (Fig. 1)**

The aggressive inflammatory reaction seen with stents manufactured wholly from non-metallic (organic) substances has resulted, understandably, in few studies using this technique as a platform for local drug delivery. One of the very few studies was in the field of gene therapy. Polylactic acid/polycaprolactone tubes soaked in a solution of recombinant adenovirus and implanted into rabbit carotid arteries produced transgene
expression in the media and adventitia at day 5[19]. Paclitaxel- and hirudin-coated biodegradable stents, when placed in a culture of smooth muscle cells obtained from human coronary atherosclerotic plaque, produced severe destruction of cytoskeletal components of the cells, suggesting a possible strategy for in vivo use, assuming the problems of inflammation and radial strength can be overcome[20].

**Drug-presenting stent coatings**

The most elegant, simplest and, probably, cheapest option for local drug delivery in the context of stent implantation is the use of a drug-presenting or eluting coating on a metal stent. Much experience has now been gained with heparin, with its anti-thrombin and, at least in vitro, anti-proliferative effects.

The Benestent-II pilot study and randomized trial used the Palmaz-Schatz (Cordis) stent with Carmeda (multiple layers of polyamine and dextran sulphate) surface-covalently-end-bonded heparin. In the final 50 patients in the pilot study (who received no systemic heparin after the implantation), 92% patients were event-free (compared with 80% in the Benestent-I stent group), with 0% bleeding (compared with 13% in Benestent-I)[21]. Final results from the trial (n=827 randomized) revealed a clinical event rate of 13% at 6 months compared with 19% in the PTCA group, and a reduction in restenosis (defined as >50% stenosis) from 31% to 16% in the stent group (P<0.001)[16]. Other, far smaller trials, yield supportive data for the use of heparin coatings[22]. In one series of heparin-coated Wiktor (Medtronic) stents, the clinical event rate was 2/100 patients at 30 days[23].

The 1/621 sub-acute thrombosis rate in Benestent-II stimulated a trial of heparin-coated Palmaz-Schatz stents in acute myocardial infarction. In the pilot series, procedural success was 97% without lytic therapy or significant use of GPIIb/IIIa inhibitors, with major adverse cardiac events in 2/101 patients[24]. These are unquestionably excellent results. But it should be noted that Benestent-II-type trials primarily compare modern stenting methods (achievement of a large lumen with thorough stent deployment plus a Carmeda coating) with PTCA in a highly selected group of patients, rather than comparing coated and non-coated stents.

Furthermore, the heparin in these studies may be regarded as a stent ‘coating’ rather than a local drug delivery system designed to elute.

Other heparin-containing coatings have been studied. A reduction in indices of thrombus formation (labelled fibrinogen and platelets and clot weight), but not neointima, was found with Palmaz–Schatz stents coated with Duraflo II (heparin on a hydrophobic binding agent)[25]. Acute benefit without reduction in late neointima has been a consistent finding with heparin coating of various kinds[26–30]. An exception to this rule has been bonded heparin on the Cordis stent in the baboon carotid artery, where neointima was reduced at 30 days[31].

**Drug-eluting coatings (Fig. 2)**

More potent anti-thrombotic agents alone, and combined with anti-platelet agents, have been examined. A polyactic acid coating containing hirudin and prostacyclin demonstrated freedom from thrombus in a human stasis model[32]. The potential for elution of drug, when maintenance of local levels was the aim, has been a concern. Hirudin and iloprost (a stable prostacyclin analogue) on a polyactic acid-polyethylene glycol coating, in flowing human plasma, retained an anti-thrombotic effect for more than 30 days[33]. When Palmaz–Schatz stents with this coating were implanted in sheep coronary arteries, neointima was reduced by 30% compared with uncoated stents (P<0.05)[34].

The use in stent coatings of local GPIIb/IIIa inhibitors, a class of drug already shown to be valuable when given systematically, tests the hypothesis that blocking the receptors on platelets adherent at the site of injury may be sufficient for a local effect, whilst avoiding bleeding complications. Cross-reaction with the avfβ3 integrin receptor may also have a beneficial effect on cell proliferation and restenosis. Retention of such an agent is possible; 48% of a dose of the 7a3 antibody to IIb/IIIa was held in a polymer coating on stent wires in a flow model for 8 days[35]. It may be retained on the stent despite sterilization and storage[36] and is capable of reducing platelet deposition on the stent[37]. In a parallel model, urokinase and the IIb/IIIa antagonist AZ1 retained 19 and 38% activities at 10 days, respectively[38]. A composite stent containing IIb/IIIa inhibitor reduced platelet adhesion in dog coronary arteries by 65% at 2 h (P=0.01)[39]. A similar study, with the antibody absorbed into a polymer coating on stents implanted in rabbit iliac arteries, demonstrated 0/10 vessels occluded at 28 days in the antibody group compared with 3/5 animals in the base polymer group and 3/5 in a group treated with an unrelated antibody. There was a non-significant trend towards reduction of in-stent restenosis in the antibody-treated group[40]. When conjugated with urokinase, an enhanced local anti-platelet effect was observed, with less cyclic flow variation than in control stents[41].

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Angiopeptin, a synthetic octapeptide and analogue of somatostatin, has been shown to reduce the tissue response to growth hormone, insulin-like growth factor and interleukin-1-mediated endothelial cell adhesion. Encouraging results from systemic delivery have been reported in terms of reduced clinical events after PTCA in clinical trials\[42,43\] and in terms of neointimal growth in a porcine coronary artery stent model\[44\]. Wiktor stents which had been coated with the biodegradable polymer poly-organophosphazene, were loaded with angiopeptin and implanted in porcine coronary arteries. Angiopeptin was retained for a clinically useful period, and the minimum lumen diameter was increased by 40% and morphometric lumen area by 132% \(P<0.01\)\[45\]. Our group has shown that angiopeptin may be absorbed into the phosphorylcholine coating of a BiodivYsio (Biocompatibles) stent, with 43% of the administered dose retained in the stent or the adjacent tissue at one week\[46\]. Angiopeptin has also been given by adjuvant local delivery (see below).

It is apparent from both necropsy specimens and animal studies that the early period after arterial balloon injury is dominated by both thrombotic and inflammatory processes. Steroids, given locally, might, therefore, be expected to have a beneficial effect upon the vascular reaction to stenting. Steroids in stent-based local drug delivery have, however, shown somewhat mixed results in animal studies. A polylactic acid matrix loaded with dexamethasone has been applied to Wiktor stents implanted in pig coronary arteries. The local concentration was \(3 \times 10^5\) higher than in the serum at 24 h, and \(3 \times 10^5\) higher at 28 days. Despite this, there was no significant reduction in neointima at 28 days\[47\]. Methylprednisolone in an organophosphazene matrix on a metal stent in porcine coronary arteries did show a 22% reduction in area stenosis \(P=0.002\), but this may have been because this polymer, without the steroid, induces a severe histiolympocytic and fibrocellular reaction\[48\].

Other agents have been studied in animals. The tyrosine kinase inhibitor ST638 has been absorbed into a PLA stent and implanted into porcine coronary arteries. Minimum lumen diameter was increased by 46% compared with control \(P<0.01\)\[49\]. The microtubule-stabilizing agent paclitaxel (Taxol), already used in cancer chemotherapy, was applied to a chondroitin sulphate and gelatin biodegradable polymer and coated on the Gianturco-Roubin II stent (Cook). When implanted in pig coronary arteries, it produced a 40% reduction in neointimal thickness \(P<0.05\); whereas, in the same study, dexamethasone, dexamethasone with heparin and angiopeptin failed to produce such an effect\[50\]. A similar study in rabbit iliac arteries also showed a significant reduction in neointima\[51\]. A polynitrosated albumen NO donor, dip-coated onto Palmaz–Schatz stents, reduced platelet adhesion by a factor of 4·5, and increased the lumen area by 37% in pig carotid arteries at 7 days\[52\]. Activated protein C, a potent endogenous anti-thrombotic agent, was applied to stent wires in vitro, and resulted in a significant reduction in fibrin deposition\[53\].

**Adjuvant local drug delivery (Fig. 3)**

In the field of adjuvant local drug delivery, early experimental work preceded the technological development of endoluminal delivery catheters. Seminal work showed that heparin released from perivascular ethylene-vinyl acetate copolymer placed around denuded rabbit iliac arteries, into which stainless steel stents had been implanted, was associated with a sub-acute thrombosis rate of 0/9 vessels compared with 3/10 controls \(P<0.05\). There was also a 40% reduction in neointima area compared with controls\[54\]. Since then, experience has been accumulating with ‘weeping’ balloon devices. These are capable of delivering volumes of drug many orders of magnitude greater than that contained within a stent coating. The HIPS trial used an infusion of 5000U heparin via either guide catheter or InfusaSleeve (LocalMed) prior to implantation of a Palmaz–Schatz stent, with clinical, angiographic and intravascular ultrasound end-point reductions. No reduction in in-stent neointimal volume was seen; but useful safety data was obtained\[55\]. Bartorelli and colleagues also found no reduction in late lumen loss in 35 patients who received 2·4000U heparin via the InfusaSleeve catheter after pre-dilatation but before stent placement\[56\].

Low molecular weight heparin has also been studied. When delivered locally via an iontophoretic catheter prior to oversize stenting in porcine coronary arteries, low molecular weight heparin produced no injury or...
change in neointimal thickness additional to that seen after stent implantation alone\textsuperscript{[57]}. The POLONIA study randomized 100 patients to 10,000 units heparin i.v. or 2500 units heparin i.v. plus 10 mg enoxaparin delivered to the lesion through a Transport (Boston Scientific) catheter during lesion pre-dilatation. Early reports suggest a significant reduction in neointima formation in the locally-treated group at 6 months in the first 64 patients studied\textsuperscript{[58]}. Methylprednisolone (60 ± 23 mg) was delivered via the Infiltrator (intra-mural micro-injector catheter, Interventional Technologies) prior to stenting in 36 lesions. Major procedural events dominated the results of this trial. The catheter failed to cross the lesion in 10% and there was non-Q wave myocardial infarction in 8%, sub-acute thrombosis in 3% and restenosis in 40%\textsuperscript{[59]}.

These relatively poor results, however, may relate more to imperfections of the drug delivery system employed than the drug delivered.

The ITALICS study built on the efficacy of antisense oligonucleotide to the proto-oncogene c-myc in animal models of restenosis after PTCA. The agent was given via the Transport (Boston Scientific) catheter after successful Wallstent ( Schneider) placement in 80 patients. The primary end-point was neointima volume assessed by intravascular ultrasound at 6 months. This was potentially a landmark trial; the first in which genetic material was applied to modify a disease state in the coronary arteries. Local delivery would seem to be particularly suited to the requirements of a trial such as this. Nevertheless, the results were negative, with no significant difference between the control and antisense groups in any parameter\textsuperscript{[60]}. This has stimulated lively debate as to whether the drug lacks efficacy, whether the mode of delivery (with all the attendant variables such as dose, volume, timing—before or after stent placement—efficiency, retention, washout, degradation etc.) was imperfect or whether the study design, with a control group without fluid delivery, masked a positive biological effect of the antisense. Perhaps the cardinal problem in the design of this study was the use of the Wallstent, which is capable of maintaining chronic stretch in the artery weeks after deployment (and, therefore, weeks after local drug delivery).

Other promising agents studied in the context of adjuvant drug delivery include angiopoietin. In an outstanding study, when delivered via the Dispatch catheter, systematically or by both routes, to the site of implantation of Palmaz–Schatz stents in pig coronary arteries, a significant reduction in neointima formation compared with control was observed in all three treatment arms\textsuperscript{[61]}. Another chemotherapeutic agent studied in a similar porcine coronary artery model is paclitaxel. When delivered via the Infusasleeve in the context of stent placement, no significant reduction in in-stent neointima was found\textsuperscript{[62]}. An elegant approach is to passivate the stented endoluminal surface by accelerating endothelialization. Naked plasmid DNA encoding for vascular endothelial growth factor was delivered via a hydrogel polymer-coated balloon after implanting Palmaz–Schatz stents in intimally denuded rabbit iliac arteries. At 7 days there was 87% endothelial coverage in the treated stents compared with 33% in the controls (P<0.005), and a 54% reduction in intimal area at 28 days (P<0.0001)\textsuperscript{[63]}. Entire cells may also be ‘sodded’ onto stented vessels. Endothelial cells have been infused via the Dispatch catheter into the site of Palmaz–Schatz stent implantation in rabbit iliac and pig coronary arteries, with 82% endothelial coverage at 4 h (compared with 0% in controls); although both groups showed >90% coverage at day 14\textsuperscript{[64]}. The very success of this type of experiment raise the question as to the validity of stent polymer coatings; by enhancing biocompatibility, do they delay endothelialization and, in the end, do more harm than good? Preliminary data from the phosphorylcholine-coated BiodivYsio stent (Biocompatibles) in the porcine coronary artery suggests that there is no delay in re-endothelialization\textsuperscript{[65]}.

As for the best timing of adjuvant delivery, there are a number of issues to consider. Delivery could be before or during pre-dilatation (as performed, for example, in the POLONIA and HIPS trials). The delivery catheter in these cases is probably tight against the lesion, but possibly lacking in apposition elsewhere, with the potential for excess drug loss downstream. Delivery after pre-dilatation may take advantage of increased uptake in areas of mural damage. The balloon/artery ratio would, however, be speculative, with more potential for downstream losses. Delivery after stent deployment (as used, for example, in the ITALICS trial) would minimize the variance in the device-artery ratio, but the risk would be of spoiling an otherwise good stent implantation, because there are indications that fluid delivery per se can exacerbate neointima formation\textsuperscript{[66]}. Autologous vein and other 'natural' coatings

A completely different approach has been to apply an autologous vein graft to stents. When implanted in porcine iliac arteries, vein-covered Palmaz–Schatz stents exhibited no thrombus and complete endothelial coverage. Mild atrophy of the media was also noted\textsuperscript{[67]}. Whilst requiring time and skill to prepare, this technique has been used in 35 patients with complete procedural success and no cases of sub-acute thrombosis\textsuperscript{[68]}. In the porcine coronary artery, neointima was reduced with this approach\textsuperscript{[69]}. The Athens group, with the greatest experience of this technique, reported that 89% of a selected population treated with this technique were event free at two years\textsuperscript{[70]}. In a retrospective, comparative study, they described a reduction in late loss of lumen diameter in a vein-covered stent group (n=55) compared with a conventionally stented group\textsuperscript{[71]}. There is a report, however, of increased late loss with this technique\textsuperscript{[72]}. The potential advantages of this approach may lie in reducing vascular injury\textsuperscript{[73]} or of isolating the damaged vessel wall from the blood. Fibrin coating may
also reduce thrombus formation. A fibrin-covered sleeve has been applied to metal stents and implanted in porcine coronary arteries. Three out of 31 of these were occluded by 28 days compared with 12/12 polyurethane controls[74]. A fibrin covering on tantalum stents in pig coronary arteries, shown to degrade over months, showed no excess vascular reaction[75]. When fibrin was loaded with RGD peptide (an inhibitor of platelet-fibrinogen interaction) on a novel stent in the athero-sclerotic rabbit, neointima was reduced by 79% [76].

**Inorganic coatings**

Inorganic strategies may also have potential. Silicon carbide has been investigated for its ability to alter the electro-chemical properties of the stent surface. It has been suggested that the initiation of thrombosis is at least partly due to degeneration of blood proteins by electron transfer to the metal. The ideal surface, from this point of view, is a semi-conductor such as silicon carbide. But, being brittle, silicon carbide can only be applied as a thin layer. Systematic testing of the effect of the silicon-carbide coated Tensum (Biotronik) stent upon cytotoxicity, haemolysis, mutagenicity and haemocompatibility produced favourable results when compared with Palmaz-Schatz (Cordis) and HepaMed (heparin) coated Wiktor (Medtronic) stents[77]. Tantalum stents, coated in the compound, were deployed in rabbit iliac arteries. Complete endothelialization with minimal intimal proliferation was observed[78]. Placement of eight silicon carbide-coated Palmaz-Schatz stents into patients suffering from abrupt closure post-PTCA showed, at coronary angiography the next day, patency of all the stents with no visible thrombus[79]. A series of 165 patients with 215 stents has now been published using the Tensum (Biotronik) tantalum, balloon expandable, silicon carbide-coated stent deployed in a group at high risk of restenosis and thrombosis. There were 2% stent thrombosis. At six months, 32% of patients (24% of stents) had had a cardiac event[80]. There were 2% stent thrombosis. At six months, 32% of patients (24% of stents) had had a cardiac event[80]. Notwithstanding this disappointing result, other inorganic coatings demonstrate useful properties. A ‘diamond-like’ carbon-coated stent (not, therefore, strictly speaking, inorganic), exposed to flowing, platelet-rich plasma produced less platelet activation and deposition and ion release than uncoated stents[81,82]. Gold would seem to be the ultimate inert stent coating. A 5 μm thick gold coating was applied to a stainless steel stent and, indeed, showed more than a halving of adherent thrombus mass compared with an uncoated stent[83]. But, disappointingly, a randomized study of 730 patients receiving a gold-coated or bare stainless steel stent revealed an excess of clinical events in the gold-coated group at one year (24% vs 13%)[84].

**Conclusions**

There may well be a role for local drug delivery in the era of stent implantation. Retention of a metal core to maintain the ability to scaffold the artery seems likely for the foreseeable future. Polymers simply do not have the right physical strengths, and many of them elicit an inflammatory reaction. A coating alone appears insufficient to prevent in-stent restenosis, but may be used as a vehicle to deliver an anti-proliferative drug, rather than simply being biologically ‘neutral’. Excellent haemocompatibility alone, though, might prove useful in adverse conditions predisposing to subacute thrombosis. As a carrier, the coating may be required to carry (stably, in storage), hold (for a biologically relevant period of time in vivo) and elute (slowly, into the wall of the artery) sufficient drug to have a useful local effect, without loss by friction with the catheter or artery or washout into the bloodstream. A tall order, by any standards, especially when it is realized that metal coverage is typically only 10–20% of the surface area of the vessel. It may, indeed, be an impossible order for a thin coating. The answer may lie with adjuvant local drug delivery. The argument then becomes practical and economic. Is a reduction in in-stent restenosis worth the trouble, time and extra expenditure on adjuvant drug delivery via a separate catheter? Technology may help here. A ‘dream ticket’ might be a single device for pre-dilatation, stent implantation, post-dilatation and intra-mural delivery together with a drug-eluting stent coating for longer-term, even more highly localized delivery. Some of the currently available devices, coatings and stents are getting close to making this aim an achievable reality.

**References**


