Percutaneous treatment of coronary artery disease has rapidly evolved during the last two decades. Percutaneous transluminal coronary angioplasty (PTCA) has been associated with two major risks. In the short term, (sub)acute occlusion caused by early arterial recoil or dissection may occur. In the long term, the main limitation of PTCA is the recurrence of stenosis, caused mainly by constrictive remodeling and/or increased neointimal hyperplasia. Despite intense research efforts, no pharmaceutical agent has conclusively shown an effect against restenosis. Once more, the only widely available and effective treatment against restenosis is stenting. Yet this mechanical support still fails in about 10–25% of cases.1

Restenosis rates are greater in high-risk patients, such as in diabetics, in patients with saphenous vein graft stenoses, as well as in small vessels (< 2.5 mm in diameter) and long lesions.1 Moreover, new methods such as laser angioplasty, atherectomy, and brachytherapy, which are attempting to reduce the restenosis rate, have been evolving throughout the past years. Nevertheless, despite their effectiveness in specific indications, important complications may occur with these approaches. The disruption of vessel wall integrity by large dissections, perforations, or the formation of aneurysms and pseudoaneurysms of the arterial wall are the severe side effects of new technologies. The treatment of these complications is still a challenge in interventional cardiology.

Coating and covering materials. The aim of all attempts regarding the improvement of metallic stents is to provide biocompatibility, accelerate endothelialization, and reduce vascular wall injury, thus eliminating tissue growth after the implantation of metallic stents. While the struts of the stent may create the problem, they may also present the solution by carrying a coating or covering material. The list of coating and covering materials used to reduce thrombogenicity and decrease intimal hyperplasia is consistently increasing. Several experimental studies have been performed with coated or covered stents, while the experience in the clinical practice is increasing as well. The gold-coated stents are commercially available.2 The silicone carbide-coated stents have also been applied clinically.3 In addition, an extended experimental4–6 and clinical experience has been obtained with heparin-coated stents.7 Regarding the latter, the reduction in the rate of thrombosis in animal studies led to their clinical evaluation in the BENESTENT II randomized trial, in which the incidence of thrombosis was almost eliminated, being less than 0.2%.7 In addition, in vivo baboon and porcine studies have demonstrated the safety, thromboresistance and long-term biological neutrality of phosphorylcholine-coated stents.8–9

Another approach has involved passivating the stent surface with fibrin in order to provide a platform for the recolonization of endothelial cells.10 Also, a fibrin-covered sleeve has been applied to metal stents and implanted in porcine coronary arteries.11–13

An interesting approach is the use of pharmaceutical compounds to inhibit neointimal hyperplasia. Rapamycin is a potent anti-rejection agent that inhibits the proliferation of smooth muscle cells by blocking cell cycle progression. This novel strategy to prevent tissue growth is promising and clinical results are expected to determine its efficacy in the near future.14 Covering the complete surface of stents by Dacron has also been proposed, but carries an increased risk of acute and subacute thrombembolic complications.15

Biodegradable and non-biodegradable polymers have been associated with marked inflammatory response. However, it seems that not all polymers have deleterious effects. A complete polymer membrane has been applied as a sandwich between two metallic stents. This device was constructed with a sandwich technique whereby an ultra-thin layer of expandable

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polytetrafluoroethylene (PTFE) that is specially developed for integration into a stent graft system is placed between 2 stents with reduced strut thickness. The early reports of its use suggest that it is safe and there are beneficial effects with the use of PTFE-covered stents in saphenous vein grafts. However, in another study, the target lesion revascularization and restenosis rates were increased. Although the concept of complete plaque coverage is intriguing, the bulky profile of the device, the issue of biocompatibility, and the relative stiffness are constraints of its widespread use.

The use of bovine pericardium as a sleeve for metallic stents has also been recently reported for the septal myocardium ablation in a patient with hypertrophic obstructive cardiomyopathy.

Experimental Studies

**Autologous vascular grafts.** Another approach in covered stents has been to apply autologous vascular, venous or arterial grafts to metallic stents. In this type of covered stent, the stent may be completely covered, both externally and internally, by the graft. Although the stent should ideally be completely wrapped in the autologous vascular graft, the device profile is significantly increased by such a process. Thus, the stents are covered externally by the venous or arterial graft. The experimental studies have shown a beneficial effect of covered stents on biocompatibility, endothelialization and vascular injury.

**Biocompatibility.** The use of autologous vascular grafts eliminates the problem of biocompatibility, since there is no foreign-body reaction. In addition, inflammatory cells were not observed after the implantation of covered stents. Moreover, stents covered by autologous vascular grafts provide sequestration of the atherosclerotic plaques and thus a smooth luminal surface is yielded, in contrast to the rough surface of conventional stented segments. This feature may be particularly important in thrombus-containing lesions, in degenerated saphenous vein grafts or in severely diseased lesions.

**Endothelialization.** The process of endothelialization plays a significant role in the acute or subacute formation of thrombus. In uncovered stents, complete endothelial coverage occurs after 4 weeks. The use of autologous vascular grafts as covering materials for metallic stents accelerates the process of endothelialization. The results of scanning electron microscopy demonstrated that 7 days after the implantation, 81% and 84% of the luminal surface was covered by a new endothelial layer in arterial- and venous-graft covered stents, respectively, as opposed to a 55% coverage observed in uncovered stents. Thus, covering the stent with an autologous vascular graft either externally or completely seems to enhance the formation of the new endothelial surface.

**Vascular injury.** The inciting stimuli involved in restenosis include mechanical factors that disrupt the medial smooth muscle cell layer. The contact of this disrupted layer with circulating blood factors and mitogens serves as further stimulus of neointimal formation. Vascular injury sets into motion a cascade of events that result in the final hyperplastic response. Thus, the protection of the arterial media is necessary in order to avoid laceration of the internal elastic lamina and proliferation of smooth muscle cells. However, although the high-pressure implantation technique used by the majority of operators leads to greater acute gain in lumen diameter, the injury to the vascular wall is greater. Covering the metallic struts of the stent by an autologous vascular graft reduces the injury to the arterial media. Although covered and non-covered stents had similar oversizing ratios in the experimental studies, the injury score was greater in uncovered stents. The autologous vascular graft-covered stent prohibits the contact between the stent struts and the internal elastic lamina and neither disruption of the internal elastic lamina nor penetration of the arterial media are likely to occur during implantation. Thus, the injury score is less in covered stents as a result of protection of the arterial media by the anatomical barrier of the autologous venous or arterial graft. Accordingly, the maximal intimal thickness tends to be reduced with covered stents.

**Radiation and covered stents.** In the era of new developments in interventional cardiology, covered stents may be used in combination with external radiation. In previous experimental studies, the application of γ-radiation was associated with reduction of intimal hyperplasia. Despite the favorable results regarding the restenosis rate, the delayed endothelialization may induce late thrombosis. In an effort to combine the biocompatibility and the accelerated endothelialization of covered stents with the anti-proliferative properties of γ-radiation, *ex vivo* radiation was applied on autologous venous grafts. These radiated grafts were used for stent coverage. Venous grafts were radiated *ex vivo* by γ-radiation (¹⁰⁰Co, 25 Gy). The porcine coronary model was used for the evaluation of this approach and similar results were observed in the endothelialization rate between radiated and non-radiated venous-covered stents. Moreover, the thickness of the radiated venous graft was less and the maximal intimal thickness had a trend to be less in this group.

**External non-invasive heating of stents.** In order to use other forms of energy with anti-proliferative
properties, we have applied electromagnetic energy to heat metallic stents from a distance (Figure 1). It has been suggested that hyperthermia has anti-proliferative and apoptotic effects. It was demonstrated that gentle heating suppresses pro-inflammatory cytokines and promotes macrophage apoptosis, and thus mitigates inflammation in atherosclerotic plaques. Accordingly, hyperthermia may be applied for the elimination of intimal hyperplasia.\textsuperscript{25,26} The method for external non-invasive gentle heating of metallic stents was based on the properties of metals when placed into an alternative magnetic field. The electromagnetic energy of a generator (approximately 20 MHz) is driven to an inductor to create an alternating magnetic field. As the magnetic force on the stent periodically changes, additional energy is drained from the generator to compensate for the lagging of the magnetic flux and appears on the metallic target as heat. This method was applied in the porcine coronary model and the metallic stents were heated from a distance of 15 cm. The temperature of the stent had a linear correlation with the generator’s output power, while it was inversely correlated with the distance of the inductor from the stent. This method is under experimental testing for the determination of the dose-dependent efficacy and the safety of the magnetic field. In addition, other investigators use non-invasive ultrasound to induce heating of stents. \textit{In vitro} studies showed that heating may be produced using levels of therapeutic ultrasound frequency (1–3 MHz) and intensity (0.5–2.5 W/cm\textsuperscript{2}).\textsuperscript{27}

\textbf{Clinical Experience}

\textbf{Autologous vascular graft-covered stents.} The experimental application of this technique has been succeeded by considerable clinical practice.\textsuperscript{28} The duration of covered stent preparation is not prolonged, but in emergency situations the patient has to be hemodynamically stable until the completion of the covered stent preparation. Harvesting the vascular graft and stabilization on the stent may be performed by cardiologists, without the requirement of surgical assistance. The learning curve is steep and the technique may be performed in all catheterization laboratories.

In the case of autologous venous graft-covered stents, \textit{in vitro} studies have shown that the major determinant of successful deployment is the selection of the appropriate vein, in terms of diameter and thickness of the vein wall. \textit{In vitro} testing has shown that the cephalic vein is appropriate for the preparation of covered stents. Our experience has included implantation of autologous vein-graft covered stents in elective lesions, ostial lesions, totally occluded vessels, thrombus-containing lesions, bypass venous grafts, and coronary aneurysms, as well as in bail-out cases.\textsuperscript{29–32} A population of 56 patients, including 16 patients with acute coronary syndromes, have already been followed for a period extending up to 42 months. Acute thrombosis was not observed and only one patient presented with subacute thrombosis. Neither death nor myocardial infarction were reported during the follow-up period. The target vessel revascularization rate was 12\% and the event-free survival was 86\%. However, in patients with acute coronary syndromes, the target vessel revascularization rate had a trend to be lower in covered stents compared with uncovered stents (6.2\% versus 21\%, respectively). Additionally, in patients with acute coronary syndromes, the event-free survival rate was 93\% in the group of covered stents versus 78\% in patients in whom uncovered stents were implanted.\textsuperscript{30}

Moreover, in patients in whom the implanted venous graft had greater thickness (graft harvested from the anterobrachial region), the event-free survival rate was greater compared with patients in whom the venous graft was harvested from the deltoideopectoral sulcus (Figure 2). A relative risk of 5.8 was found in patients in whom thin venous grafts were used.\textsuperscript{30} Accordingly, the thickness of the venous graft is a significant predictor of late outcome, probably acting by the elimination of intimal hyperplasia after stent implantation. It seems that covering stents with venous grafts with increased thickness is associated with improved clinical outcome. Grafts from the saphenous vein may further improve the results, although the
delivery of the covered stent may be limited to vessels with large diameters.

For the arterial graft-covered stents, a graft from the radial artery is used for stent coverage. Several reports have demonstrated the successful use of the radial artery as a free bypass graft. In a large number of patients, the long-term results were excellent and the technique was not associated with complications. In addition, the diameter of the radial artery is appropriate for human coronary arteries. The technique of stent coverage is identical to that for the preparation and implantation of venous-graft covered stents. Fifteen patients with autologous arterial-graft covered stents have already been followed for up to 2 years. Angiographic restenosis was noted in 3 of 15 lesions; target vessel revascularization was required in 2 patients and the event-free survival rate at 2 years was 87%.

Several case reports have shown the potential for the successful use of venous-covered stents for other indications besides coronary artery disease. Thus, venous-covered stents were successfully used for the treatment of coronary or peripheral aneurysms and pseudoaneurysms, rupture of the coronary vessels, and for the closure of arteriovenous fistulas (Figure 3). In one recent study, the restenosis rate was similar between covered and uncovered stents, although the late lumen loss was greater in the first group. It seems that the absolute indication for autologous vascular graft-covered stent implantation is the treatment of arterial wall disruptions and there are data suggesting that they may have beneficial effects on thrombus-containing lesions. Also, in saphenous vein grafts, covered stents may play a significant role by sequestrating the degenerative lesions, thus eliminating the risk for peripheral emboli during conventional balloon angioplasty and stent implantation. Covered stents by autologous vascular grafts may be used for local delivery of anti-thrombotic and anti-proliferative agents, since these substances may be directly delivered at the culprit lesion for higher localized concentration.

Conclusions. Coated and covered stents may have a significant role in interventional cardiology during the new century. The target of all these devices should be to provide biocompatibility, accelerated endothelialization, less injury to the arterial wall, and minimal proliferative response. In this field, the autologous vascular grafts seem to provide such properties and may be used as covering sleeves of coronary stents. Moreover, covered stents by autologous vascular grafts may be an appealing approach to local drug delivery technology. Finally, new approaches for the prevention of intimal hyperplasia may be combined with covered stents. Ex vivo radiation of the autologous vascular grafts may be a new approach for the application of covered stents. In addition, non-invasive gentle heating of stented segments may inhibit tissue growth after stenting, although more studies are required for the assessment of safety and efficacy.

REFERENCES

Covered Stents by Autologous Arterial Grafts


