REVIEW ARTICLE

THE ROLE OF INTRACORONARY STENTS IN THE PREVENTION OF RESTENOSIS - FACTS AND FALLACIES

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ABSTRACT

Ten years after the first stents were implanted in human coronary arteries by Dr Sigwart, stenting has proved itself to be a highly effective solution to acute or threatened closure associated with failed balloon angioplasty, and in the prevention of restenosis. Despite these salutary and exciting outcomes, there remain a number of issues of deep-seated concern including stent thrombosis and anticoagulation-related bleeding complications. Recently, these two latter problems have been largely rectified by evolving technical refinements in stent implantation and the use of less aggressive post-stent antithrombotic regimens. The technology, however, has also created a new, potentially complex situation - that of stent overuse and the implantation of stents for non evidence-based indications.

Keywords: balloon angioplasty, coronary artery disease, coronary stents, lesion recurrence, stent thrombosis

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INTRODUCTION

Although it is well-established that percutaneous transluminal coronary angioplasty (PTCA) is an effective and relatively safe nonsurgical revascularisation procedure in the treatment of coronary artery disease, affording immediate improvement in the degree of ischaemia, its long-term results remain tainted by a restenosis rate of 30% to 50%, with recurrence commonly occurring within the first 6 months after the procedure[1]. Restenosis is thus truly the Achilles' heel of PTCA. It is strongly influenced by a number of clinical, anatomic and balloon-related factors, including the presence of diabetes, baseline chronic total occlusion, stenoses located in the proximal-mid segment of vein grafts or at the ostium of native coronary arteries, multivessel/ multilesional angioplasty, suboptimal post-PTCA outcome (residual lesion ≥30% diameter stenosis from vessel recoil or intimal dissection) and the use of undersized balloons for the procedure[1]. Several animal, human postmortem and antemortem (tissue specimens obtained during directional atherectomy) studies have demonstrated beyond doubt that the pivotal process of restenosis is that of exuberant smooth muscle proliferation together with a large volume of extracellular matrix generated by the smooth muscle cells[1,2].

Because of this unacceptable high incidence of restenosis and its profound health-cost implications, not surprisingly, there has been intense experimental and clinical research attempting to solve this problem. Current anti-restenosis treatment strategies can be divided into approaches which involve systemic or local administration of pharmacologic agents to suppress smooth muscle cell proliferation and matrix production, and those using newer mechanical devices to enhance the vascular luminal dimensions. Of these latter technologies, stents appear to be the most effective and most promising, and will be the focus of this article.

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Pharmacologic Strategies

As neointimal growth is a normal reparative response to vascular injury, and a small amount of it is essential and clearly desirable, the ideal pharmacologic strategy in the prevention of restenosis should thus be targeted at controlling excessive intimal growth rather than totally inhibiting it. In the animal model, numerous pharmacologic agents appear to have a positive impact on the control of intimal hyperplasia. Unfortunately, these experimental benefits have not been convincingly demonstrated in clinical trials involving drugs such as calcium antagonists, antiplatelet agents, anticoagulants, and those with anti-inflammatory, antiproliferative and lipid-lowering actions[2,3].

Second-Generation Non-Stent Devices

The failure of pharmacologic therapy in curbing restenosis has led to a shift in focus with attention now being directed at newer nonballoon-based intracoronary mechanical technologies which ablate or debulk the stenotic lesions rather than fracturing the atheroma or dissect the media to enlarge the vessel lumen as is observed in conventional balloon angioplasty. Unfortunately, data accrued from both observational and randomised trials examining some of these devices, in particular, excimer laser angioplasty and the various types of atherectomy procedures (rotational, extractional and directional) have generally been discouraging with no overall success in checking the risk of restenosis[2,3]. Although the initial gains in the immediate lumen dimensions may be larger after these procedures with (so-called facilitated angioplasty) or without adjunctive PTCA, these luminal benefits appear to be negated by a greater loss in late diameter, resulting in little or no net gain during follow-up. It is likely that the more extensive damage imparted on the vessel wall by these rather aggressive devices may have induced more intimal hyperplasia which in turn was reflected in more late loss and no overall difference in the restenosis rates compared with stand-alone conventional balloon angioplasty. In the absence of definitive evidence demonstrating any long-term benefits, advocates of some of these devices have now relegated them to a "lesion-specific" approach in which the choice of device is targeted at specific lesion morphology to improve the acute outcome of the procedure. Even this line of approach appears to have either minimal or negative impact; recent data derived from studies[4-10] examining such "niche" strategy for some of these

devices have revealed only limited indications, more expenses incurred and no persuasive evidence to support this strategy. In fact, on the contrary, their utilisation has been demonstrated to be associated with more complications.

STENTS

Luminal Benefits

In contrast to the disappointing late outcome of the devices mentioned above, the restenosis risk after stenting compared with PTCA is promising. Since it was first performed in human coronary arteries by Sigwart et al in 1986[1], stents have been shown to be an extremely useful bailout tool for threatened and acute closures during PTCA, frequently converting the most malignant-looking and complex dissection into a cosmetically attractive luminal outcome and obviating the need for emergency surgery and markedly reducing the extent of ischaemic damage[3,11-15]. Subsequent observational studies[2,16-21] also showed that stenting consistently outperforms PTCA in terms of reducing the risk of restenosis, particularly in larger-sized vessels. It does this by restoring the vascular integrity by various mechanisms. First, it provides a stable scaffold, thus counteracting elastic recoil. Second, it limits exposure of deep tissue to blood components and ensures high antegrade flow through a smooth-contoured lumen, thereby diminishing unfavourable rheologic factors. Lastly, it totally eliminates stenosis by achieving maximal acute gain - often with negative residual stenosis at the lesion site - through radial compression and circumferential redistribution of the atheromatous plaque without tissue removal. The result is that the immediate gain after stenting is often larger than any other debulking interventional device in our armamentarium (Fig 1a and 1b). Thus, although stenting, like the other second-generation interventional devices, also promotes more intimal hyperplasia, the maximal lumen dimensions it engenders allow the vessel to accommodate the extra intimal growth without resulting in restenosis (the "bigger is better" paradigm). It is also clear from the literature[21-23] that instent restenosis follows the same timeframe as restenosis after PTCA, ie within the first 6 months after the procedure.

These salutary clinical benefits of stenting were recently confirmed by 2 moderate-sized, landmark, randomised studies[24,25] comparing single Palmaz-Schatz stent implantation vs PTCA in *de novo* native coronary focal lesions in a head-to-head design in over 900 patients. Six-month angiographic follow-up data showed that there was indeed a larger net gain in luminal size in the stent-treated group of patients compared with the PTCA-treatment arm. This was translated into a significantly lower restenosis rate [22% vs 32%, p=0.02, a 33% relative reduction in the Benestent trial[24], and 32% vs 42%, p=0.016, a 25% relative reduction in the STRESS trial[25]] and a reduced incidence of repeat intervention for recurrent ischaemia of the treated lesions in patients who received the Palmaz-Schatz stents. With current practice of routine post-stent dilatation using high-pressure inflations and/or larger balloons for luminal optimisation, the 6-month instent restenosis rate may be further lowered [as low as 6% in phase IV of the Benestent II pilot study[26].]

Major Drawbacks of Stents

Despite its proven efficacy, there are 2 major drawbacks in the use of stents.

1. Early Stent Thrombosis

Current stents available in clinical practice are all made of metal (either stainless steel or tantalum), and are thus highly thrombogenic until the metal struts have undergone complete

Fig 1a – A tight tubular lesion in the mid-segment of the right coronary artery before intervention.

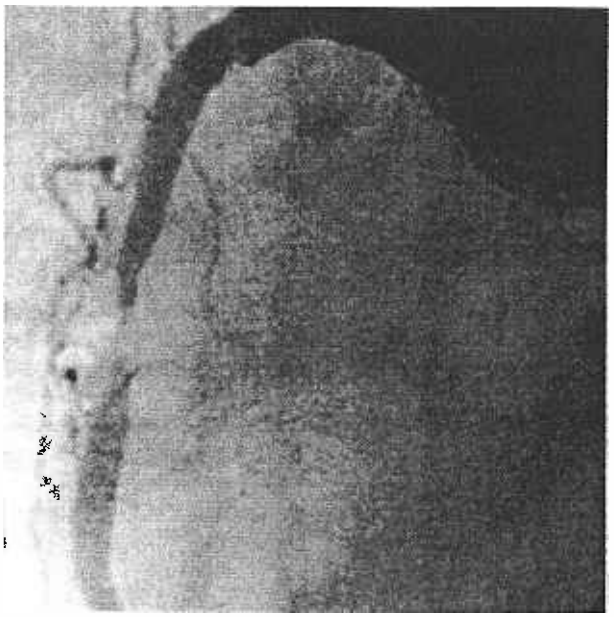
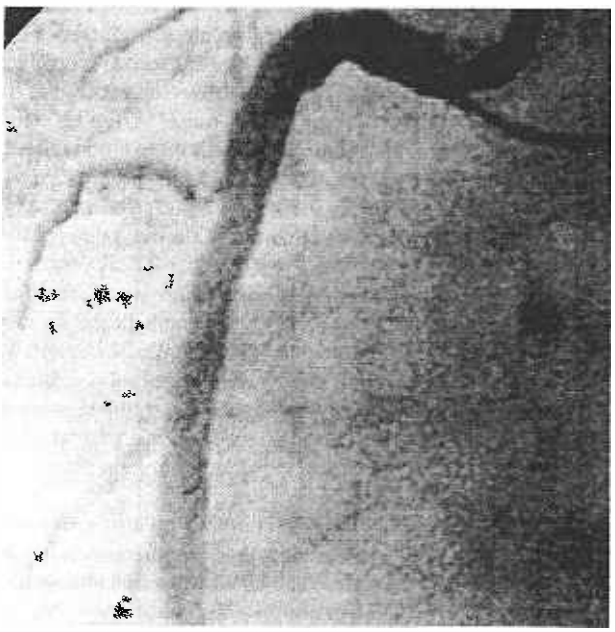


Fig 1b – There is almost complete obliteration of the stenosis after implantation of a 3.5-mm diameter Palmaz-Schatz stent.



neoendothelialisation which normally takes several weeks[2]. As the balloon-traumatised surface is already in itself thrombogenic, the addition of another thrombogenic factor is a matter of serious concern to interventionalists. Stent thrombosis which commonly strikes between the 3rd and 14th post-procedure day, can occur outside the medical institutions, remote from emergency facilities[12,13,16,24,25,27-30]. Stents are thus like a double-edged sword; they can confer clinical benefits, but they can also kill patients without warning if not optimally used. Not surprisingly, this fear of early stent thrombosis and its major clinical sequelae, namely that of myocardial infarction or death, has led to stent investigators in the past strongly recommending the use of mandatory aggressive antithrombotic therapy consisting of intensive intravenous heparin followed by high-dose warfarin for several months, dextran, and dipyridamole plus aspirin.

Subsequent experience, however, showed that this complication could indeed be reduced substantially from about 3%-5% for elective stenting (8%-18% incidence for bailout stenting indication) to <1% simply by using short-term (1 month) ticlopidine and/or low molecular weight heparin and aspirin without warfarin, optimisation of instent lumen size and geometry by further high-pressure balloon dilatations within the stent, and ensuring complete coverage of any dissection created by prior PTCA[26,30]. Incomplete coverage of dissections have been linked with an increased risk of stent thrombosis[27,31]. Recent preliminary data suggest that the use of avant garde technologies, particularly heparin-coated stents[26] and those made from naturally occurring biodegradable materials, may further attentuate the risk of early stent occlusion[2].

2. *Bleeding and Vascular Complications*

Another major limitation encountered in the early experience of stent usage was that of bleeding and vascular complications. These untoward events were noted in about 10%-16% of patients who were subjected to the old regime of aggressive anticoagulation[18,24,25,27]. Increased operator skill and the adoption of current simplified but effective anti-thrombotic regimen without systemic anticoagulation, however, have partly solved this problematic issue; the incidence of major bleeding and vascular complications has now fallen to a manageable ≤3%[26,30]. Also associated with this new approach was a significant abbreviation of hospital stay, and *ipso facto* cost reduction.

Overuse and Abuse

The overall superior outcome of elective stenting compared with conventional PTCA, together with the dramatic reduction in the risk of stent thrombosis, bleeding and vascular complication rates with current stent management, and the sudden widespread availability of stents following FDA (USA) approval in 1994 of the Palmaz-Schatz stents for elective stenting in selected patients to prevent restenosis, have led to a very rapid embracement of this device by many interventional cardiologists. Unfortunately. these favourable outcomes of stents have also seduced some interventionalists into overusing the device for sometimes feeble or even unproven indications. Thus, it is imperative that at this juncture, the true clinical utility as an anti-restenotic strategy should be placed in its proper context.

Although we now have irrefutable evidence derived from randomised trials[24,25] indicating a better outcome for stents compared with PTCA in terms of a lower restenosis rate and less ischaemic clinical manifestations following stenting in de *novo* native coronary lesions, similar data for many other clinical scenarios are not yet available. For example, there are no published randomised trials to date on stenting versus PTCA for saphenous vein graft or post-PTCA restenosis lesions. Having said that, we do, however, have persuasive data from observational historical studies[2,5] demonstrating a superior outcome for stents placed in large-sized vein grafts compared with PTCA. Hence, it makes sense that large bypass vein grafts should be stented particularly if the luminal results following PTCA are obviously suboptimal. It is also well-known that the restenosis rate after repeat PTCA for restenotic lesions is significantly higher than the first PTCA[3]. Short of a better solution, it is thus not unreasonable to consider elective stenting in such a situation although whether this strategy will afford a lower restenosis rate remains speculative; it has not yet been examined in a randomised trial. In contrast. it is exceedingly difficult to justify stent implantation for *de novo* lesions which already have "stent-like" luminal outcome (≤20% residual stenosis without obvious angiographic dissection) (Fig 2a and 2b) after conventional PTCA, particularly in small vessels or

Fig 2a – A critical focal stenosis located in the mid-segment of the right coronary artery prior to intervention.

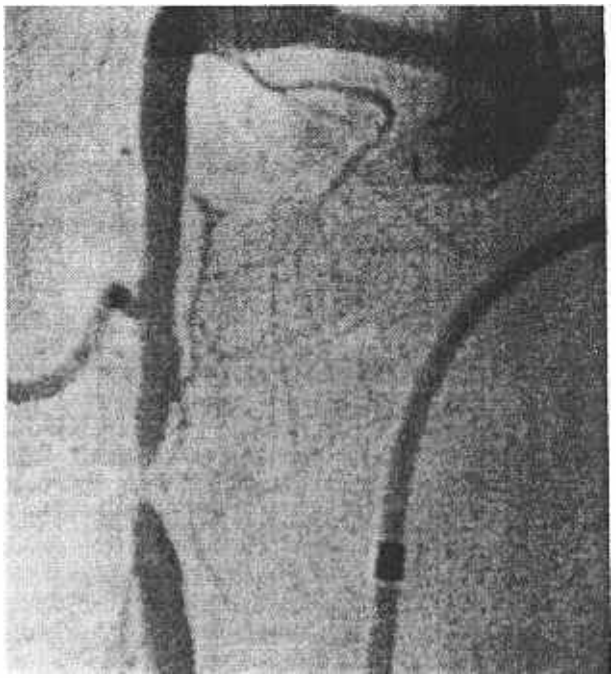
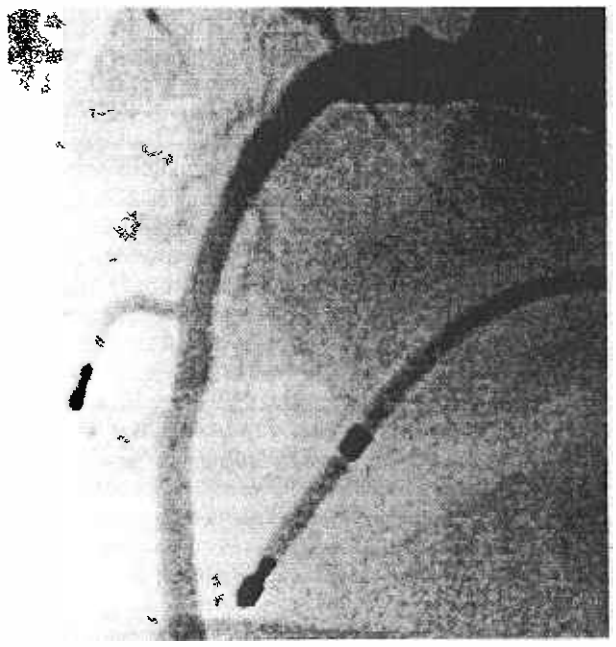


Fig 2b – After only conventional balloon angioplasty without stent placement, a 'stent-like' luminal outcome is obvious with very minimal residual stenosis and no angiographic evidence of dissection.



when multiple stents are required, where the evidence demonstrating a superior long-term outcome for stenting compared with PTCA is lacking and where its efficacy in the prevention of recurrent stenosis is unproven. Thus, stents should not be implanted in every patient.

If overuse and abuse of stents, especially when performed by neophytes. is left unchecked, the prevalence of stent thrombosis. stent embolisation and snagging, and vessel ruptures will inevitably increase at the expense of the patients. Because of the extraordinary initial angiographic luminal appearance conferred by stent implantation, even experienced operators may

be seduced into the flippant and unscientific application of this technology. And as it is almost impossible for any establishment (official or unofficial) to monitor the use of stents, the final responsibility for their application must surely rest on the shoulders of the interventionalists who should, in turn, use them wisely and safely.

Which stent to use?

The lucrative market for stents has suddenly created an abundance of this device in various designs and configurations, making it almost impossible for interventionalists to keep up or be familiar with them. Not all stents are built the same way; they have different characteristics and mechanical properties in terms of profiles, radial strength, flexibility, fluoroscopic opacity, recoil and interfilament spacing[2,5]. Thus, although all of the major clinical stents may be effective in correcting dissections, and as bailout measures, their restenosis rates appear different. The Wallstent is the first stent model to be used in humans and historical observational studies have proved it to be associated with a low restenosis rate but because of its somewhat high thrombosis rate, it is perhaps best suited for long lesions in large vessels such as bypass vein grafts[2]. The Gianturco-Roubin, Wiktor, Cordis, Strecker and NIR stents are highly effective for bailout situations but lack randomised studies[2]. The Palmaz-Schatz stent design is currently the only one with the most robust data in terms of proven efficacy in the prevention of restenosis[24,25].

CONCLUSION

Stents are here to stay. Their clinical utility for selected indications is no longer controversial. They are highly useful as an emergency tool in patients who develop acute or threatened closures after PTCA; they consistently confer an optimal luminal outcome and are superior to PTCA in reducing restenosis in some situations. However, being made of metal, they are associated with an increased risk of early thrombosis which, in the past, has engendered the mandatory use of aggressive anticoagulation regimen to circumvent its occurrence. The present practice of optimal stent deployment and expansion using high-pressure balloon inflations with slightly larger balloon sizes, and stringent antiplatelet therapy without warfarin (in elective stenting) has significantly reduced this risk of stent thrombosis. The elimination of warfarin and intensive heparin administration from the post-stent regimen has also decreased the bleeding and vascular complication rate substantially. Results of current research into a combined device-drug approach in which the rigid scaffold of the stent is coupled with local delivery of novel antithrombotic and antiproliferative drugs appear promising; the risk of stent thrombosis and restenosis may be further lowered. All these favourable clinical outcomes of stents have, in turn, created a tendency to overuse the device, implanting the latter indiscriminately for dubious indications which are not evidence-based. We need to be reminded that it remains our responsibility as healthcare providers to apply this technology safely, wisely and scientifically to only patients who will benefit from them and not because it yields a cosmetically appealing immediate angiographic outcome.

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