Review

Long-term outcome after coronary stenting

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Abstract

The present review assesses the data on long-term outcome after coronary stenting. Histological, angiographical and intravascular imaging data have shown that the insertion of stents constitutes only a transient stimulus to lumen renarrowing, that this process is almost complete at 6 months and that a certain degree of neointima regression is also possible after this time. Clinical data have confirmed the sustained benefit of stenting in the long term. Careful selection of optimal stent designs and application of the recent advances in adjunctive pharmacological therapy are currently effective strategies to improve both short- and long-term results with coronary stenting. However, further efforts are needed and are ongoing to combat restenosis, a process that counters the excellent short-term results of stenting in the long term.

Keywords: coronary artery disease, long-term outcome, restenosis, stents, thrombosis

Introduction

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA), the first use of coronary stenting in clinical practice in 1986 [1••] was the major breakthrough in the treatment of patients with coronary artery disease. Coronary stenting was introduced to combat two limitations of conventional PTCA: acute vessel closure and late lumen renarrowing. Now, after 15 years of continuous refinement, stenting has become the dominant percutaneous coronary intervention. Over these years, stent designs, stent delivery systems, stent deployment techniques and adjunctive antithrombotic therapy have all changed dramatically [2].

The earliest concern with the use of stenting was its thrombogenicity and potential for disastrous early severe thrombotic complications [3]. Potent anticoagulation therapy with prolonged heparin administration followed by coumarin derivatives only amplified the risk of bleeding complications, without resolving the problem of stent thrombosis [4]. Considerable efforts were then focused on understanding the principal mechanisms of stent thrombosis [5], on technical refinements aimed at improving the immediate lumen gain through high-pressure inflation under the guidance of intravascular ultrasound [6], and on the search for more effective antithrombotic therapies [7].

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous coronary transluminal angioplasty; TVR = target vessel revascularization.

The ISAR (Intracoronary Stenting and Antithrombotic Regimen) trial in 1996 [8••] and the other trials that followed in 1998 [9,10••] definitively established the role of the combined antiplatelet therapy (ticlopidine plus aspirin) in minimizing the risk of stent thrombosis. The favourable results achieved more recently with newer antiplatelet agents such as glycoprotein IIb/IIIa inhibitors [11••] further strengthened the value of the pharmacological approach in the prevention of thrombotic events after stenting. The trials mentioned above were critical in defining stent placement protocols and in guiding future efforts in this field; this became even more apparent after the demonstrated failure of high-pressure deployment to favourably impact on the risk of thrombosis and restenosis after stenting [12•].

Several randomized trials have examined the value of coronary stenting in various subsets of lesions and patients. For selected lesions situated in native coronary vessels with a diameter of 3 mm or more, the BENESTENT (Belgium-Netherland Stent) [13••] and STRESS (Stent Restenosis Study) [14••] trials demonstrated a significant reduction in angiographic restenosis and need for target vessel revascularization (TVR) achieved with stenting compared with PTCA. Stenting also proved superior to PTCA for lesions in coronary bypass grafts, as shown by the significant reduction in incidence of adverse clinical events at 8 months and the trend toward a lower rate of angiographic restenosis [15•]. However, these advantages of stenting could not be reproduced for lesions in smaller native vessels [16].

When compared with primary PTCA, primary stenting in acute myocardial infarction (AMI) was associated with decreased restenosis and need for TVR, but without any benefit in hard end-points such as death or reinfarction [17]. In contrast, optimizing the adjunctive antithrombotic therapy with the addition of glycoprotein IIb/IIIa blockade (abciximab) enabled greater myocardial salvage and better clinical outcome with stenting than with thrombolysis in patients with AMI [18]. However, the present review does not discuss the results of primary stenting in AMI due to the paucity of long-term data.

There is no doubt about the excellent acute and good mid-term results achieved with stenting. This is the reason why this treatment option is used so frequently, even for indications that have not been proven by properly designed randomized trials. However, there are doubts regarding the long-term advantages of this intervention. The introduction of a new treatment strategy often raises the question of long-term results. This question is even more important in the case of stenting. Stenting consists of the permanent implantation of a foreign body, with the potential of adverse effects in the long term through the lasting interaction with the vessel wall and the chronic strain imposed on that structure. On the other extreme of concerns regarding this treatment, stents might collapse with time, thereby abrogating the initial benefit. The 15 years of experience with this treatment and the plethora of data from histopathological, angiographical, intravascular imaging and clinical studies have enabled a more realistic perspective about the long-term efficacy of coronary stenting.

Histopathologic data

The pathobiological responses of the vessel wall to stent insertion have been characterized by numerous animal studies and fewer human investigations that used stented vessels obtained at autopsy, stented vein grafts excised at surgery and vessel wall tissue specimens retrieved with atherectomy. The response of the vessel wall to stenting is qualitatively characterized by the typical features of a response to injury. Stent-induced injury triggers a sequence of events that may be categorized as thrombosis, inflammation and proliferation [19•]. Stents provoke a higher degree of injury than does balloon dilatation alone, and this is followed by mural deposition of platelet-rich thrombi, which occurs within the first few days [20] and is demonstrable until 30 days after the intervention [21]. Another important response to stent-induced injury is the inflammatory reaction, as demonstrated by the accumulation at the injury site of acute inflammatory cells (neutrophils) during the first 30 days and chronic inflammatory cells (lymphocytes and macrophages) thereafter [20]. The degree of the inflammatory reaction correlates with the degree of injury, and both thrombosis and inflammation are also dependent on the stent design used [22•].

The higher degree of injury, thrombosis and inflammation observed after stenting is associated with more extensive neointima formation than after plain PTCA [23]. Restenotic tissue from patients after stenting is richer in smooth muscle cells and is poorer in collagen than restenotic tissue from patients after PTCA [24]. Also, neointima presents more apoptosis after stenting than after PTCA [25]. Both inhibition of smooth muscle cell proliferation and/or enhancement of apoptosis are logical targets of strategies for prevention of restenosis. Finally, remodelling, which is the principal mechanism of restenosis after PTCA, plays almost no role at all in in-stent restenosis [19•].

Although the differences in the magnitude of the components of restenosis between stenting and PTCA have been well described, an accurate characterization of the time course of the restenotic processes that occur after these interventions is still lacking. The data available from separate pathological studies suggest that the healing process after stenting does not take much longer than that after PTCA. Full re-endothelialization and stability of the neointima overlying the stent seem to be achieved by 12 weeks after stenting, on the basis of autopsy studies in humans [26]. Therefore, the histopathological data do not provide reasons to believe that the documented advantages of stenting over PTCA will be eliminated in the long run.

Table 1

Clinical results at 1 year in major randomized trials with coronary stenting

Study/Procedure	*n*	Angiographic restenosis rate (%)	Death (%)	MI (%)	CABG (%)	PTCA (%)	MACE (%)
BENESTENT [13••,17]							
Stent	259	22*	1.2	3.5	6.9	10.0*	23.2*
PTCA	257	32	0.8	1.9	5.1	20.6	31.5
STRESS [14••,38]							
Stent	205	32*	1.5	3.4	5.8	15.1	21.0
PTCA	202	42	2.0	3.5	8.9	16.4	26.2
BENESTENT II [35]							
Stent (heparin coated)	413	16*	1.0	1.9	1.9	9.4*	15.7*
PTCA	410	31	1.0	1.5	1.5	15.6	22.4
EPISTENT [11••]							
Stent + abciximab	794	31†	1.0	4.4	5.8	13.6*	18.6*
PTCA + abciximab	796	40	2.1	6.4	6.3	18.3	24.9
ARTS [39]							
Stent	600	N/A	2.5	5.3	4.7*	12.2*	26.3*
CABG	605	N/A	2.8	4.0	0.5	3.0	12.2

Study acronyms are defined in the text. *$P < 0.05$ for the comparison between stent and respective control arm (PTCA or CABG). †Restenosis data presented at the 48th Annual Scientific Session of the American College of Cardiology, New Orleans, LA, USA, 1999. MACE, any major adverse clinical event; MI, myocardial infarction (defined as either Q-wave infarction or creatine kinase elevation ≥5 times the upper normal limit); N/A, not available.

Angiographic and intravascular imaging data

Although stenting reduces the incidence of angiographic restenosis by 25–30% in comparison with PTCA [13••,14••], restenosis remains the major drawback for this intervention also. Restenosis mostly affects particular subsets of patients [27], and baseline conventional clinical, lesion-related and procedure-related variables may only partly explain the risk for this complication [28]. A significant part of this risk appears to be related to known or as yet unknown genetic factors [29].

Intravascular ultrasound investigations [30] have confirmed neointima formation and remodelling as the major contributors to restenosis after stenting and PTCA, respectively. The temporal pattern of luminal changes appears to be similar within the first 6 months after stenting and PTCA [31]. Most of the lumen renarrowing takes place within the first 3 months after stenting, with virtually no change occurring between 6 and 12 months; the incidence of restenosis was 22% after 3 months, 32% after 6 months, and remained essentially constant at 33% by 1 year [32•]. More importantly, the minimal lumen at the stented site initially was surprisingly enlarged during the interval between 1 and 3 years after the procedure [33•]. In fact, serial angioscopy in patients after stenting has shown that thinning of neointima occurs after 6 months [34]. The mechanism that may lead to altered expression of genes that interfere with apoptosis in the neointima tissue remains to be investigated. If confirmed, these findings may also have important implications regarding how asymptomatic patients with in-stent restenosis should be managed.

Routine angiographic follow up is believed by some to increase the risk of 'oculostenotic reflex', which increases the number of reinterventions. The number of reinterventions was twice as high among stent patients who were subrandomized to angiographic restudy than among those assigned only clinical follow up in the BENESTENT II trial [35]. On the other hand, PTCA patients with systematic angiographic follow up at 6 months had a higher rate of reinterventions, but a lower mortality at 10 years after the procedure than did their counterparts without angiographic restudy at 6 months [36].

Clinical data

Table 1 shows the clinical results at 1 year that were reported by the major randomized trials that compared stenting with conventional PTCA or coronary artery bypass grafting (CABG). Where data are available, the incidence of angiographic restenosis at 6 months is also shown. The BENESTENT [13••,37], BENESTENT II [35] and STRESS [14••,38] trials included selected subsets of patients and lesions. The ARTS (Arterial Revascularization Therapy Study) [39] enrolled patients with multivessel interventions. The device used was the Palmaz–Schatz stent (Cordis, a Johnson & Johnson Company, Warren, NJ, USA) in the BENESTENT, STRESS and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) [11••] trials, the heparin-coated Palmaz–Schatz stent in the BENESTENT II trial, and Crown (Cordis) or CrossFlex (Cordis) stent in the ARTS trial. As adjunctive pharmacological therapy to stenting, full anticoagulation was used in the BENSTENT and STRESS trials, and aspirin plus ticlopidine in the

Table 2

Clinical results at 24 months or more after coronary stenting

Reference	*n*	Follow up (months)†	Death (%)	MI (%)	TVR (%)	MACE (%)
[42]	123	42	13	22	21	49
[4]	301	24	4.6	4.3*	20.4	29.3
[43]	65	39	10.8	6.2	30.8	44.0
[44]	175	54	13.7	12.6	39.4	49.7
[33•]	143	36	9.1	5.6*	20.4	25.4
[45]	229	48	2.7	2.2*	12.0	16.9
[46]	259	60	5.9	7.8	25.0	34.5
[47]	1000	29	8.2	12.8	30.3	45.0

*Nonfatal infarctions. †Mean or median follow-up period. MACE, major adverse clinical event; MI, myocardial infarction.

BENESTENT II, EPISTENT and ARTS trials. In addition, glycoprotein IIb/IIIa inhibition with abciximab was given periprocedurally in the EPISTENT trial.

As shown in Table 1, stenting is associated with a relative reduction of 20–30% in the cumulative 1-year incidence of adverse clinical events when compared with PTCA. This is exclusively the result of the reduced need for reinterventions. On the other hand, the ARTS trial showed that multivessel stenting may achieve similar clinical results at 1 year to those of CABG in terms of hard endpoints, such as mortality and myocardial infarction, at the cost of more frequent need for reinterventions, mostly percutaneous coronary interventions. However, when the ARTS results are interpreted in the context of the previous trials that compared PTCA with CABG, multivessel stenting seems to reduce the difference in the incidence of adverse clinical events between the surgical and the percutaneous approaches.

In addition to the experimental evidence, there are now sufficient clinical data to support the independent role of stent type in the long-term results achieved with stenting. In a randomized comparison of five stent types [40], 1-year event-free survival varied from 69.4 to 78.9% ($P<0.02$) depending on the stent design used. These findings show the potential of stent technologies to improve the long-term outcome of patients treated with this technique.

For several years, the use of stents remained limited and mostly confined to bail-out situations or coronary bypass grafts. Following reports of advantages of stenting over PTCA and the radical improvement in antithrombotic therapy, there has been a great increase in the use of stents during the past 5 years. This explains why studies with follow-up periods longer than 1 year usually include a limited number of patients. Several factors should be considered that can have a profound influence on the long-term clinical findings. The results with coronary stenting are dependent on the characteristics of patients included [29], on the antithrombotic regimen used as an adjunct to stenting [8••,10••,11••], and on the particular stent design implanted [40,41]. Long-term outcome after stenting also reflects the progression of coronary atherosclerosis, prevention of which should represent the primary focus of the management of these patients.

A summary of the long-term results reported by studies with a follow-up period of at least 24 months is presented in Table 2. The risk profile of the patients included in these studies is considerably different, with only selected lesions in native vessels for some studies [13••,14••,33•] and bail-out situations in others [4,42]. The Palmaz–Schatz stent was used in most of the studies [4,33•,43–46]. Eeckhout *et al* [42] used the Wallstent (Boston Scientific Corp, Natick, MA, USA) and van Domburg *et al* [47] use different stents, including the Wallstent. Except for the study of van Domburg *et al* [47], all of the other studies applied full anticoagulation as the poststenting regimen.

Two studies reported on the long-term results of randomized comparisons between stent and PTCA. At 5 years, BENESTENT investigators [46] reported a 34.5% rate of adverse events after stenting, and a 40.2% rate after PTCA, which represents a nonsignificant relative reduction of 14%. This was exclusively due to a significant reduction of 37% in the need for repeat PTCA (17.3% in the stent and 27.6% in the PTCA arm). Similar results were reported by the other randomized trial, conducted by Betriu *et al* [45]. The incidence of adverse events at 4 years decreased significantly from 29.9% after PTCA to 16.9% after stenting, mostly because of the reduction in the rate of repeat PTCA from 22.3% to 10.7%.

In the retrospective study of van Domburg *et al* [47], a comparative analysis between the subgroup treated with anticoagulation therapy and that treated with antiplatelet agents was performed at 2 years after stenting. Interestingly, the advantages of antiplatelet therapy in terms of reduced risk of myocardial infarction and need for repeat interventions were maintained over the entire follow-up period. The concept that even short-term antithrombotic therapy is able to achieve a long-term benefit is best illustrated by the EPISTENT [11••] results: adding abciximab to the periprocedural therapy was associated with a significant 57% reduction in 1-year mortality (1.0% in stent plus abciximab versus 2.3% in stent plus placebo). It is readily conceivable that this is the result of the drastic reduction in the rate of postprocedural myocardial infarction observed with abciximab. These findings indicate another source of improvement of long-term results after stenting, namely further optimization of the adjunctive pharmacological therapy.

In-stent restenosis poses a major threat to long-term outcome after stenting; it may be focal or diffuse [48]. Particularly when diffuse, in-stent restenosis is a real management challenge for interventional cardiologists because of its high recurrence rate. Various forms of percutaneous coronary intervention, including plain PTCA, repeat stenting, directional and rotational atherectomy, and excimer laser angioplasty, have been used to treat in-stent restenosis. Considering that lumen encroachment in the stented site is the consequence of an exuberant neointimal tissue growth, debulking techniques appear to be attractive strategies for treating this complication. Contrary to expectations, however, rotational atherectomy, followed by low-pressure balloon dilatation proved to be inferior to plain PTCA in the ARTIST (Angioplasty versus Rotation for the Treatment of In-Stent Stenosis/Occlusion) randomized trial [49].

The experience to date indicates that several strategies designed to prevent restenosis have yielded disappointing results, but brachytherapy may have promise. In a small series of 55 patients with a particularly high risk for restenosis who were randomly assigned to either intracoronary γ-radiation or placebo therapy during the intervention [50], there was a significant reduction in the need for reintervention at 3 years, from 48.3 to 15.4%. Encouraging results in reducing the recurrence of in-stent restenosis were also reported with the use of intracoronary β-radiation [51]. Intensive work is being done in this field and results from large clinical trials are still pending.

Conclusion

Coronary stenting is increasingly being used because of the excellent short-term results, the ability to prevent abrupt vessel closure that may occur after plain PTCA, and the reduced risk of restenosis that has been demonstrated for a number of indications. Histologic, angiographic and intravascular imaging data have evidenced the different mechanisms of restenosis between stenting and PTCA. They have also shown that the insertion of stents constitutes only a transient stimulus to lumen renarrowing, that this process is almost complete at 6 months, and that a certain degree of neointima regression is also possible after this time. Clinical data have confirmed the sustained benefit of stenting in the long term. Careful selection of optimal stent designs and application of the recent advances in adjunctive pharmacological therapy are currently effective strategies to improve both short-term and long-term results with coronary stenting. However, further efforts are needed and are on-going to combat restenosis, a process that counters the excellent short-term results of stenting in the long term.

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