Hotline Editorial

Coronary stent implantation: a panacea for the interventional cardiologist?

Introduction

Since the introduction of balloon angioplasty in 1977 by Andreas Grünzig, the technique has gained widespread acceptance. The popularity of balloon angioplasty lies in the simplicity, safety and relative patient friendliness of this technique for treating coronary obstructions.

Many other devices (laser, atherectomy, suction, ultrasound etc.) have been introduced, most using balloon angioplasty as a platform; however, none has gained a definitive place in interventional cardiology. Balloon angioplasty is effective in the majority of cases, but suffers from an often unpredictable unfavourable immediate outcome, (as a result of acute vessel closure (<5%), and an unfavourable late outcome, a 6 month restenosis rate, which ranges from 20% (large vessels, short lesions) to 60% in unfavourable lesions (complicated, long calcific lesions in small vessels)).

Coronary stenting has been shown to be successful in more than 95% of cases in both elective stable patients and in patients with acute coronary syndromes. The two predominant indications for intracoronary stenting are: (1) the need for an effective bail-out procedure for (threatening) acute vessel closure or optimization of suboptimal balloon angioplasty, (2) as an antirestenosis device. The new third and fourth generation stents are easily and rapidly delivered and safe to use.

The availability of balloon angioplasty and intracoronary stent implantation has made percutaneous coronary intervention a rapid, safe and predictable procedure which has significantly reduced the acute procedural complication rate, and thus the need for surgical stand-by in cases of irreversible vessel closure.

Proven indications for stent implantation

Elective stent implantation has been compared to balloon angioplasty in several randomized trials setup to investigate their efficacy in reducing the rate of restenosis (Table 1)[1–12].

These trials convincingly demonstrated that stent implantation significantly reduced the restenosis rate for (1) short (<10 mm) de novo lesions in native coronary arteries, (2) isolated lesions in the left anterior descending coronary artery, (3) restenosis after balloon angioplasty in native coronary arteries, (4) de novo lesions in saphenous vein grafts and (5) chronic total occlusions. In a subanalysis it was also shown that stenting was associated with a lower restenosis rate in vessels smaller than 3 mm[6]; this finding needs support from further randomized trials.

Several randomized trials have shown that intracoronary stent implantation is more efficacious in the reduction of early reocclusion or late restenosis in the setting of direct percutaneous coronary intervention for acute ST-segment elevation myocardial infarction than balloon angioplasty (Table 2)[13–16]. Stent implantation in these patients can reduce the target vessel revascularization rate and 1-year adverse coronary events.

Stent implantation is safe and efficacious in patients with unstable angina, as has been shown in a subanalysis of the BENESTENT II trial[3] (Fig. 1).

Adjunctive pharmacological treatment during stent implantation

Adjunctive treatment with GPIIb/IIIa inhibitors has been shown to significantly reduce the acute
major complication rate of percutaneous coronary interventions, including stent implantation. In the EPISTENT trial, the combination of stent implantation and adjunctive treatment with GPIIb/IIIa abciximab was associated with a lower major complication rate than balloon angioplasty and abciximab or stent implantation with placebo[17] (Fig. 2). In addition, the combination of stent implantation and abciximab was also associated with an improved 1 year survival[18]. An extremely important observation was that the combination of stent implantation and abciximab resulted in a significant reduction of adverse coronary events at 6 months in patients with diabetes, known to have a poor outcome after balloon angioplasty[19] (Fig. 3).

### Table 1

**Elective stenting vs balloon angioplasty to reduce restenosis**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>De novo coronary lesion</th>
<th>Restenosis (%)</th>
<th>TVR (%)</th>
<th>Composite end-point (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stent</td>
<td>Balloon</td>
<td>Stent</td>
</tr>
<tr>
<td>STRESS[1]</td>
<td>407</td>
<td>32</td>
<td>42</td>
<td>10.2</td>
</tr>
<tr>
<td>BENESTENT[2]</td>
<td>516</td>
<td>22</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>BENESTENT IP[3]</td>
<td>827</td>
<td>16</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Versaci (LAD)[4]</td>
<td>120</td>
<td>19</td>
<td>40</td>
<td>na</td>
</tr>
<tr>
<td>START[5]</td>
<td>452</td>
<td>22</td>
<td>37</td>
<td>9.3</td>
</tr>
<tr>
<td>Savage[6]</td>
<td>331</td>
<td>44</td>
<td>54</td>
<td>16</td>
</tr>
</tbody>
</table>

### Restenosis coronary lesion

- **Erbel[7]**
  - Stent implantation: 383, Restenosis: 18, TVR: 32, Composite end-point: 11
  - Balloon angioplasty: 27, Composite end-point: 16
- **Savage venous bypass graft**
  - Stent implantation: 220, Restenosis: 37, TVR: 46, Composite end-point: 27
  - Balloon angioplasty: 42

### Chronic total occlusions

- **SICCO[9]**
  - Stent implantation: 117, Restenosis: 32, TVR: 72, Composite end-point: 21
  - Balloon angioplasty: 39, Composite end-point: 21
- **GISSOC[10]**
  - Stent implantation: 110, Restenosis: 32, TVR: 68, Composite end-point: 5
  - Balloon angioplasty: 22, Composite end-point: na
- **SPACTO[11]**
  - Stent implantation: 85, Restenosis: 33, TVR: 64, Composite end-point: 28
  - Balloon angioplasty: 45, Composite end-point: 30
- **TOSCA[12]**
  - Stent implantation: 410, Restenosis: 55, TVR: 70, Composite end-point: 9
  - Balloon angioplasty: 16, Composite end-point: 24

TVR=target vessel revascularization; Composite end-point=death, myocardial infarction and repeat revascularization; na=not available; LAD=left anterior descending coronary artery; STRESS=Stent Restenosis trial; BENESTENT=Belgium, Netherlands STENT trial; START=Stent And Radiation Therapy trial; SICCO=Stenting in Chronic Coronary Occlusion trial; GISSOC=Gruppo Italiano di Studio Sallo Stent nelle Occlusioni Coronariche; SPACTO=Stenting Pro Angioplasty for Chronic Total Occlusion; TOSCA=Total Occlusion Study of Canada.

### Table 2

**Stenting vs balloon angioplasty to reduce restenosis in acute coronary syndromes**

<table>
<thead>
<tr>
<th>Acute ST-segment MI</th>
<th>Patients (n)</th>
<th>Restenosis %</th>
<th>TVR %</th>
<th>MACE %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stent</td>
<td>Balloon</td>
<td>Stent</td>
<td>Balloon</td>
</tr>
<tr>
<td>Suryapranata[13]</td>
<td>227</td>
<td>na</td>
<td>na</td>
<td>4</td>
</tr>
<tr>
<td>FRESCO[14]</td>
<td>150</td>
<td>na</td>
<td>na</td>
<td>7</td>
</tr>
<tr>
<td>PASTA[15]</td>
<td>136</td>
<td>17</td>
<td>38</td>
<td>na</td>
</tr>
<tr>
<td>Stent PAMI[16]</td>
<td>900</td>
<td>21</td>
<td>34</td>
<td>8</td>
</tr>
</tbody>
</table>

TVR=target vessel revascularization; MACE= major adverse coronary event; na=not available; FRESCO=Florence Randomized Elective Stenting in Acute Coronary Occlusions trial; PASTA=Primary Angioplasty versus Stent Implantation in Acute Myocardial Infarction trial; Stent PAMI=Stent Primary Angioplasty in Myocardial Infarction Study Group.

### Stent implantation versus bypass surgery

Two randomized trials have compared stent implantation with bypass surgery using arterial conduits[20,21] (Table 3). Bypass surgery and stenting had a similar incidence of death, myocardial infarction and stroke, but the need for revascularization during the first year was still higher after stenting. However, this difference is now less than the historical difference between bypass surgery and balloon angioplasty (the need for revascularization after balloon angioplasty was about 30–40% at the 1 year follow-up) indicating again that stent implantation has reduced the occurrence of restenosis.
Late outcome after stent implantation

The long-term follow-up of stent implantation appears to be favourable despite concerns about potential metal fatigue, stent migration or chronic inflammatory stimulus. Kimura et al.\(^2\) showed, in a 3 year serial angiographic study, that although stent implantation evokes neointimal hyperplasia, which reduces the lumen width, this process stops at 6 months and even seems to improve between 1 and 3 years after implantation resulting in a wider lumen.

Also, the majority of adverse coronary events occur within 6 months of stent implantation, with very few additional events occurring later\(^{5,23,24}\) (Fig. 4).

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**Figure 1** Subanalysis of the BENESTENT-II trial, comparing the outcome of balloon angioplasty (n=79) with stent implantation (n=96) in patients with unstable angina. Events=death, myocardial infarction, CABG and rePTCA; \(p(LR)=p\) log rank test=0·003; \(p(\text{FE})=\)Fisher exact test=0·003; relative risk=0·29 [0·12, 0·70].

**Figure 2** Composite 30-day end-point — death, myocardial infarction and target vessel revascularization — of three randomized groups: stent+placebo (\(\square\), n=809), stent+abciximab (\(\blacksquare\), n=796) and balloon+abciximab (\(\square\), n=794). The results presented are of all trial patients and of a subanalysis of patients with unstable angina (UAP) <48 h and <7 days’ duration.
Direct stent implantation

Direct stenting without balloon pre-dilatation, appears a safe and highly successful (96%) procedure in selected patients, and has the advantage that it may save time, contain costs and reduce radiation exposure time[25]. Direct stenting is an attractive technique, in particular for the treatment of multiple lesions in one session and may be expected to gain great popularity in the near future.

Provisional stenting

In-stent restenosis (in particular long diffuse in-stent restenosis) is notoriously difficult to treat and is often considered a ‘malignant’ disease. This contrasts with the benign nature of balloon angioplasty restenosis, which is relatively easy to treat and has a high success rate.

This has prompted the practice of provisional stenting, whereby balloon angioplasty is performed only in cases with an optimal immediate result, and stent implantation in cases with a suboptimal result or threatening occlusion. An optimal immediate balloon angioplasty result is based on an angiographic (stent-like) appearance, or on pressure wire or Doppler wire measurements, which are reported to have an equal risk for restenosis at 6 months.

This practice is reasonable and indicated in situations where a similar or greater risk of restenosis is expected after stenting than after balloon angioplasty, even if a suboptimal balloon angioplasty result has been obtained, such as may be the case in diffuse long lesions in small vessels.

However, the issue of provisional stenting will lose much of its significance as soon as new stent designs or adjunctive treatment significantly reduces the risk of in-stent restenosis.

Stent implantation: (sub)acute occlusion, embolization and late restenosis

The combination of aspirin and ticlopidine or clopidogrel, (which appears to be safer than ticlopidine...
alone) has been shown to be very effective in the reduction of (sub)acute thrombotic occlusions of less than 2% \([25-31]\).

Distal embolization of plaque material, which may also occur during stent implantation (in particular using high pressure delivery) may be prevented by using protection devices such as Percusurge and Angioguard.

In-stent restenosis, as a result of neointimal hyperplasia, is a bothersome phenomenon which is resistant to repeat interventional treatment, irrespective of which percutaneous technique is used. In particular, diffuse in-stent restenosis ( \( \geq 20 \) mm length) has a high repeat in-stent restenosis rate (up to 40–70%). This has prompted the search for new treatment modalities such as brachytherapy. Five randomized trials have shown that brachytherapy (either using a gamma source or a beta-source) significantly reduces the repeat in-stent restenosis rate \([32-36]\) Fig. 5). However, more research is needed to provide sufficient answers and solutions to the issues of delayed healing (persistent dissections) aneurysm formation, late thrombotic

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**Figure 4** Short- and long-term outcome of stent implantation compared to balloon angioplasty demonstrated in the START (STent And Radiation Therapy) and SICCO (Stenting in Chronic Coronary Occlusion) trials. TVR=target vessel revascularization; MACE=major adverse coronary event.

**Figure 5** Randomized trials demonstrating the efficacy of either gamma-radiation or beta-radiation in reducing the repeat restenosis rate after treatment of in-stent restenosis compared to no radiation treatment. □=stent; ■=placebo. SCRIPPS=Scripps Coronary Radiation to Inhibit Proliferation Post Stenting; WRIST=Washington Radiation for In-Stent restenosis Trial; GAMMA=Gamma radiation therapy to inhibit restenosis; START=STent And Radiation Therapy.
occlusions (up to 13%; possibly reduced by longer term ticlopidine/clopidogrel treatment) or late (up to 3 years) proliferative response with restenosis in radiated segments. A 3-year follow-up study (SCRIPPS) after gamma radiation reported some late proliferative responses, whereby the minimal luminal diameter decreased by 0.37 mm between 1 and 3 years after treatment in the radiated group with no change in the placebo group. More research needs to be done on the dosage of radiation, and to which target, (endothelium, media, adventitia), and how this radiation dose must be delivered. Dose delivery may be via a beta or gamma source and will vary depending on whether the lesions are eccentric or non-centred.

Intracoronary ultrasound guidance
Application of intravascular ultrasound guidance to stent implantation indicates that larger expansion of the stent, leading to a larger cross-sectional area is possible in up to 80% of cases. This may be thought to be associated with a better 6 month outcome (less restenosis) but so far unpublished preliminary data from randomized trials (RESIST=RESstenosis In Stent Trial; OPTICUS=OPTimization with ICUS to reduce stent restenosis; AVID=Angiography Vs Intravascular Ultrasound Directed at coronary stent placement; CRUISE=Can Routine Ultrasound Influence Stent Expansion?), looking into the presumed lower restenosis rates by intravascular ultrasound as opposed to angiographic guidance, have not convincingly shown that this is the case.

Excellent clinical outcomes have been reported with the empirical use of high pressure post dilatation without ultrasound in large registries. Recently, other modalities have been proposed for guidance of optimal stenting, namely intracoronary pressure and Doppler velocity measurements, but their clinical applicability and necessity remains to be investigated in controlled trials.

Prevention of in-stent restenosis: radioactive stents
Radioactive stents may reduce in-stent restenosis. Two recently published feasibility studies have shown that implantation of radioactive stents is safe and that the restenosis rate can be reduced using higher radioactivities (3–6 μCi or 6–12 μCi) to 3% and 0% respectively. However, the price to be paid was the occurrence of severe restenosis at the edges of the radioactive stents (candy-wrapper phenomenon) which increased the intra-lesion (treated vessel segment) restenosis rate by about 50%.

This may be partly due to the occurrence of ‘geographical miss’. Geographical miss occurs if the length of the radioactive stent does not exactly match the balloon injured segment because the balloon is longer than the stent and hence may induce restenosis at the edges. This might be overcome by using a square-shouldered balloon which exactly matches the length of the radioactive stent design, in combination with a radioactive stent: the hot end stent, which has greater radioactivity at either ends of the stent, so that the vessel segment 1–3 mm proximal and distal to the stent also receives radioactivity. A self-expanding radioactive stent without balloon trauma may present an alternative solution. Another possible explanation for edge restenosis is the inevitable fall-off of radiation exposure at the edges, which may actually trigger restenosis. To correct this edge restenosis problem depends on the nature of this process: neointimal hyperplasia or negative vessel wall remodelling. Negative vessel wall remodelling can be counteracted by using different radioactive stent designs (for example a cold end stent with radioactivity in the mid portion of the stent and no radioactivity at either end). But if neointimal hyperplasia is predominantly involved then this clearly poses a significant problem with no immediate apparent solution. It may be concluded that while radioactive stenting remains a topic of great interest, there is as yet no clinical evidence of its superiority over standard stenting. Extensive and careful further study is required to reach a clinically acceptable product for everyday use in mainstream interventional cardiology.

Stent coatings
Coating of the stent with inert or active materials may reduce the frequency of restenosis. In small-sized non-randomized trials the restenosis rate is less than 10% with the use of a silicon carbide coated stent.

The results of phosphatidyl coating, evaluated in a registry, were not acceptable clinically or angiographically. It was suggested that efficacy could be enhanced in smaller vessels (<2.5 mm) and subsequently stents are now available in 2.0 and 2.5 mm sizes. Carbon coating, evaluated in a single centre study, reported unimpressive results, and is now to be evaluated further using a multicentre method. Heparin coating was associated with excellent acute results in the BENESTENT II pilot, in BENESTENT II randomized, and DEBATE=Doppler End-point Balloon Angioplasty Trial in Europe II; stenting with
this heparin-coated Palmaz-Schatz stent produced clinical restenosis in $\pm 10\%$ of patients. Currently studies are underway evaluating rapamycin and taxol stent coatings for restenosis reduction and the results of these trials are eagerly awaited.

Single figure clinical event rates at 1 year would indeed be an impressive outcome with possible immediate consequences for daily practice.

Conclusions

The combination of balloon angioplasty and stent implantation is a rapid, safe procedure, with a predictable outcome, which has already had a considerable impact on the expanding indications of percutaneous coronary intervention. These now include chronically occluded vessels, multivessel disease and left main disease\[40\]. Nowadays, percutaneous coronary intervention outnumbers bypass surgery with continued attention to improving late outcomes. This trend will continue, and it is certainly not unthinkable that percutaneous coronary intervention will replace CABG in the majority of patients within a decade.

P. J. DE FLEYER D. FOLEY
University Hospital Rotterdam Rotterdam, The Netherlands

References


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