Stent design related neointimal tissue proliferation in human coronary arteries

An intravascular ultrasound study

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Aims Histological restenosis models in animals have indicated that stent design has a significant impact on vessel trauma during stent implantation and on the amount of subsequent neointimal tissue proliferation. The impact of different stent designs on intimal hyperplasia in human atherosclerotic coronary arteries has not been determined.

Methods and Results Angiographic and intravascular ultrasound studies were performed at the 6 month follow-up in 131 consecutive native coronary lesions of 131 patients treated with 50 Multi-Link®, 40 InFlow® stents and 41 Palmaz–Schatz® stents. Lumen and stent cross-sectional areas (CSA) were measured at 1 mm axial increments. Mean intimal hyperplasia cross-sectional area (stent CSA − lumen CSA) and mean intimal hyperplasia thickness were calculated. Intravascular ultrasound demonstrated different levels of intimal hyperplasia proliferation for the three stents. Mean intimal hyperplasia thickness was 0·16 ± 0·08 mm for Multi-Link stents, 0·26 ± 0·19 mm for Palmaz–Schatz stents and 0·39 ± 0·14 mm for Inflow stents (P<0·001). Multivariate analysis proved that stent type was the only independent predictor of intimal hyperplasia thickness at follow-up (P<0·001).

Conclusion Coronary stent design has a significant impact on subsequent intimal hyperplasia after implantation into atherosclerotic human coronary arteries. The corrugated ring design of the Multi-Link stent proved to result in less tissue proliferation at 6-month follow-up than the tubular slotted design of Palmaz–Schatz and InFlow stents. (Eur Heart J, 2001; 22: 2007–2014, doi:10.1053/euhj.2001.2606)

Key Words: Intimal hyperplasia, intravascular ultrasound, restenosis, stent.

Introduction Restenosis is a major limitation of stent therapy with intimal hyperplasia being the mechanism of stent restenosis[1,2]. Intimal hyperplasia has been shown to be a function of vessel trauma during stent implantation[3,4]. Animal models indicated that stent design has a significant impact on vessel trauma and the amount of subsequent intimal hyperplasia[5,6]. Smoother stent struts, a less traumatic stent expansion pattern on the intimal vessel layers and greater vessel coverage with a more evenly distributed vessel stretch have been considered to result in less intimal hyperplasia. However, new endovascular stent designs introduced into clinical practice have focused on ease and safety of the refined devices. Thus, new stent designs have been evaluated for their flexibility, tracking ability, expansion, radiovisibility and side-branch access in an attempt to obtain easier-to-use devices. Angiographic studies were used to prove equivalency of new stents designs regarding the frequency of restenosis compared with the approved Palmaz–Schatz stent[7–11].

Most angiographic studies showed no significant differences between different tubular slotted stent designs or corrugated-ring stent designs. Only the Gianturco-Roubin (GR-II) stent was shown to be
associated with higher restenosis rates compared with the Palmaz–Schatz stent\(^{[13]}\). However, these angiographic studies did not allow the direct assessment of intimal hyperplasia. While intravascular ultrasound is known to provide a very precise assessment of intimal hyperplasia, lumen dimensions and late lumen loss determined by angiography are limited in their ability to accurately reflect intimal hyperplasia growth within stents\(^{[13–15]}\). The aim of this intravascular ultrasound study was to determine whether different commonly used stent types result in differences in intimal hyperplasia at a 6-month follow-up in human atherosclerotic coronary arteries.

**Methods**

**Patients and lesions**

Patients included in this study were initially part of three other studies which required routine intravascular ultrasound follow-up at 6 months. In each study a different stent had been used: the ACS RX Multi-Link HP\(^{[9]}\) stent (Guidant, Santa Clara, CA, U.S.A.), the InFlow coronary\(^{[9]}\) stent (InFlow Dynamics, Munich, Germany) and the Palmaz–Schatz\(^{[9]}\) stent (Johnson & Johnson, Warren, NJ, U.S.A.). Lesion and patient inclusion criteria were similar for the three protocols. Coronary lesions of ≤15 mm length had to be located in a native artery of 2·5 to 4·0 mm diameter. Criteria for exclusion of a lesion were diffuse disease, left main stenosis, or location in a restenotic, ostial or bifurcated lesion. Follow-up rates were 91% for the Multi-Link stents, 88% for the InFlow stents and 92% for the Palmaz–Schatz stents. In this comparative analysis, only lesions treated with a stent 14 or 15 mm long, with follow-up angiography including intravascular ultrasound studies, were included. Subsequently, 131 consecutive lesions in 131 patients fulfilled the inclusion criteria of this study. Fifty lesions were treated with an ACS RX Multi-Link HP stent and 40 lesions with an InFlow steel stent, at the University of Aachen, Germany. Forty-one lesions were treated with a spiral Palmaz–Schatz stent at the University of Munich, Germany. There were 106 men and 25 women in the study (mean age 59.7 ± 9.7 years).

**Stent placement**

Stents were implanted according to standard protocols. The coronary lesion was pre-dilated with an undersized balloon, of 2·0 to 2·5 mm in the majority of cases, before the stent was delivered to the coronary artery. The size of the stent delivery balloon was defined by the reference vessel diameter assessed by angiography. The ACS RX Multi-Link HP stent is pre-mounted on a non-compliant high pressure balloon. It has a corrugated ring stent design. The InFlow and Palmaz–Schatz stents, which are tubular slotted stents, were manually crimped on a non-compliant high pressure balloon. The ACS RX Multi-Link HP stent and the InFlow were 15 mm long; the double spiral Palmaz–Schatz stent was 14 mm long. Stents were implanted by high-pressure (≥12 atm) balloon dilatation. The implantation technique for the Palmaz–Schatz stents deployed at the University of Munich required intravascular ultrasound-guided optimized stent deployment as described recently\(^{[10]}\).

**Angiographic analysis**

All cineangiograms were analysed by an angiographic laboratory blinded to early and late clinical outcomes. They were analysed off-line using a computer-assisted, automated, edge-detection algorithm (CAAS II System, PieMedical, Maastricht, The Netherlands) with the external diameter of the contrast-filled catheter used as the calibration standard. The minimal lumen diameter was measured in diastole before and after the intervention and at follow-up from multiple projections. The result from the single ‘worst view’ was recorded. The reference segment diameter was averaged from user-defined, 5 mm-long, angiographically normal segments proximal and distal to the lesion but between any major side branches. Lesion length was measured as the distance from proximal to distal shoulder in the projection with the least amount of foreshortening. Acute lumen gain (post-intervention minus pre-intervention minimal lumen diameter), late lumen loss (post-intervention minus follow-up minimal lumen diameter) and percent diameter stenosis (1-minimal lumen diameter/reference diameter) were calculated. Angiographic restenosis was defined as a diameter stenosis of ≥50%.

**Intravascular ultrasound imaging protocol**

All intravascular ultrasound studies were performed after intracoronary administration of 200 μg of nitroglycerin. Studies were performed using one of two commercially available systems. The first system (Cardiovascular Imaging Systems, Inc., Sunnyvale, CA, U.S.A.) used a 30 MHz single element beveled transducer, mounted on the end of a flexible shaft, and rotated at 1800 rpm within either a 2·9 F long monorail/common distal lumen imaging sheath. The second system (Endosonics, Inc., CA, U.S.A.) incorporates 64 crystals in an annular array, 20 MHz, beveled within a 3·0 F short monorail catheter. With both systems, the transducer was withdrawn automatically at 0·5 mm s\(^{-1}\) to perform the imaging sequence. The transducer was positioned approximately 10 mm beyond the stented lesion, the video recorder was turned on, the motorized transducer pullback device was activated, and imaging continued until the transducer reached the aorto-ostial junction. Intravascular ultrasound studies were recorded on 0·5 inch high-resolution s-VHS tape for off-line analysis.

Patients were studied only after giving written, informed consent. Intravascular ultrasound studies have

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Table 1  Clinical and procedural data

<table>
<thead>
<tr>
<th></th>
<th>Multi-Link (n=50)</th>
<th>Palmaz–Schatz (n=41)</th>
<th>InFlow (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.6 ± 9.9</td>
<td>60.0 ± 10.3</td>
<td>60.9 ± 7.0</td>
<td>0.7971</td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
<td>78%</td>
<td>90%</td>
<td>0.217</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16%</td>
<td>17%</td>
<td>15%</td>
<td>0.968</td>
</tr>
<tr>
<td>Smoking</td>
<td>46%</td>
<td>44%</td>
<td>40%</td>
<td>0.838</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52%</td>
<td>66%</td>
<td>60%</td>
<td>0.408</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>56%</td>
<td>68%</td>
<td>62%</td>
<td>0.488</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>18%</td>
<td>17%</td>
<td>18%</td>
<td>0.917</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>52%</td>
<td>58%</td>
<td>50%</td>
<td>0.721</td>
</tr>
</tbody>
</table>

been approved by the individual institutional review boards.

Quantitative intravascular ultrasound measurements

Motorized transducer pullback through a stationary imaging sheath permitted cross-sectional area measurements at 1 mm axial increments throughout the length of the stent. Cross-sectional area measurements by intravascular ultrasound have been previously validated[17,18]. Area measurements were performed with a commercially available programme for computerized planimetry (TapeMeasure, Indec Systems, CA, U.S.A.). The stent and lumen cross-sectional area were measured in the stented segments. At the proximal and distal reference segments only the lumen cross-sectional area was measured. Each border was routinely traced three times, and the results were averaged. If the neointimal tissue appeared to encompass the imaging catheter, the lumen cross-sectional area was assumed to be the physical size of the imaging catheter (0.9 mm²). The following calculations were then performed within the stent length:

1. Intimal hyperplasia cross-sectional area (mm²) = stent cross-sectional area – lumen cross-sectional area at follow-up
2. Mean stent diameter (mm) = 2*√(stent cross-sectional area/π)
3. Mean lumen diameter (mm) = 2*√(lumen cross-sectional area/π)
4. Mean intimal hyperplasia thickness (mm) = (mean stent diameter – mean lumen diameter at follow-up)/2
5. Mean intimal hyperplasia cross-sectional area/stent cross-sectional area.

The reference segment was defined as the most normal-looking cross section within 5 mm proximal and distal to the stented lesion, but before any major side branch. The results for each stent were averaged over the stent length to obtain mean values.

Statistics

Statistical analysis was performed using SAS (Statistical Analysis Systems, SAS Institute Inc.). Continuous data are presented as mean ± SD. Categorical data are presented as frequencies. Comparisons between groups were performed using chi-square statistics and Fisher’s exact test for categorical variables, paired and unpaired t-tests for continuous variables or factorial ANOVA. Univariate and multivariate regression analysis was used to identify predictors of intimal hyperplasia cross-sectional area and intimal hyperplasia thickness at follow-up. Variables included in the model were stent type, stent implantation pressure, maximal balloon diameter, age, gender, cardiovascular risk factors, reference vessel diameter, minimal lumen diameter before intervention and mean stent cross-sectional area. Univariate parameters with significant impact (P value <0.2) were entered into the multivariate model. A level of 0.05 was considered statistically significant.

Results

Patient and lesion characteristics

Table 1 demonstrates that there were no differences in baseline patient characteristics between patients treated with a Multi-Link stent, an InFlow stent or a Palmaz–Schatz stent. Similarly, lesion characteristics including minimal lumen diameter, reference diameter and qualitative lesion characteristics were similar between the three different stent types (Table 2).

Procedural results

The acute lumen gain was 1.80 ± 0.62 mm for the Multi-Link stent group, 1.85 ± 0.62 mm for the InFlow stent group and 2.15 ± 0.58 mm for the Palmaz–Schatz stent group. Thus, acute lumen gain was larger for the Palmaz–Schatz stent group than for the other two stent groups (Table 2), probably reflecting the result of intravascular ultrasound guidance for stent implantation with a more aggressive stent implantation technique. Both maximal implantation pressure and final balloon diameter were largest in the Palmaz–Schatz stent group.

Angiographic follow-up

Minimal lumen diameter, percent diameter stenosis, late lumen loss and restenosis rate were not significantly

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different between the different stent groups (Table 3). There was a trend towards a higher late lumen loss and greater restenosis rates for the InFlow stent group. However, a sample size of 1350 cases is necessary for each stent group to prove a significant difference in late lumen loss between the Multi-Link stent and the Palmaz–Schatz stent at an α of 0.05 with a power of 90% if the difference in late lumen loss between both stents is only 13% of the standard deviation of each group as observed in this study.

Intravascular ultrasound results

Intravascular ultrasound measurements demonstrated similar reference vessel cross-sectional areas for the three study groups. Minimal stent cross-sectional area as well as mean stent cross-sectional area were similar for the Multi-Link and InFlow stents. For the Palmaz–Schatz stent both minimal and mean stent cross-sectional area were larger (Table 4). Minimal and mean lumen cross-sectional area were largest at follow-up for the Palmaz–Schatz stent and smallest for the InFlow stent. The smaller lumen cross-sectional areas for the InFlow compared with the Multi-Link, in spite of similar stent cross-sectional areas, were due to more intimal hyperplasia. There was a significant difference between the three stent groups in mean intimal hyperplasia cross-sectional area (Table 4). Mean intimal hyperplasia cross-sectional area was 112% larger for the InFlow compared to the Multi-Link (P<0.001) and 30% larger for the InFlow compared to the Palmaz–Schatz (P=0.007). Mean intimal hyperplasia cross-sectional area for the Palmaz–Schatz stents was 62% larger than for the Multi-Link stents (P<0.001). The mean lumen cross-sectional area at follow-up remained larger in the Palmaz–Schatz group because of significantly greater stent expansion. The greater intimal hyperplasia cross-sectional area translated into a greater intimal hyperplasia thickness for the InFlow compared to the other stent types, while intimal hyperplasia thickness were smallest for the Multi-Link (Table 4).

Segmental analysis demonstrated that intimal hyperplasia reaction was uniformly greater over the entire stent length for the InFlow compared to the Palmaz–Schatz and the Multi-Link (Fig. 1). A similar result was found for intimal hyperplasia thickness (Fig. 2). Furthermore, segmental analysis demonstrated that

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Table 2 Baseline angiographic data

<table>
<thead>
<tr>
<th>Vessels</th>
<th>Multi-Link</th>
<th>Palmaz-Schatz</th>
<th>InFlow</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>21/50 (42%)</td>
<td>20/41 (49%)</td>
<td>18/40  (45%)</td>
<td>0.911</td>
</tr>
<tr>
<td>LCX</td>
<td>9/50 (18%)</td>
<td>8/41 (20%)</td>
<td>6/40   (15%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>20/50 (40%)</td>
<td>13/41 (32%)</td>
<td>16/40  (40%)</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA lesion type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>8/50 (16%)</td>
<td>6/41 (15%)</td>
<td>9/40   (36%)</td>
<td>0.838</td>
</tr>
<tr>
<td>B</td>
<td>39/50 (78%)</td>
<td>31/41 (76%)</td>
<td>28/40  (70%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3/50 (6%)</td>
<td>4/41 (10%)</td>
<td>3/40   (8%)</td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>9.7 ± 2.7</td>
<td>10.5 ± 3.5</td>
<td>8.9 ± 3.3</td>
<td>0.181</td>
</tr>
</tbody>
</table>

Table 3 Angiographic data at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Multi-Link</th>
<th>Palmaz-Schatz</th>
<th>InFlow</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter (mm)</td>
<td>2.99 ± 0.46</td>
<td>3.02 ± 0.48</td>
<td>3.11 ± 0.58</td>
<td>0.538</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.80 ± 0.45</td>
<td>0.90 ± 0.46</td>
<td>1.03 ± 0.44</td>
<td>0.067</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>72 ± 18</td>
<td>70 ± 15</td>
<td>67 ± 15</td>
<td>0.442</td>
</tr>
<tr>
<td>Post-intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.16 ± 0.46</td>
<td>3.34 ± 0.47</td>
<td>3.26 ± 0.50</td>
<td>0.191</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>2.83 ± 0.42</td>
<td>3.07 ± 0.55</td>
<td>2.88 ± 0.50</td>
<td>0.083</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>10 ± 9</td>
<td>8 ± 9</td>
<td>11 ± 11</td>
<td>0.468</td>
</tr>
<tr>
<td>Acute diameter gain (mm)</td>
<td>1.88 ± 0.62</td>
<td>2.15 ± 0.58</td>
<td>1.95 ± 0.62</td>
<td>0.444</td>
</tr>
<tr>
<td>Maximal implantation pressure (atm)</td>
<td>14.1 ± 3.4</td>
<td>14.9 ± 2.8</td>
<td>13.5 ± 2.0</td>
<td>0.161</td>
</tr>
<tr>
<td>Balloon diameter (mm)</td>
<td>3.31 ± 0.33</td>
<td>3.40 ± 0.29</td>
<td>3.22 ± 0.34</td>
<td>0.061</td>
</tr>
</tbody>
</table>

LAD=left anterior descending coronary artery; LCX=left circumflex artery; RCA=right coronary artery.
intimal hyperplasia was slightly greater at the centre of the stent and smaller at the stent edges. This pattern was similar for all three stent types.

**Predictors of intimal hyperplasia**

Univariate predictors of intimal hyperplasia cross-sectional area were stent type \((P<0.001)\) and mean stent cross-sectional area \((P<0.001)\). Multivariate analysis confirmed that stent type \((P<0.001)\) and mean stent cross-sectional area \((P<0.001)\) were predictors of intimal hyperplasia cross-sectional area. Univariate predictors of intimal hyperplasia thickness were diabetes \((P=0.0282)\) and stent type \((P<0.001)\). The only multivariate predictor of intimal hyperplasia thickness at follow-up was stent type \((P<0.001)\).

**Discussion**

This angiographic and intravascular follow-up study on three different stent types implanted in atherosclerotic human coronary arteries demonstrated (1) significant disparities in intimal hyperplasia cross-sectional area and intimal hyperplasia thickness between the three analysed stent types at the 6 month follow-up, (2) that absolute differences in intimal hyperplasia thickness between the stent types were small compared to the lumen diameters measured within the stents, (3) that the pattern of intimal hyperplasia distribution over the entire stent length was similar for the evaluated stent types, and (4) failure of angiography to show significant differences between the stents.

**Animal models of stent restenosis**

An association between the degree of arterial injury and subsequent tissue proliferation could be shown in a porcine coronary overstretch restenosis model. The relationship between the degree of arterial injury and subsequent tissue proliferation was explained by a more pronounced inflammatory reaction resulting in more intimal hyperplasia in cases of greater vessel injury\(^{[19]}\). The stent design was demonstrated in animal restenosis.
models to have an important impact on stent–vessel interaction and the degree of vessel injury. The stent design determines (a) the endothelial denudation during stent expansion and (b) the degree by which stent struts incise the vessel wall with deeper stent strut penetration generating a more severe inflammatory response. Less vessel injury during stent implantation was attributed to less shear forces on the intimal layers during stent expansion, especially at the stent strut intersections, smoother stent struts and a greater vessel wall coverage. Rogers et al.[5] demonstrated that corrugated ring stents achieve the same initial lumen diameter as slotted tubular stents, but impose a 42% ($P<0.0001$) lower arterial injury score. This resulted in 38% less neointimal hyperplasia. These results were confirmed in a finite element analysis showing that high inflation pressures, wider stent–strut openings, and more compliant balloon materials cause more vascular injury during stent implantation[19]. Barth et al.[6] demonstrated in an animal restenosis model using Palmaz–Schatz stents, tantalum Strecker stents and wallstents that the tantalum Strecker stent is affected by significantly greater neointima formation. Recently, Garasic et al.[20] demonstrated that stent geometry has an important impact on intimal thickening, even independent of arterial injury. A two-fold greater neointimal area was observed if stents with 8 instead of 12 struts per cross-section were used, confirming again in an animal model that stent design has an important impact on intimal hyperplasia.

**Clinical trials on angiographic restenosis**

Although histological studies indicated design dependence in stent restenosis, there is still controversy as to whether results of restenosis models can be translated into the clinical setting of human atherosclerotic coronary arteries. Various levels of angiographic restenosis have been reported for different stent types. Restenosis rates of 9–7% to 30% were reported for the Palmaz–Schatz stent deployed in so-called ‘BENESTENT-STRESS’ lesions[7,8,16,21]. Low restenosis rates have been reported for the Multi-Link stent in the WEST-I and WEST-II trials[22,23]. A recent study on the InFlow study demonstrated a restenosis rate of 38% for the InFlow steel stent, with an even higher restenosis rate for the InFlow gold-coated stent[24]. Thus, a high restenosis rate was reported for this stent even if it is considered that more complex lesions were included in the study. While these differences in stent restenosis rates may indicate a discrepant vessel response to different stent types, there is only a limited number of stent restenosis studies with direct comparison of stents. Clinical trials performed to date comparing stents did not, with the exception of Gianturco-Roubin II (GR-II) data, demonstrate a significant difference in angiographic parameters of restenosis including the minimal lumen diameter, the late loss or the binary restenosis rate between different stent designs[9–12]. The failure of most angiographic comparison studies to translate results of animal models to human clinical trials might be due to different reasons: (1) the experimental animal restenosis model, with controlled vascular injury induced to a non-diseased vessel, behaves differently from the complex human coronary lesion; (2) differences in biological reaction are too subtle to be detected in clinical studies evaluating clinical event rates and angiographic restenosis rates; (3) other factors, such as lesion morphology and deployment strategy dilute the effect of different stent designs; (4) angiography allows only the determination of late loss at follow-up while angiography does not give direct access to the measurement of intimal hyperplasia. Thus,

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**Figure 2** Plot of the mean ± SD of the follow-up intravascular ultrasound intimal hyperplasia thickness over the entire stent length in 1 mm axial increments for the three stent types. ● = InFlow; ▲ = Palmaz–Schatz; ● = Multi-Link.
it is rather insensitive for the detection of differences in tissue proliferation. The sample size of 1350 cases per group necessary to demonstrate a difference in late lumen loss between the Multi-Link and Palmaz–Schatz stents calculated from the angiographic results of this study gives evidence of the insensitivity of the method in determining differences in tissue proliferation between stents. Clinical trials comparing different stent types had smaller sample sizes. This might explain the failure of most clinical angiography-based studies to demonstrate differences between stents in the intimal hyperplasia reaction. In contrast, taking the same basis for a calculation related to the use of intravascular ultrasound would have resulted in a sample size of 37 to show a difference between Multi-Link and Palmaz–Schatz stents and an even smaller sample size to show a difference between Multi-Link and InFlow stents.

**Stent dependent intimal hyperplasia**

Significant differences in intimal hyperplasia proliferation between the evaluated stent types could be demonstrated in this intravascular ultrasound follow-up study. Absolute differences in intimal hyperplasia thickness between the evaluated stents were small compared with the lumen dimensions achieved within the stents. However, there were great relative differences in intimal hyperplasia thickness, with a 112% greater intimal hyperplasia thickness for the InFlow compared with the Multi-Link. Considering the small absolute differences in intimal hyperplasia thickness, the binary angiographic restenosis rate is a rather insensitive parameter with which to determine differences in intimal hyperplasia proliferation induced by different stent types. Restenosis rates are largely determined by the obtained final stent dimensions. In this study, the restenosis rate was slightly lower in the Palmaz–Schatz stent group compared with the Multi-Link stent group, probably due to intravascular ultrasound guided stent implantation, with a more aggressive stent implantation technique resulting in greater final stent dimensions, in spite of greater intimal hyperplasia thickness in the Palmaz–Schatz stent. Late lumen loss determined by angiography is known to over-estimate late loss compared to intravascular ultrasound measurements and to poorly correlate with intimal hyperplasia. In contrast, the intimal hyperplasia thickness, determined by intravascular ultrasound allows a more accurate assessment of tissue proliferation induced by the stent type, which is independent of the obtained stent dimensions. The intimal hyperplasia thickness as well as the intimal hyperplasia cross-sectional area/stent cross-sectional area ratio, which both correct for different lumen sizes of stents and are therefore ideal parameters for an accurate assessment of the vessel reaction after stent placement, confirmed a difference in intimal hyperplasia reaction between the three stent types. Intravascular ultrasound has been proven to be a method with excellent accuracy in the determination of lumen dimensions and intimal hyperplasia proliferation within stents. It was concluded that studies using intravascular ultrasound endpoints require much smaller sample sizes to show differences in tissue proliferation between different stent treatment strategies than studies using clinical endpoints or angiography to determine lumen dimensions.

**Limitations**

This has not been a randomized study. However, due to the inclusion criteria lesion and patient characteristics were similar between the three stent groups. The stent length was similar for the three groups. In each group consecutive lesions were studied. Thus, factors to explain the difference in observed intimal hyperplasia, apart from the stent type, have been minimized. Stent expansion reflected as stent cross-sectional area was larger for stents of the Palmaz–Schatz group compared to the other two groups. This was the consequence of the controlled, aggressive, intravascular ultrasound stent implantation technique used for this stent type. We cannot rule out that this different implantation strategy yielded higher neointimal proliferation by itself. However, this aspect does not come into consideration for the comparison between the Multi-Link and the InFlow stents. InFlow and Palmaz–Schatz stents were manually crimped on the deployment balloon, while Multi-Link stents were pre-mounted on a delivery balloon. Manual crimping of stents on a deployment balloon potentially results in distortion of the stent structure with subsequently greater trauma to the vessel. The impact of manual crimpling of stents on the delivery balloon as compared to mechanical mounting still has to be determined.

**Conclusions**

Stent design has an important impact on the intimal hyperplasia response to coronary stents implanted in atherosclerotic human coronary arteries. The corrugated ring stent design of the Multi-Link was found to result in the smallest tissue response. Stent design considerations, which take vessel injury induced by the stent into account, should give greater attention to reducing stent restenosis. Thus, stent design should incorporate minimal vessel trauma in addition to improved stent delivery and safety.

**References**


