Catheter-based Cardiovascular Therapy — The Impact of Stenting in Coronary Artery Disease

B. HEUBLEIN
Division of Thoracic and Cardiovascular Surgery, Hannover Medical School, Hannover, Germany

Summary

Coronary stenting has doubtlessly revolutionized the clinical practice of interventional cardiology by partially overcoming some of the shortcomings of balloon angioplasty, particularly abrupt vessel closure and restenosis. Stenting today is safe, with a success-rate of 98%. Despite their proven benefits, metallic stents are still accompanied by several limitations. Uncoated metallic stents are thrombogenic, leading to a post-procedural acute or subacute stent thrombosis rate of 1 to 2% in normal lesions and 4 to 8% in primarily high-risk lesions. Permanent metallic stents provoke an exaggerated proliferative myo-intimal response over time, leading to a later marked loss of lumen. Approaches to reducing stent thrombogenicity are varied. One new concept for improving material hemocompatibility is to coat the material with an active passivation semiconductor. Adjunctive pharmacologic therapy in coronary stenting is beneficial in patients with unstable angina, acute thrombotic events, residual thrombus formation and so-called type C lesions. Despite the proven phenomenal benefits of stent technology, placement and adjunctive therapy, stents need further improvement in the future. The incidence of stent restenosis is still unacceptably high.

Key Words

Stent, interventional cardiology, hemocompatibility, tissue reaction

Introduction

Since the first application of percutaneous transluminal coronary angioplasty (PTCA) in humans in 1977, catheter-based revascularization has seen tremendous growth. The indications have been expanded; innovative technologies combined; knowledge about the pathobiology of tissue reactions increased; and new frontiers in pharmaceutical and molecular biology research chartered [31]. Now PTCA is accepted as an efficient therapy in the treatment of coronary artery disease. However, some limitations of balloon angioplasty are apparent. Such identified problems are (a) the inability to dilate resistant or elastic lesions; (b) inefficiency in controlling or preventing vessel dissection; and (c) the inability to control restenosis effectively, particularly in long lesions and after recanalization of chronic or acute (thrombotic) vessel closure. These shortcomings led to "new" devices that intended to reduce these problems.

Of these new devices, coronary stenting has doubtlessly revolutionized the clinical practice of interventional cardiology by partially overcoming some of the described limitations of balloon angioplasty, particularly abrupt vessel closure and restenosis. The rate of de novo or provisional stenting in coronary catheter-based interventions has increased to more than 60%. A broad spectrum of new indications led to a reduction in surgical revascularization procedures and stimulated the widespread use of catheter-based coronary interventions, including ambulatory procedures (Table 1). The questions remain: Are these strategic approaches being subjected to properly controlled clinical trials? Or is this seemingly zealous fervor with which many practitioners support universal stent implantation based only on the allure of the immediate angiographic results and the ease of implantation [21]? Are coronary stents a breakthrough technology or just another small step [19]?

Proven	Questionable	No indication
Acute thrombotic occlusion	Small vessels (< 3 mm)	Type-A obstruction with good results after balloon dilatation without dissection
Abrupt or threatened vessel closure during angioplasty	Side branch included in lesion	Permanent low flow in diffuse diseased vessel
Restenosis in vessels > 2.5 mm	Y-stenosis	
Restenosis (early recoil) > 20%	Long lesion	
Focal lesions in vein grafts	Ostial lesion	
Recanalization of (chronic) totally occluded vessels	Non-flow limiting	
	Type-A dissection	
Focal lesion in transplantvasculopathy	Unprotected left main stem	

Table 1. Indications for coronary stenting in uncoated metallic stents.

Arterial Stenting

Most human coronary stents are composed of fenestrated stainless-steel tubes with plastic qualities that permit expansion by balloon inflation. Such pre-mounted balloon-stent systems are advanced across the lesion (over a guide wire) after pre-dilatation of the obstruction or de novo stenting. When fully expanded, the diameter of the selected stent is about 15% larger than the normal lumen of the target vessel (oversizing). The stent length spans the entire arterial segment. The results are confirmed by angiography or intravascular ultrasound. Electively treated patients receive heparin (procedural dosage only) and are (pre-) treated with antiplatelet agents (ticlopidine, aspirin) over a one-month period.

Advantages and Disadvantages of Permanent Metallic Stent Implantation

Stenting today is safe, with a success-rate of 98%; has an improved early and late (6 months) outcome in combination with antiplatelet therapy; allows increasing the spectrum of indications in chronic and acute coronary artery disease; and lends safety in practicing coronary interventions without in-house heart surgery (stenting as a back-up procedure).

Despite their proven benefits, metallic stents are still accompanied by several limitations. Uncoated metallic stents are thrombogenic, leading to a post-procedural acute or subacute stent thrombosis rate of 1 to 2% in normal lesions and 4 to 8% in primarily high-risk lesions. While conventional balloon angioplasty applies a transient strain to the vessel wall, stent deployment transfixes the artery into a permanently altered shape. The cellular proliferation, known to be induced by the transient strain, may be further potentiated by the more prolonged stimulus of permanent stenting (adjacent regions). One result is that permanent metallic stents provoke an exaggerated proliferative myointimal response over time, leading to a later marked loss of lumen. Thus, stent-induced shape change in the arterial segment is somewhat analogous to that observed in interposition vascular grafts. Just the junctions of stented and native arterial segments are subject to abrupt transitions in contour, rigidity, diameter and flow behavior. Currently implanted stents need further future improvements with respect to their long-term biocompatibility, antithrombogenicity and antiproliferative capabilities. Considering these limitations, the optimal strategy for stent use should be determined by the results of properly designed clinical trials.

Results of Clinical Trials

Subacute/acute closure

Advances in stent deployment techniques (high-pressure inflation, oversizing) and stent design (smooth surface, thin stent struts, low turbulence, increased stent-to-vessel-wall adaptation) have achieved low thrombosis rates (1 to 2%) with conventional antiplatelet therapy alone (ADP- and cyclooxygenase-inhibition) in carefully selected cases [2][6]. However, in many clinical situations, such as unstable angina, acute myocardial infarction, post-angioplasty failure (bail-out), low flow conditions, identifiable thrombus, recanalized chronic total occlusion, the risk of stent thrombosis is increased to 4 to 8% [1][7][12][17][20]. In the majority of such cases, acute stent thrombosis leads to myocardial infarction. Thus, clinicians and stent manufacturers are still seeking the best means to lower this thrombotic risk potential.

Restenosis/late outcome

Restenosis, which occurs in 30 to 50% of the patients, is an important limitation of conventional balloon angioplasty. Different risk factors are identified, for example: previous myocardial infarction, small diameter of the reference segment, asymmetric lesion, localized thrombosis, vein graft obstructions, extensive plaque burden, higher grade of residual stenosis, diabetes mellitus, and proximal lesions in the left anterior descending artery. Taking these problems into consideration, three randomized trials were conducted (STRESS, BENESTENT, REST). In the BENESTENT and STRESS trials [9][25] the use of balloon angioplasty or stenting in patients with new lesions was studied. The purpose of the REST trial [8] was evaluating stenting as compared with standard balloon angioplasty in the treatment of restenosis after angioplasty. The STRESS trial showed that stents could reduce restenosis rates from 42% to 32%, and the BENESTENT trial had a similar rate of reduction, 32% to 22%. In the REST trial stenting resulted in a lower rate of recurrent stenosis after conventional balloon angioplasty when compared with stand-alone balloon angioplasty (32% to 18%). This obviously beneficial effect of stenting is presumably due to better vessel geometry, because stents induce more neointima formation than balloon angioplasty alone.

Nevertheless, restenosis remains a highly problematic entity. It should be kept in mind that the carefully randomized STRESS and BENESTENT studies involved about 20% of the lesions treated in daily practice. Most lesions encountered in clinical practice are "complex" lesions and are excluded from these studies. Thus, in another trial, the SAVED trial, routine stent placement for vein graft lesions was not associated with a significant reduction in restenosis when compared with standard balloon angioplasty. Different single- and multicenter clinical trials considering the restenosis rate of long-term stent or multiple stent implantation showed restenosis rates of about 35% [21]. On the other hand, stent trials — most are still in progress — demonstrat-ed a trend toward lower restenosis rates (and higher primary success rates) of coronary stenting in myocardial infarction (PAMI).

Compared with the results of stand-alone angioplasty, stenting of non-acute total coronary occlusions lowers the 6-month restenosis/reocclusion rate of 50 to 70% to about 30% [23]. Elective stent placement provides angiographic and clinical outcomes superior to balloon angioplasty in vessels slightly smaller than 3 mm [24]. The restenosis rate occurred in 34% of the patients assigned to stenting and in 55% of the patients assigned to conventional angioplasty. This effect remains stable after one year with an event-free survival of 78% in the stented group and 67% in the angioplasty group. A continued benefit over time (12 months) using de novo stenting as opposed to balloon angioplasty could be demonstrated in transplant vasculopathy [13]. The observed restenosis rate of 17% after 12 months was accompanied by a significantly lower rate of incidence for cardiac events over a two-year follow-up period when compared with balloon-dilated patients.

Innovations in Coronary Stenting

Surface coating/degradation

Approaches to reducing stent thrombogenicity are varied. The heparin-coated stent [11] evaluated in the BENESTENT II study yields important benefits and reduces the rate of acute/subacute stent thrombosis, and obviously the restenosis rate as well, in this carefully selected patient group.

Another new concept for improving material hemocompatibility is to coat the material with an active passivation semiconductor [3,4]. Using an amorphous alloy of silicon and carbon as a coating substance (hybrid design), electronic requirements are fulfilled

for reducing the electron transfer from the metallic surface to the fibrinogen. Such fast electron transfer is necessary for breaking the fibrinopeptide bonds (the fibrinogen activation), and the subsequent fibrin-monomer polymerization will be avoided. Also, such material coating allows a continuous adjustment of the electronic parameters without fundamentally changing the mechanical properties. These coated stents have nearly the same strut thickness as uncoated stents and can also be applied with 6-French guiding catheters. Preliminary clinical results from this stent type in patients with a primarily high risk of stent thrombosis are encouraging with respect to the stent thrombosis rates and the cumulative late follow-up data [14][18].

Other types of coating (using phosphorylcholine, fibrin, stent wrapping with autologous vein material or synthetic polymer (PTFE) or cell seeding/sodding) may be additionally improved, but material costs and some logistical problems are difficult to solve and long-term data do not currently exist to confirm the lack of late sequelae associated with these strategies. In addition to these "barrier-orientated" systems, endovascular stents as a reservoir for temporarily administering drugs to prevent restenosis are receiving attention. Without systemic side effects, stented segments can provide a high concentration of drugs or drug composites at the lesion site. To this end, metallic stents are coated with controlled release matrices. To date, several types of drugs have been considered (for example, hirudin; prostaglandin; platelet-inhibitors, including IIb/IIIa antagonists; naked DNA or viral vectors; oligosensnucleotides; and others).

Another promising strategy might be the development of completely biodegradable intravascular implants. Biodegradable implants in younger patients avoid the necessity of further dilatation or sometimes surgical resection of stents, because the range of further stent dilatation is limited to reach the adequate size for an adult [26]. Even such types of implants allow the vessel to grow. Using such implants, a more controllable and long-term local drug delivery could be included to prevent excessive myo-intimal hyperplasia in and adjacent to the stent location (multipotent carrier function). After degradation a full reconstitution of the physiologic regional vascular compliance should be expected, a more physiologic repair (including growth if necessary) is not inhibited. However, using synthetic polymers, a significantly inflammatory and, consequently, enhanced thrombotic response and an exaggerated neointimal proliferative response could be generally demonstrated [15][32]. Nevertheless, new types of polymers and/or different conceptions of degradation may show some promise.

Brachytherapy

The radiotherapy is currently being tested as an adjunctive therapy to angioplasty. Stent-bound radioactive sources can deliver effective doses of radioactivity to the vessel wall. There is clear evidence that such local radiotherapy can reduce the neointimal proliferative response in humans. In contrast to other (loading) methods, beta-emitting radioactive stents provide a more favorable dosimetry. Just the local dose (depending on the lesion) and the timing are critical to success. Obviously, brachytherapy remains high on the list of potentially efficacious treatment modalities. However, the question will remain "Too little, too big, too soon?" [28]

Adjunctive pharmacologic treatment

With respect to hemocompatibility, the dominant abnormality after implantation of vascular stents is related to platelet activation [22]. Consequently, the benefit of an adjunctive antiplatelet approach (aspirin/ticlopidine/clopidogrel) over the traditional therapy in the early phase of coronary stenting was impressive. Combined with a more optimal stent deployment (higher dilatation pressures), this adjunctive therapy resulted in a marked reduction in the incidence of stent thrombosis. In parallel, the simplification of such a combined interventional-pharmacologic regimen has greatly reduced the cost by making overnight hospital stays routine, along with the possibility of transforming stent implantation to an outpatient procedure in some patients [16]. Considering the knowledge that a final common pathway for platelet aggregation exists (the glycoprotein IIb/IIIa receptor), new types of impressive platelet inhibitors were developed on a monoclonal antibody basis [5] and non-antibody-basis [27]. At this time, the greatest treatment benefit using such new adjunctive pharmacologic therapy in coronary stenting appears to be in patients with unstable angina, acute thrombotic events, residual thrombus formation and so-called type C lesions. In addition to the clear benefit in the acute phase during and shortly after stenting, a salutary effect should be expected regarding restenosis. A long-term inhibition of a platelet aggregation response results in a lesser local re-

lease of growth factors and other vasoactive amines. On the other hand, IIb/IIIa antagonists inhibit the vitronectin receptor, which is responsible for smooth muscle cell migration. Preliminary results regarding in-stent restenosis are encouraging [29].

Need for Further Improvement

Despite the proven phenomenal benefits of stent technology, placement and adjunctive therapy, stents need further improvement for the future. The incidence of stent restenosis remains unacceptably high. The extent of plaque burden may determine the prognosis, not the degree of enlargement on the luminogram at the interventional site. The "oculostenotic reflex" (that is to perform angioplasty/stenting in all "significant" lesions) does not prevent myocardial infarction significantly. Unstable lesions that cause plaque-rupture and myocardial infarction are not necessarily severely stenotic, and stenotic lesions are not necessarily unstable [30][10]. We have to switch (or to expand) our focus from the current modes of local treatment to more general plaque passivation with the purpose of further advancing the long-term outcome of patients treated with intravascular stents.

References

[1] Antoniucci D, Valenti R, Santoro GM, et al. Systematic direct angioplasty and stent-supported direct angioplasty therapy for cardiogenic shock complicating acute myocardial infarction: In-hospital and long-term survival. J Am Coll Cardiol. 1998; 31: 294-300.

[2] Bittl JA. Coronary stent occlusion: Thrombus horribilis. J Am Coll Cardiol. 1996; 28: 368-370.

[3] Bolz A, Amon M, Özbek C, et al. Coating of cardiovascular stents with a semiconductor to improve their hemocompatibility. Texas Heart Inst J. 1996; 23: 162 - 166.

[4] Bolz A, Schaldach M. Haemocompatibility optimisation of implants by hybrid structuring. Med Biol Eng Comput. 1993; 31: 123 - 130.

[5] Coller BS. Platelet GP IIb/IIIa antagonists: the first anti-integrin receptor therapeutics. J Clin Invest. 1997; 99: 1467 - 1471.

[6] Colombo A, Hall P, Nakamura S et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation. 1995; 91: 1676 - 1688.

[7] Eeckhout E, Kappenberger L, Goy JJ. Stents for intracoronary placement: Current status and future directions. J Am Coll Cardiol. 1996; 27: 757 - 765.

[8] Erbel R, Haude M, Höpp HW, et al. Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. N Engl J Med. 1998; 339: 1672-1678.

[9] Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994; 331: 496 - 501.

[10] Forrester JS, Shah PK. Lipid lowering versus revascularization. An idea whose time (for testing) has come. Circulation. 1997; 96: 1360 - 1362.

[11] Hardhammar PA, van Beusekom HM, Emanuelsson HU, et al. Reduction in thrombotic events with heparin-coated Palmaz-Schatz stents in normal porcine coronary arteries. Circulation. 1996; 93: 423 - 430.

[12] Heublein B, Özbek C, Pethig K. Silicon carbide-coated stents: Clinical experience in coronary lesions with increased thrombotic risk. J Endovasc Surg. 1998; 5: 32 - 36.

[13] Heublein B, Pethig K, Böttcher M, et al. Catheter intervention in coronary allograft vasculopathy - the impact of primary stenting. J Heart Lung Transplantation. 1998; 17: 102.

[14] Heublein B, Pethig K, Elsayed A-M. Silicon carbide coating-A semiconducting hybrid design of coronary stents. A feasibility study. J Invas Cardiol. 1998; 10: 255 - 262.

[15] Holmes DR, Camrud AR, Jorgenson MA, et al. Polymeric stenting in the porcine coronary artery model: Differential outcome of exogeneous fibrin sleeves versus polyurethane-coated stents. J Am Coll Cardiol. 1994; 24: 525 - 531.

[16] Kiemeneij F, Laarman GJ, Slagboom T, et al. Outpatient coronary stent implantation. J Am Coll Cardiol. 1997; 29: 323 - 327.

[17] King SB, Yeh W, Holubkov R, et al. Balloon angioplasty versus new device intervention: Clinical outcomes. A comparison of the NHLBI PTCA and NACI registries. J Am Coll Cardiol. 1998; 31: 558 - 566.

[18] Koolen J, Hanekamp C, Bonnier H. A highly flexible slotted tube stent design coated with a-SiC:H. First clinical experiences. Prog Biomed Res. 1998; 3: 40 - 44.

[19] Leon MB, Wong SC. Intracoronary stents. A breakthrough technology or just another small step? Circulation. 1994; 89: 1323 - 1327.

[20] Mak KH, Belli G, Ellis SG, et al. Subacute stent thrombosis: Evolving issues and current concepts. J Am Coll Cardiol. 1996; 27: 494 - 503.

[21] Narins CR, Holmes DR, Topol EJ. A call for provisional stenting: The balloon is back! Circulation. 1998; 97: 1298 - 1305.

[22] Neumann FJ, Gawaz M, Ott I, et al. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. J Am Coll Cardiol. 1996; 27: 15 -21.

[23] Rau T, Schofer J, Schlüter M, et al. Stenting of nonacute total coronary occlusions: Predictors of late angiographic outcome. J Am Coll Cardiol. 1998; 31: 275 - 280.

[24] Savage M, Fischman DL, Rake R, et al. Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. J Am Coll Cardiol. 1998; 31: 307 - 311.

[25] Serruys PW, de Jaegere P, Kiemeneij F,et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994; 331: 489 - 495.

[26] Shaffer KM, Mullins CE, Grifka RG, et al. Intravascular stents in congenital heart disease: Short- and long-term results from a large single-center experience. J Am Coll Cardiol. 1998; 31: 661 - 667.

[27] Tcheng JE, Lincoff AM, Sigmon KN, et al. Platelet glycoprotein IIb/IIIa inhibition with Integrelin during percutaneous coronary intervention: The IMPACT II Trial. Circulation. 1995; 92: Suppl. I: I - 543.

[28] Teirstein P. Beta-radiation to reduce restenosis. Too little, too soon? Circulation. 1997; 95: 1095 - 1097.

[29] The EPISTENT Investigators. Randomised controlled trial to assess safety of coronary stenting with use of abciximab. Lancet. 1998; 352: 85 - 90.

[30] Topol EJ, Nissen SE. Our preoccupation with coronary luminology.The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995; 92: 2333 - 2342.

[31] Topol EJ, Serruys PW. Frontiers in interventional cardiology. Circulation. 1998; 98: 1802 - 1820.

[32] van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and non-biodegradable polymers in porcine coronary arteries. Circulation. 1996; 94: 1690 - 1697.