A Randomised Trial of Endoluminal Reconstruction Comparing the NIR Stent and the Wallstent in Angioplasty of Long Segment Coronary Disease: Results of the RENEWAL Study

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Background The role of coronary stents in reducing the incidence of acute complications and late restenosis after angioplasty has been established in randomized studies focusing on simple, short coronary lesions. The development of long coronary stents has provided a safe and predictable means of treating long coronary lesions, but this carries with it a higher risk of restenosis. By comparing the outcome of treating long lesions with two different stent types, we aimed to assess the influence of stent design rather than the nature of long lesions per se on the relatively high restenosis rates in this subgroup.

Methods This study was designed to assess procedural complications and 6-month restenosis rates in a randomized trial comparing a slotted tube stent with a self-expanding stent for the treatment of long coronary lesions. Randomization of vessels to either stent occurred after successful balloon angioplasty. Intravascular ultrasound (IVUS) was used to assess and optimize stent deployment. The patients were restudied angiographically and by IVUS at 6 months.

Results A total of 82 patients (85 vessels) were recruited (slotted tube stent, n = 44 vessels; self-expanding stent, n = 41 vessels). Successful deployment occurred in 41 (100%) of 41 of the self-expanding stent group and 41 (93%) of 44 of the slotted tube stent group. There was no difference in lesion length between the two groups (slotted tube stent, 26.6 ± 6.9 [SD] mm; self-expanding stent, 28.7 ± 9.8 [SD] mm, P = .2), but the mean length of the self-expanding stent was greater than that of the slotted tube stent (41.6 ± 18.8 [SD] mm vs 35.4 ± 16.2 [SD] mm, respectively; P < .05). There was no significant difference in the rate of major events between the two groups at 6-month follow-up. The angiographic restenosis rate at follow-up was less in the slotted tube stent group, but this did not reach statistical significance (26% vs 46%, respectively; P = .1) and the target lesion revascularization rate was similar for both groups (7.9% vs 7.7%, respectively; P = .8). IVUS assessment of plaque/stent ratios suggested a greater plaque burden in the self-expanding stent compared with the slotted tube stent at follow-up (0.42 ± 1.2 [SD] vs 0.3 ± 0.08 [SD]), but this was not statistically significant (P = .1).

Conclusions Long stents can be safely and successfully deployed in long segment coronary disease, with an acceptable 6-month target lesion revascularization rate. Our results showed a trend toward lower angiographic restenosis and a lesser in-stent plaque burden at follow-up in the slotted tube stent compared with the self-expanding stent. This suggests that stent design may influence the restenotic process in long coronary lesions. [Am Heart J 2001;141:971-6.]
ber of longer stents have become available, but there are no data from controlled trials to support their use.

It remains unclear whether the higher restenosis rates associated with long stents are primarily related to the inherently complex nature of long lesions or to the actual design of the stents used to treat them.

We have performed a randomized trial to compare the immediate and long-term clinical and angiographic results of using the NIR stent (Boston Scientific, Galway, Ireland) (slotted tube) with the Wallstent (self-expanding mesh) for the treatment of patients with long segment native coronary artery disease (>20 mm in length).

Methods

Patients

All patients enrolled in this study gave fully informed consent. The study had the approval of our local ethics committee and was conducted in keeping with the declaration of Helsinki.

From October 1996, all patients with stable or unstable angina who were seen at our institution were considered for entry into this study. We excluded patients with long segment disease in coronary vessels <3 mm in diameter assessed by quantitative coronary analysis. There were no specific exclusion criteria for age, left ventricular ejection fraction, coronary morphology, or associated coronary risk factors.

Stent implantation

Patients with a de novo lesion in a native coronary artery >20 mm in length were considered eligible for inclusion in this study. The operator had to agree at the outset that either a Wallstent or an NIR stent would be suitable for deployment. Patients received 300 mg aspirin before the procedure and 10,000 units heparin was administered after insertion of the femoral arterial sheath. Vessels were randomized to receive either an NIR or a Wallstent after successful angioplasty and before elective stent insertion. Before the availability of the premounted NIR stent, the first 19 NIR stents had to be hand-crimped onto a balloon.

In vessels randomized to receive a Wallstent, the diameter of stent chosen was oversized by 0.5 mm from quantitative coronary analysis of the reference vessel diameter. All stents were deployed at relatively high pressures (14 to 16 atm). Intravascular ultrasound (IVUS) was performed only once a satisfactory angiographic result was achieved by the operator. Any further intervention was guided by IVUS assessment.

All patients received ticlopidine for 2 weeks (250 mg twice daily for first week, 250 mg daily for second week), in addition to low-dose aspirin (75 mg/d). No further heparin was given after the procedure, and no patients received glycoprotein IIIb/IIa inhibitors.

Quantitative coronary angiography

All coronary angiograms were assessed by two independent observers. During this trial, our catheter laboratory was upgraded from a 35-mm cinesystem to CD-based digital technology. Cinefilms were analyzed with a PC-based frame digitizer and a validated angiographic analysis package with an edge-detection algorithm (Cine Graphics Inc, Grand Prairie, Tex). Angiograms acquired on digital recordings were analyzed with the Quancor coronary analysis package (Siemens Medical Inc, Berke, UK).

All measurements were made from end-diastolic frames. The index vessel was pretreated with 1 mg isosorbide dinitrate (Isoket, Schwartz Pharma) before acquisition. Follow-up angiography was performed by the same methods, with matched angiographic views.

The minimal luminal diameter (MLD) within the stented area and the reference diameters of the normal vessel immediately proximal and distal to the stented segment were measured. Restenosis was defined as intimal hyperplasia within the stented segment, or the segment 5 mm proximal or distal to it, which is evident more than 14 days after the procedure, and leading to a follow-up MLD of <50% of the mean of the proximal and distal reference segments. The pattern of in-stent restenosis was defined as diffuse or focal.

The mean of the two independent observers’ calculations was then taken as the final result.

IVUS assessment

After PTCA and stent deployment, a 0.014-inch, high-torque floppy guide wire was passed into the stented artery to allow passage of an UltraCross 2.9F, 30-MHz coronary imaging catheter (Boston Scientific) to the distal portion of the stented segment, which was then pulled back (slow manual pullback or motorized pullback at 0.5 mm/s) through the stented segment, with continuous recording onto super-VHS videotape for subsequent analysis. In cases in which our assessment showed suboptimal stent deployment, further in-stent balloon dilatation with larger balloons and/or higher inflation pressures was carried out to maximize stent expansion and optimize apposition against the vessel wall.

Plaque and stent volume calculations

Automated pullback recordings were analyzed with a dedicated PC-based system (Echoplaque, Indec Systems, Inc, Boston Scientific), which uses edge-detection and signal density analysis to calculate plaque volume. Stent volume was determined with the same package, by manual tracing of the stent boundary on IVUS cross sections at 0.5-mm intervals. The data were then expressed as a ratio of plaque to stent volume.

Clinical events

Acute stent thrombosis was defined as the development of occlusive thrombus within the stented segment, after the removal of the guide catheter but within the first 12 hours after the procedure. Subacute stent thrombosis was defined as the development of occlusive thrombus after 12 hours but within 14 days of the primary interventional procedure. Target lesion revascularization was defined as a further percutaneous interventional procedure or coronary artery bypass graft surgery to the target vessel as a result of symptomatic restenosis of the target segment. Myocardial infarction was diagnosed in the presence of any two of the following: a clinical episode of chest pain >20 minutes in duration, suggestive of myocardial infarction; the development of new pathological Q waves in 2 or more contiguous leads on the resting 12-
lead electrocardiogram; and a rise in the serum creatine kinase level to twice the upper limit of normal (150 mmol/L). Major adverse cardiac events were defined as Q-wave myocardial infarction (QWMI), death (irrespective of cause) and emergency coronary artery bypass surgery (CABG) within 1 month.

Follow-up

All patients attending for follow-up underwent clinical and invasive assessment at 6 months. Patients were evaluated by coronary angiography performed in views matched to those taken at the time of stent deployment. IVUS was attempted in all cases studied in this way at the time of intervention to assess the mean in-stent area and degree of intimal hyperplasia, in addition to the analysis of the ratio of plaque volume to final stent volume.

Statistical analysis

Continuous data are expressed as mean ± SD and categoric data as frequencies (percentages). The Student t test was used in group comparisons for continuous variables and Pearson χ² test for categoric variables. A value of P < .05 was considered statistically significant. Data analysis was performed with the StatView software package (Abacus Concepts, Inc, Berkeley, Calif).

Results

The two groups were well matched for age, sex, angina class, and vessel site (Table I).

Angiographic outcome immediately after stent deployment

The length of stent (mean ± SD) deployed was significantly greater in the Wallstent group (41.6 ± 18.8 mm; range, 24 to 125 mm) compared with the NIR stent group (35.4 ± 16.2 mm; range, 25 to 104 mm) (P < .05). However, there was no significant difference in lesion length between the two groups (NIR group, 26.6 ± 6.9 mm; Wallstent group, 28.7 ± 9.8 mm) (Table II). There were no significant differences between the NIR and Wallstent groups in MLD at baseline (1.26 ± 0.69 mm vs 1.19 ± 0.86 mm, respectively; P = .68) or immediately after stent deployment (2.98 ± 0.53 mm vs 3.11 ± 0.48 mm, respectively; P = .8).

IVUS assessment was performed successfully in 70 (82%) of 85 vessels. In the remaining 15 cases, IVUS was not performed because of patients requesting follow-up at their local district hospitals (which did not have access to IVUS) or, in a small number of cases, because of technical equipment difficulties. In 20 cases (10 in each group), IVUS demonstrated poor apposition of the stent to the vessel wall, and further balloon dilatation had to be performed to optimize the final result.

Procedural events

Forty-four vessels in 43 patients were randomized to receive a long NIR stent (1 patient had 2 vessels randomized to receive an NIR stent). In 3 cases, the hand-crimped 32-mm NIR stent could not be deployed because of excessive vessel tortuosity proximal to the lesion. This led to abrupt vessel closure in 1 case, which was resolved with the deployment of 2 long Wallstents. In the other 2 cases, a Wallstent was electrolytically placed without complication.
Forty-one vessels in 39 patients were randomized to receive a Wallstent. In one case there was abrupt vessel closure on deployment of the Wallstent, which, despite further prolonged attempts to reopen the vessel, led to a Q-wave infarction. In all other cases, there were no immediate procedural complications with stent deployment (Table III).

Clinical events at 30 days

One patient who had a successfully deployed Wallstent in a large right coronary artery, with excellent angiographic and IVUS results, had subacute stent thrombosis on day 3 with development of a QWMI (Table III).

Clinical events at 6 months

A total of 75 patients (37 patients in the NIR group and 38 patients in the Wallstent group) were followed up for a mean of 26.6 weeks (range, 21 to 34 weeks).

In the NIR stent group, 4 patients did not attend for angiographic follow-up. Two patients had QWMIs at 3 and 4 months, respectively. Melanoma developed in a third patient, who was undergoing chemotherapy during the follow-up period; the fourth patient declined to attend for personal reasons. Neither of the last two patients had a significant clinical event in the intervening period. Therefore, 39 (95%) of 41 eligible vessels were restudied at 6 months (Table III).

Angiographic outcome at 6 months

Angiographic restenosis occurred in 10 (26%) of 38 patients in the NIR group and 18 (46%) of 39 in the Wallstent group. In the NIR stent group, 3 patients required further treatment of the target vessel. One patient underwent CABG surgery with a left internal mammary artery graft to a restenotic lesion in the left anterior descending coronary artery. One patient had unstable angina at 3 months, requiring urgent angioplasty for severe diffuse in-stent restenosis. One patient underwent PTCA for in-stent restenosis for stable anginal symptoms.

Of the Wallstent group, 3 patients had class II stable angina requiring further percutaneous intervention. One patient underwent lesion debulking with high-speed rotational atherectomy followed by PTCA, and the other two patients proceeded directly to PTCA. The pattern of restenosis was similarly distributed within the two groups, with diffuse restenosis being the predominant pattern (NIR stent, 70%; Wallstent, 72%) (Table IV).

Subanalysis on intention-to-treat basis

Of the 3 patients initially randomly assigned to receive a Wallstent, 2 patients had QWMI and were excluded from further analysis. One patient who was eligible for 6-month follow-up refused coronary angiography but was able to provide his clinical data by telephone. He had not had a significant clinical event in the intervening period. Therefore, 39 (95%) of 41 eligible vessels were restudied at 6 months (Table III).

| Table III. Major adverse cardiac events in-hospital and after discharge |
|-----------------|-----------------|
|                  | NIR (n = 44 vessels) | Wallstent (n = 41 vessels) |
| **Procedural events** |               |                        |
| Transient AVC    | 1 (2.3%)         | 0                       |
| Permanent AVC    | 0                | 1 (2.4%)                |
| **Events at 30 d** |               |                        |
| Death            | 0                | 0                       |
| Repeat PTCA      | 0                | 0                       |
| CABG             | 0                | 0                       |
| QWMI             | 1 (2.3%)         | 2 (4.8%)                |
| **Events at 6 mo** |               |                        |
| Death            | 0                | 0                       |
| Repeat PTCA      | 1 (2.6%)         | 0                       |
| CABG             | 2 (5.3%)         | 3 (5.9%)                |
| QWMI             | 2 (5.3%)         | 2 (5.1%)                |

| Table IV. Angiographic outcome at 6 months |
|-----------------|-----------------|
|                  | NIR (n = 38)    | Wallstent (n = 39)   |
| **Target lesion** | 7.9% [3/38]*    | 7.7% [3/39]†        |
| **Angiographic restenosis** | 26% [10/38]    | 46% [18/39]         |
| **Mean MLD ± SD** | 1.99 ± 0.78     | 1.68 ± 0.73         |
| **Diffuse restenosis** | 7/38 [18.4%]  | 13/39 [33.3%]       |
| **Focal restenosis** | 5/38 [13.2%]   | 5/39 [12.8%]        |

*1 CABG, 2 repeat PTCA.
†1 Rotablator (Boston Scientific), 2 PTCA.
Therefore, there was no difference in outcome when analyzing the data on an intention-to-treat basis from that outlined in Table IV.

**IVUS assessment data**

Twenty-eight vessels in each group had a successful motorized pullback of sufficient quality to undergo analysis at 6-month follow-up.

The mean in-stent cross-sectional area (MISA) (± SD) at 6 months was compared with that obtained immediately after stent deployment (Table V). This showed that the Wallstent had further expanded from an MISA of 7.66 mm² (± 1.80) to 9.25 mm² (± 1.25), whereas the MISA for the NIR stent remained relatively constant at 8.15 mm² (± 1.84) after deployment and 7.90 mm² (± 0.96) at 6 months. However, this was offset by a greater degree of in-stent intimal proliferation, as reflected by a higher plaque/stent volume ratio in the Wallstent group (0.42 ± 1.2) compared with the NIR stent group (0.30 ± 0.08), although this difference did not reach statistical significance ($P = .1$).

**Discussion**

The treatment of long segment coronary artery disease continues to present a challenge to both the interventional cardiologist and the cardiac surgeon. Surgical endarterectomy gives disappointing results, and enthusiasm for PTCA has been curtailed by relatively high restenosis rates in this lesion subset. The evolution of coronary stenting provides a potentially useful tool to deal with long segments of coronary atheroma and the rapid expansion in the variety of long stents has led to an enthusiastic increase in their use. However, there are no randomized controlled trial data to support the use of stents in the treatment of patients with long segments of diffuse coronary disease. Multiple shorter stents have been used safely to cover longer coronary lesions, but at the expense of a high restenosis rate.16,17

The first long stent to become available was the Wallstent.18 We have had substantial clinical experience with the Wallstent and have shown that it is possible to treat long coronary lesions with a low procedural complication rate, but at the expense of a significant angiographic restenosis rate of 40%.10 It remains unclear, however, whether this high restenosis rate was attributable to the morphology and length of the initial coronary lesion or whether it is the actual degree of the stent that is the predominant contributing factor.

Our randomized trial of the two distinct and frequently used stent designs of the Wallstent (self-expanding mesh) and the NIR stent (slotted tube) attempts to address this issue. In three cases, we were unable to deploy a long NIR stent due to vessel tortuosity. In each of these cases, the NIR stents had to be hand-cramped by the operator, and this may have been an important factor in explaining the lack of stent flexibility. When premounted NIR stents became available halfway through the study, there were no subsequent failures of NIR stent passage and deployment. Our protocol allowed crossover to the Wallstent, which was subsequently deployed in all three cases. All Wallstents randomized to that group were successfully deployed.

IVUS was performed only once a satisfactory angiographic result was achieved by the operator. In 28.6% of cases (10 in each group), IVUS revealed constrained and submaximally expanded stents that required further dilatation with larger and/or higher inflation pressures to optimize stent apposition to the vessel wall. This finding highlights the potential shortfalls of angiographic assessment of stent deployment in complex, long coronary lesions. The clinical implication is that angiographic assessment alone is sometimes insufficient to accurately determine the adequacy of stent expansion and therefore would support the selective use of IVUS to optimize stent deployment.19

The rates of major adverse events were similar for both stent types, both in the hospital and at 6-month follow-up. Assessment of Canadian Cardiovascular Society angina status showed a similar improvement in symptoms between the two groups at follow-up.

Our data did not demonstrate a statistically significant difference in acute angiographic outcome between the two different stent groups. There was a trend toward a higher angiographic restenosis rate in the Wallstent group ($P = .1$). This might be explained by the significant difference in deployed stent length between the two groups, despite there being no difference in the actual lesion length. However, the volume of restenotic intimal plaque, expressed as a ratio of stent volume, reflects the plaque burden within the stent independent of its length. Analyzed in this way, our data suggest that there is a trend toward increased intimal hyperplasia in relation to the Wallstent. It is possible that the greater metal coverage with the Wallstent is an important factor in determining the hyperplastic response or that our practice of slightly oversizing the

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<thead>
<tr>
<th>Table V. IVUS assessment data</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>MISA (mm²) ± SD after stent deployment</td>
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<tr>
<td>MISA (mm²) ± SD at 6 mo</td>
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<td>Plaque/stent volume ratio at 6-mo follow-up</td>
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<td>Mean ± SD</td>
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There is no evidence of stent recoil in either group; there is a suggestion of greater plaque burden within the Wallstent at 6 months.
Wallstent may exert continual stretch on the arterial wall, which in turn leads to an exaggerated intimal response.

Despite the relatively high angiographic restenosis rates in both stent groups, the majority of these patients were asymptomatic and thus did not warrant further intervention, hence the disproportionately low target revascularization rates in both groups. The phenomenon of asymptomatic angiographic in-stent restenosis is difficult to explain but is unlikely to be a feature of stent design alone.

This study was limited by the size of the randomized groups. The calculations for the size of the study were made by using our known angiographic restenosis rate for the Wallstent (40%) and from our initial experience with the long NIR stent suggesting a lower restenosis rate of approximately 20%. Whereas the differences were not statistically significant at a level of 5%, there was a clear trend toward less restenosis in the NIR stent population.

One of the advantages of having a variety of stents readily available in the catheter laboratory is that appropriate stents can be specifically selected for individual coronary lesions. It may well be possible to modify and improve the restenotic process in long lesions after successful stent deployment. Better understanding of the complex interactions of the lesion-stent interface may see further improvements in minimizing plaque hyperplasia and clinical restenosis, which does not seem to be a uniquely intrinsic property of lesion length and complexity per se but may also be significantly influenced by stent design.

References

9. Williams IL, Thomas MR, de Belder A. Immediate and medium term outcome following the use of multiple stents in the treatment of very long (> 50 mm) coronary lesions [abstract]. Heart 1997;77:72.