Clinical and angiographical follow-up after implantation of a 6–12 μCi radioactive stent in patients with coronary artery disease


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Aims This study is the contribution by the Thoraxcenter, Rotterdam, to the European 32P Dose Response Trial, a non-randomized multicentre trial to evaluate the safety and efficacy of the radioactive Isostent in patients with single coronary artery disease.

Methods and Results The radioactivity of the stent at implantation was 6–12 μCi. All patients received aspirin indefinitely and either ticlopidine or clopidogrel for 3 months. Quantitative coronary angiography measurements of both the stent area and the target lesion (stent area and up to 5 mm proximal and distal to the stent edges) were performed pre- and post-procedure and at the 5-month follow-up. Forty-two radioactive stents were implanted in 40 patients. Treated vessels were the left anterior descending coronary artery (n=20), right coronary artery (n=10) or left circumflex artery (n=10). Eight patients received additional non-radioactive stents. Lesion length measured 10 ± 3 mm with a reference diameter of 3·07 ± 0·69 mm. Minimal lumen diameter increased from 0·98 ± 0·53 mm pre-procedure to 2·29 ± 0·52 mm (target lesion) and 2·57 ± 0·44 mm (stent area) post-procedure. There was one procedural non-Q wave myocardial infarction, due to transient thrombotic closure. Thirty-six patients returned for angiographical follow-up. Two patients had a total occlusion proximal to the radioactive stent. Of the patent vessels, none had in-stent restenosis. Edge restenosis was observed in 44%, occurring predominantly at the proximal edge. Target lesion revascularization was performed in 10 patients and target vessel revascularization in one patient. No additional clinical end-points occurred during follow-up. The minimal lumen diameter at follow-up averaged 1·66 ± 0·71 mm (target lesion) and 2·12 ± 0·72 mm (stent area); therefore late loss was 0·63 ± 0·69 (target lesion) and 0·46 ± 0·76 (stent area), resulting in a late loss index of 0·65 ± 1·15 (target lesion) and 0·30 ± 0·53 (stent area).

Conclusion These results indicate that the use of radioactive stents is safe and feasible, however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

Key Words: β-particles, angioplasty, radioisotope, restenosis, stent.

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Introduction

In-stent restenosis is almost exclusively caused by neointimal hyperplasia formation, which occurs due to trauma of the arterial wall, caused primarily by the stent struts and balloon dilatations[1,2].

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high-activity $^{32}$P radioactive stents may promote an ‘atheromatous' neointima by the 6-month follow-up$^{11}$. Controversially, in normal canine coronary arteries, radioactive stents result in a larger fibrin-rich neointima at follow-up, as compared to a control group$^{12}$. In patients treated with implantation of $^{32}$P radioactive stents with activities ranging from 0.75 to 12 µCi, angiographic restenosis was reported in 43–62% of the cases, with the restenosis primarily located at the edges of the stent$^{13}$. The edges represent an area where tissue is subjected both to balloon-induced trauma and a lower dose of radiation, which may stimulate edge restenosis$^{[9,14]}$. Our group reported that the implantation of a radioactive stent with an activity of 0.75 to 1.5 µCi was feasible and safe, with an in-stent restenosis rate of 17% and no occurrence of edge restenosis$^{[14]}$. The aim of this study was to evaluate the safety and efficacy of implantation of a radioactive stent, with an activity level of 6-12 µCi, in patients with single, native, coronary artery disease.

**Methods**

**Patient population**

The European $^{32}$P Dose Response Trial was a non-randomized multicentre trial to evaluate the safety and efficacy of radioactive stent implantation, with activities ranging from 1.5–3.0, 3.6 and 6–12 µCi. The data presented here is the experience of the Thoraxcenter Rotterdam.

Patients with single, native, coronary lesions, with a maximum lesion length of 28 mm (treatable with a maximum of two radioactive stents, implanted in tandem position), and objective evidence of ischaemia were eligible. Exclusion criteria were: recent myocardial infarction (creatine kinase-MB >three times the upper limit of normal, within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, clopidogrel or nickel; lesions located in the left main.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study. All patients provided written informed consent before the procedure.

**Radioactive stent, dosimetry and safety issues**

The BX$^\text{®}$ Isostent (Isostent$^\text{®}$ Inc., San Carlos, CA, U.S.A.) was implanted in this trial. It was 15 mm in length and available in diameters of 3.0 and 3.5 mm. The BX$^\text{®}$ Isostent was made radioactive by Phosphorus-32 ($^{32}$P)$^{[9]}$. The initial activity of the stents was measured and thereafter the date at which the radioactivity should have decreased to 6–12 µCi (radioactivity level suitable for implantation) was calculated. The dose delivered over 100 days at 1 mm from the stent surface was calculated for each implanted stent. All personnel were trained in the appropriate handling of radioactive materials. During implantation, the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

**Quantitative coronary angiography**

Quantitative coronary angiography was performed pre-procedure, post-procedure, and at the 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II (Cardiovascular Angiographical Analysis System, Version II) (Pie Medical B.V., Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium, which has been extensively validated and applied in numerous clinical trials$^{[15–17]}$. The following measurements were obtained in each projection for the target lesion: minimal luminal diameter, reference diameter, diameter stenosis and lesion length. Lesion length was measured by means of a computer algorithm$^{[17]}$. Procedural success was defined as %diameter stenosis <20%, measured by on-line quantitative coronary angiography. Acute gain was defined as minimal luminal diameter post-procedure minus minimal luminal diameter pre-procedure. Late loss was defined as minimal luminal diameter post-procedure minus minimal luminal diameter at follow-up. The late loss index was defined as late loss divided by acute gain$^{[18]}$. For analytical purposes, three regions of interest were defined: (1) stent area, (2) target lesion and (3) target vessel. The stent area was defined as the segment which included only the radioactive stent(s). The target lesion was defined as the stent area and 5 mm proximal and 5 mm distal to the edge of the radioactive stent. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis at follow-up, located within the target lesion. Edge restenosis was defined as >50% diameter stenosis at follow-up, located at the proximal and/or distal edge. In order to quantify an edge effect, a quantitative coronary angiography subsegmental analysis was performed in 30 patients, excluding patients with ostial lesions or occlusions pre-procedure or at follow-up. Target vessel stenosis was defined as >50% diameter stenosis at follow-up, located on any segment of the treated vessel. Quantitative coronary angiography measurements were performed by means of the CAAS II analysis system. Careful matching of the segments, encompassing the proximal and distal edges and the stent area, was performed pre-, post-procedure and at follow-up (see also Fig. 1).
Procedure and follow-up

Patients received 250 mg aspirin and 10,000 international units heparin at the initiation of the procedure. The activation clotting time was maintained at >300 s. After balloon pre-dilatation, the radioactive stent was implanted at a nominal deployment pressure of 6–18 atmospheres. Extreme care was taken to minimize the trauma at both edges by taking the following, previously published[14], precautions: the best angiographic view to optimize stent visualization was chosen and the diaphragm was used to further enhance stent imaging. If needed, stent deployment was optimized using shorter post-dilatation balloons of larger diameter, to higher pressures. All post-dilatation balloons had a radiopaque marker at each end. Images were filmed in a magnified field (5 inch), using digital zoom enhancement (3 inch) in order to avoid inflating the balloon outside the stent edges (see Table 1). All patients received either ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for 3 months after stent implantation and aspirin 80 mg daily indefinitely. Creatinine kinase and creatine kinase-MB measurements were made and the electrocardiogram was recorded at 6 and 12–18 h post procedure in all patients.

Patients returned for a 1- and 5-month clinical follow-up. An electrocardiogram was recorded at each visit.

Clinical end-points were: death, Q wave myocardial infarction (using the Minnesota code criteria[19]), non-Q wave myocardial infarction (creatinine kinase-MB rise >twice normal upper limit), target lesion revascularization (reintervention of the stent area and/or revascularization of the proximal and distal edge), target vessel revascularization (revascularization of any segment of the treated vessel), non target vessel revascularization, subacute[20] and late[21] thrombotic occlusion of the target vessel. At the 5-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischaemia on exercise testing.

**Table 1** Balloon inflation and stent deployment data

<table>
<thead>
<tr>
<th></th>
<th>Pre-dilation</th>
<th>Stent deployment</th>
<th>Post-dilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nom. size balloon</td>
<td>3.09 ± 0.43</td>
<td>3.28 ± 0.25</td>
<td>3.51 ± 0.50</td>
</tr>
<tr>
<td>Balloon length</td>
<td>16 ± 3</td>
<td>16 ± 3*</td>
<td>14 ± 2*</td>
</tr>
<tr>
<td>Stent length</td>
<td>9 ± 4</td>
<td>10 ± 3</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Pressure</td>
<td>1-06:1</td>
<td>1-17:1</td>
<td></td>
</tr>
<tr>
<td>Balloon artery ratio</td>
<td>1-06:1</td>
<td>1-11:1</td>
<td></td>
</tr>
</tbody>
</table>

*38 patients with one Isostent, two patients with two Isostents.
Data are presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student’s t-test or linear regression when appropriate.

**Results**

**Baseline characteristics**

Baseline demographics and anginal state are shown in Table 2, lesion characteristics in Table 3.

**Procedural data**

All 42 stents were successfully implanted in 40 patients. Thirty-eight patients were successfully treated with a single radioactive stent, two required a second radioactive stent to cover lesions >15 mm. Eight patients received additional non-radioactive stents due to procedural dissections. There were three transient thrombotic occlusions during the procedure, two due to dissections and one due to a combination of a dissection with a low activation clotting time. Treatment was with Reopro in one patient and a combination of ReoPro and rtPA in the other two patients. Despite the Reopro and rtPA, one non-Q wave myocardial infarction occurred, leading to a maximum creatinine kinase of 673 IU/l (normal upper limit 190 IU/l) and an MB of 78 (normal upper limit 24 IU/l). All further procedures were uncomplicated. A good final angiographical result was achieved in all patients.

**Follow-up**

The mean hospital stay was 1·7 days. All patients were angina free at hospital discharge. At the 30-day follow-up no clinical end-points had occurred. Thirty-two (80%) patients were asymptomatic, whereas eight (20%) patients had recurrent angina pectoris. All 40 patients returned for the 5-month clinical follow-up (see Table 4). Twenty-six (65%) were asymptomatic and 14 (35%) patients had angina pectoris: Canadian Cardiovascular Society 1 (n=4), 2 (n=7), 3 (n=2) and 4 (n=1). The patient in angina Canadian Cardiovascular Society 4 had chest pain with ST-elevation, during his protocol-required 5-month exercise stress test. This was treated by primary angioplasty of a non-target vessel. Creatinine kinase rose to a maximum level of 257 IU/l (normal upper limit 190 IU/l) and an MB of 30 IU/l. Since there was neither a creatinine kinase rise of more than twice the upper limit of normal, nor new Q wave formation on the electrocardiogram, this was, by definition according to the protocol, not considered as a myocardial infarction.

Two late occlusions were noted, which were both proximal to the stent at angiographic follow-up. These two patients had recurrent angina >3 months after the index...
procedure, more specifically: within 1 week of discon-
tinuation of the clopidogrel, without any signs of a
myocardial infarction. Sixteen (44%) patients (including
the two total occlusions) had angiographic edge resteno-
sis. There was no in-stent restenosis in the 34 patent
vessels. Ten of the 16 restenoses occurred in patients
treated with a single radioactive stent, two restenoses
were in patients receiving two radioactive stents, four
restenoses were observed in patients receiving a combi-
nation of one radioactive and one non-radioactive stent.

Examining the four restenotic patients who had an
additional non-radioactive stent implanted at the base-
line procedure, one had a total occlusion proximal to the
Isostent, therefore it cannot be established whether the
BX-Isostent and the distally placed non-radioactive
stent were patent. Of the remaining three patients, the
restenoses all occurred at the edge, located contralateral
to the non-radioactive stent (one implanted proximal
and two implanted distal to the Isostent), whereas the
non-radioactive stent had no restenosis. One of the
patients, treated with a radioactive stent for in-stent
restenosis, had a restenosis at follow-up. This restenosis
was located at the proximal edge. In the three patients
treated initially for a total occlusion, one restenosis and
one reocclusion occurred. Nine of the 16 restenotic
patients underwent a target lesion re-PTCA, one patient
was referred to bypass surgery because it was the third
in-stent restenosis in this patient, the remaining six were
 treated medically since these patients were both
asymptomatic and had a negative stress test.

**Quantitative coronary angiography measurements**

Quantitative coronary angiography data, as measured
for the target lesion and stent area, are presented in
Table 5. Results of the subsegmental analysis of the
stent area and the edges in a subgroup of 30 patients
are shown in Table 6. Location of the restenosis is
summarized in Table 7. Restenosis was observed to
occur more often at the proximal edge compared to the
distal edge ($P=0.02$).

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**Table 5 Quantitative coronary angiography analysis of the target lesion and stent area (n=36*)**

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesion</td>
<td>Stent</td>
<td>Lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stent</td>
</tr>
<tr>
<td>MLD</td>
<td>0.98 ± 0.53</td>
<td>2.29 ± 0.52</td>
<td>2.57 ± 0.44</td>
</tr>
<tr>
<td>%DS</td>
<td>68 ± 15</td>
<td>28 ± 11</td>
<td>18 ± 11</td>
</tr>
<tr>
<td>Ref. diam.</td>
<td>3.07 ± 0.69</td>
<td>3.17 ± 0.53</td>
<td>3.03 ± 0.46</td>
</tr>
<tr>
<td>Acute gain</td>
<td>1.31 ± 0.65</td>
<td>1.60 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>Late loss</td>
<td></td>
<td></td>
<td>0.63 ± 0.69</td>
</tr>
<tr>
<td>LLI</td>
<td></td>
<td></td>
<td>0.46 ± 0.76</td>
</tr>
<tr>
<td>Restenosis, n (%)</td>
<td>16 (44%)</td>
<td>0 (0%)</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

*Results of all 36 patients, who returned for angiographic follow-up, four patients refused.
%DS = % diameter stenosis; FU = follow-up; Lesion = target lesion (stent area and up to 5 mm
proximal and distal to the stent edge); LLI = late loss index; MLD = minimal lumen diameter;
Pre = pre-procedure; Post = post-procedure; Ref. diam. = reference diameter; Stent = stent area.
Quantitative coronary angiography measurements are in mm.

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**Table 6 Subsegmental analysis of the stent area and edges (subgroup of 30 patients*)**

<table>
<thead>
<tr>
<th></th>
<th>Prox. edge</th>
<th>Stent area</th>
<th>Dist. edge</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.52 ± 0.81</td>
<td>1.09 ± 0.48</td>
<td>2.33 ± 0.70</td>
</tr>
<tr>
<td>Post</td>
<td>2.81 ± 0.53</td>
<td>2.57 ± 0.46</td>
<td>2.37 ± 0.63</td>
</tr>
<tr>
<td>FU</td>
<td>2.65 ± 0.71</td>
<td>2.26 ± 0.52</td>
<td>2.07 ± 0.63</td>
</tr>
<tr>
<td>%DS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>17 ± 10</td>
<td>55 ± 16</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>Post</td>
<td>9 ± 4</td>
<td>17 ± 8</td>
<td>13 ± 8</td>
</tr>
<tr>
<td>FU</td>
<td>22 ± 13</td>
<td>22 ± 12</td>
<td>16 ± 12</td>
</tr>
<tr>
<td>Mean. diam.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.99 ± 0.79</td>
<td>2.45 ± 0.78</td>
<td>2.68 ± 0.80</td>
</tr>
<tr>
<td>Post</td>
<td>3.09 ± 0.55</td>
<td>3.10 ± 0.43</td>
<td>2.70 ± 0.58</td>
</tr>
<tr>
<td>FU</td>
<td>2.57 ± 0.60</td>
<td>2.89 ± 0.58</td>
<td>2.44 ± 0.57</td>
</tr>
<tr>
<td>Acute gain</td>
<td>0.29 ± 0.69</td>
<td>1.47 ± 0.52</td>
<td>0.04 ± 0.61</td>
</tr>
<tr>
<td>Late loss</td>
<td>0.76 ± 0.66</td>
<td>0.31 ± 0.56</td>
<td>0.30 ± 0.66</td>
</tr>
<tr>
<td>LLI</td>
<td>NA</td>
<td>0.23 ± 0.46</td>
<td>NA</td>
</tr>
<tr>
<td>Restenosis rate, n (%)</td>
<td>10 (33%)</td>
<td>0 (0%)</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

*Excluded from subsegmental analysis were two patients with
ostial lesions, one patient with a total occlusion pre-procedure
and three patients with total occlusions at follow-up.
%DS = % diameter stenosis; Dist. edge = distal edge; FU = follow-up;
LLI = late loss index; Mean. diam. = mean diameter;
MLD = minimal lumen diameter; NA = not applicable; Prox.
edge = proximal edge; Pre = pre-procedure; Post = post-procedure.
QCA measurements are in mm.

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**Table 7 Location of the restenosis (n=16)**

<table>
<thead>
<tr>
<th></th>
<th>Proximal edge</th>
<th>Distal edge</th>
<th>Proximal and distal edges</th>
<th>Stent area</th>
<th>Unknown (proximal occlusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 (56%)</td>
<td>4 (25%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>
Radiation doses

Stent activity level was $8.6 \pm 1.6$ $\mu$Ci at implantation, resulting in a calculated cumulative dose given over 100 days delivered to a 1 mm depth from the stent surface of $58 \pm 10$ Gy. There was no correlation between stent activity or delivered dose and minimal luminal diameter or late loss index at follow-up.

Discussion

This non-randomized study illustrates that the implantation of a 6–12 $\mu$Ci $\beta$-particle emitting radioactive stent is safe and feasible, with one procedural non-Q wave myocardial infarction and no subacute or 30-day clinical events recorded. Subacute thrombosis was not seen despite the concern of delay in endothelialization, as previously reported in animal studies. Two late occlusions were seen, which were probably late thrombotic stent occlusions, since both patients had recurrent angina, within 1 week of discontinuation of the clopidogrel. However, since both occlusions were proximal to the stent, and stent patency could not be observed at angiography, severe edge restenosis cannot be fully excluded. Therefore, it may be desirable to give patients at least 6 months of clopidogrel following radioactive stent implantation.

The Milan group has previously reported restenosis not only within the stent, but also at the edges of the stent, possibly caused by a combination of balloon injury (barotrauma) and lower radiation dose at the stent edges. In this series particular attention was paid to avoid balloon injury outside the stent, in order to minimize barotrauma at the edges. Despite these precautions, edge restenosis was seen in 44%, occurring predominantly at the proximal edge. The commonly occurring narrowing observed proximal to the edge of the stent may, in combination with a complete inhibition of neointimal proliferation inside the stent, create unfavourable rheological conditions, such as a diverging flow pattern, which in itself will perpetuate the neointimal proliferations. Careful shear stress analysis could elucidate the cause of restenosis at the proximal edge.

Since in all cases the pre-dilatation was performed with a balloon longer than the BX-Iosentent and the balloon used for stent deployment extended outside the edges of the stent, geographical ‘miss’ occurred in 100% of the cases. Since geographical miss has been shown to be one of the determinants of edge restenosis, future therapies will concentrate on the prevention of geographical miss by minimizing trauma and/or increasing radiation dose at the edges. Several new therapies are currently under investigation. Direct stenting will prevent trauma caused by pre-dilatation with balloons longer than the radioactive stent. Square shouldered balloons, used for stent deployment, in which the entire balloon remains within the stent, will minimize barotrauma at the proximal and distal edges. Cold end stents, in which the centre of the stent is made radioactive, while the proximal and distal 5 mm of the stent edges are non-radioactive may prevent edge restenosis, if this restenosis is caused by negative remodelling. The final therapeutic option is the implantation of hot end stents, in which the stent edges are made more radioactive compared to the centre of the stent. This strategy increases the dose delivered to the traumatized proximal and distal edge, thereby decreasing the chance of geographical miss.

Conclusion

These results indicate that the use of radioactive stents, with an activity of 6–12 $\mu$Ci, is safe and feasible; however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

The Wenckebach prize was awarded to P. W. Serruys by the Dutch Heart Foundation and is utilized for brachytherapy research in the catheterization laboratory. The authors appreciate the efforts of the catheterization laboratory staff, the radiation staff and the department of clinical epidemiology.

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References


