# Clinical and Angiographic Safety and Efficacy Trial with a New Coronary Stent: The RESTOR Study of the R Stent

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*ABSTRACT: The RESTOR trial (R Stent Efficacy and Safety Trial by ORBUS) is an efficacy and safety evaluation of the R Stent for treatment of patients with a single de novo coronary lesion < 25 mm in length in a coronary artery of 2.75–4.0 mm diameter. This new stent utilizes a patented dual helix design for radial strength and flexibility. The aim of the study was to assess major adverse cardiac events (MACE) and angiographic outcome at 6 months after implantation.*

*From May to December 2000 a total of 121 patients with symptomatic stable or unstable angina pectoris or documented silent ischemia and a significant single, de novo coronary lesion (average reference vessel diameter 2.84 ± 0.54 mm, average lesion length 10.53 ± 3.70 mm) were included in two Dutch centers. All patients were treated with clopidogrel 75 mg/day for 1 month and with aspirin ≥ 100 mg/day.*

*The angiographic success rate (< 30% diameter stenosis post procedure) was 98.3%. Procedural success (angiographic success without in-hospital MACE) was 95.9%. The 6-month MACE rate was 12.4%. 101 of the 121 patients had an angiographic follow-up at 6 months. Minimal lumen diameter pre/post procedure and at follow-up was 0.98 ± 0.37, 2.64 ± 0.38 and 1.85 ± 0.68 mm, respectively. The resulting binary restenosis rate in this population was 20.8%.*

*The coronary R Stent is safe and effective as a primary device for the treatment of native coronary lesions in patients with stable or unstable angina pectoris, and well suitable as a platform for a drug eluting stent.*

*J INVAS CARDIOL 2004;16:402–405*

Over the last decade, coronary stent implantation has gradually become the treatment of choice in percutaneous coronary intervention (PCI).[1,2] The enhanced safety of coronary interventions, the lower complication rate, the better immediate angiographic and functional results and especially the lower restenosis rate compared to balloon angioplasty have won the battle with other interventional treatment modalities in all but a few types of lesions.[3–9] Today, a huge number of different models and makes of coronary stents are available. In the early years of the 21st century all attention is focused on the new development of drug eluting stents, promising the ultimate solution of the restenosis problem.[10,11]

An argument could exist that the mechanical properties of drug-eluting stents become increasingly important as indications shift towards more complex and multivessel PCIs. A new stent design therefore has to offer optimal radial strength, vessel conformability, side branch access, and a high flexibility and low profile for ease of delivery. Moreover, new stents still have to be evaluated with proven clinical and angiographic scientific study methods before they can safely be further developed into drug carrying and eluting platforms. The RESTOR trial (R Stent Efficacy and Safety Trial by Orbus) was undertaken to evaluate the safety and efficacy of a novel stent design, the R stent, by measuring Major Adverse Cardiac Events (MACE) at 210 days post implantation and by assessing quantitative coronary angiography (QCA) results at 6 months follow-up.

## Methods

**Patients.** Between May and December 2000 a total number of 121 patients (mean age 58.8 years, range 32–79 years, 75% male and 25% female) were included in 2 Dutch centers: the Amphia Hospital Breda and the Thoraxcenter Rotterdam. Their baseline demographic and angiographic characteristics are shown in Table 1. Patients with symptomatic stable or unstable angina pectoris or documented silent ischemia and a significant single, de novo coronary lesion of a length up to 25 mm and a reference diameter between 2.75 and 4.0 mm could be included in this trial. Patients with a total occlusion, unprotected left main stem disease, large intracoronary thrombus, acute myocardial infarction, an ejection fraction below 30%, and known allergies to aspirin, clopidogrel, heparin or stainless steel were excluded. The study protocol was approved by the local ethics committees and written, informed consent was obtained in all cases.

**Stent design.** The R Stent (Orbus Medical Technologies, Ft. Lauderdale, Florida) is a balloon expandable device fashioned from 316LVM stainless steel tubing. The patented dual helix design of the R Stent is unique. It provides more flexibility than regular slotted tube configurations yet maintains high radial strength which is a weakness of coil wire designs. The strut thickness of the R Stent results in moderate radiopacity without obscuring the lesion area. The cell geometry allows for easy side branch access and dilatation of side branch orifices up to 4.5 mm without distortion of the opposite stent wall. The R Stent is pre-mounted on a low-profile rapid exchange PTCA catheter.

**Stent implantation.** All PCI procedures were carried out through femoral artery access and 6 French guiding catheters. The R stents were implanted after predilatation with adequately sized balloon catheters. Additional stents were implanted in cases of suboptimal results or edge dissections in adjacent segments. All patients received an oral loading dose of 300 mg clopidogrel and

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This study was supported by a grant from Orbus Medical Technologies, Fort Lauderdale, Florida.

Manuscript received February 21, 2004, provisional acceptance given April 1, 2004, revised manuscript accepted June 3, 2004.

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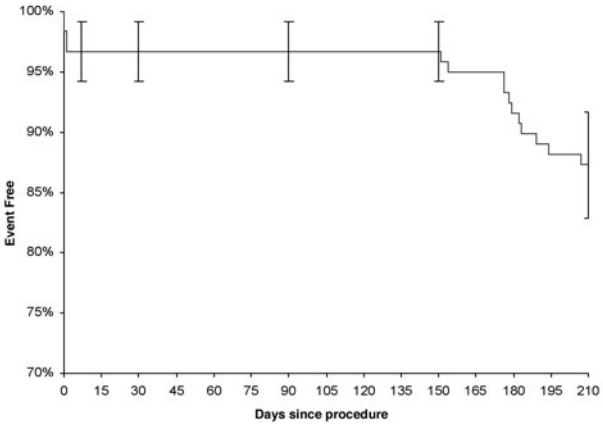


**Figure 1.** *Major adverse cardiac events life table analysis. Error bars indicate +/- 1.5 standard error and simply provide a visual display of variability. Standard error based on the Pelo formula.*

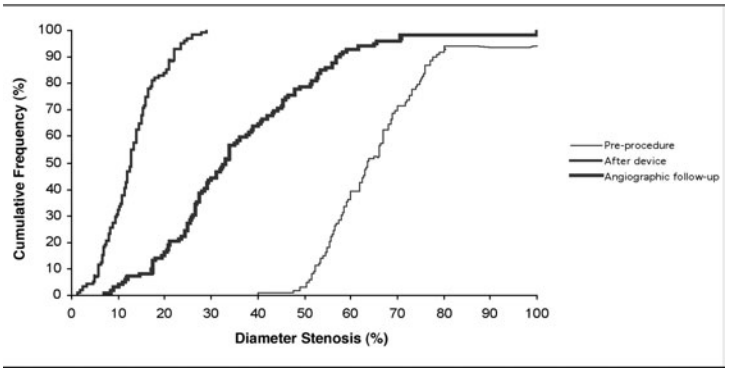


**Figure 2.** *Cumulative distribution of diameter stenosis pre- and post-PCI and at follow-up angiography.*

**Table 1.** Patient demographics and angiographic characteristics.

| Patient Parameter Measured | R Stent™ 95% | Confidence Interval |
|---|---|---|
| Age (years) | | |
| N | 121 | |
| mean ± SD | 58.8 ± 9.8 | {57.0, 60.5} |
| (min-max) | (32 – 79) | |
| Number of Men | 75.2% (91/121) | {66.5%, 82.6%} |
| Diabetes Mellitus | 9.9% (12/121) | {5.2%, 16.7%} |
| Liver insufficiency | 0.0% (0/121) | {0.0%, 3.0%} |
| Hypercholesterolemia | 71.1% (86/121) | {62.1%, 79.0%} |
| Stroke | 3.3% (4/121) | {0.9%, 8.2%} |
| Congestive Heart Failure | 1.7% (2/121) | {0.2%, 5.8%} |
| Peripheral Vascular Disease | 7.4% (9/121) | {3.5%, 13.7%} |
| Previous MI | 39.7% (48/121) | {30.9%, 49.0%} |
| Previous Cardiac Surgery | 3.3% (4/121) | {0.9%, 8.2%} |
| Previous PTCA | 9.1% (11/121) | {4.6%, 15.7%} |
| Smoking History | | |
| Previous | 46.3% (56/121) | {37.2%, 55.6%} |
| Current | 22.3% (27/121) | {15.2%, 30.8%} |
| No Angina | 0.8% (1/120) | {0.0%, 4.6%} |
| Unstable Angina | | |
| Braunwald I | 0.8% (1/120) | {0.0%, 4.6%} |
| Braunwald II | 0.8% (1/120) | {0.0%, 4.6%} |
| Braunwald III | 0.8% (1/120) | {0.0%, 4.6%} |
| Stable Angina | | |
| CCS I | 1.7% (2/120) | {0.2%, 5.9%} |
| CCS II | 30.8% (37/120) | {22.7%, 39.9%} |
| CCS III | 47.5% (57/120) | {38.3%, 56.8%} |
| CCS IV | 15.0% (18/120) | {9.1%, 22.7%} |
| Silent Ischemia | 1.7% (2/120) | {0.2%, 5.9%} |
| Number of Diseased Arteries | | |
| Single | 84.3% (102/121) | {76.6%, 90.3%} |
| Double | 13.2% (16/121) | {7.8%, 20.6%} |
| Triple | 2.5% (3/121) | {0.5%, 7.1%} |

*Numbers are % (counts/available field sample size) or mean ± Standard Deviation.*

**Table 2.** Diameters and lengths of implanted R Stents.

| | | |
|---|---|---|
| **Diameter** | | |
| | 3.0 mm | 46.0% |
| | 3.5 mm | 35.3% |
| | 4.0 mm | 18.7% |
| **Length** | | |
| | 9 mm | 15.8% |
| | 13 mm | 27.3% |
| | 18 mm | 35.3% |
| | 23 mm | 10.8% |
| | 28 mm | 10.8% |

5000–10000 units of intravenous heparin before the procedure, and were subsequently treated with ASA 80–300 mg. and clopidogrel 75 mg daily. Glycoprotein IIb/IIIa inhibitors were administered if considered necessary by the operator.

**Quantitative coronary angiography.** Coronary angiography was performed before and after PCI and at 6 months follow-up in multiple views after intracoronary administration of nitrates. Quantitative analysis with standardized edge detection techniques using the CAAS II system (Pie Medical, Maastricht, the Netherlands) was performed at the independent core laboratory (Cardialysis, Rotterdam, the Netherlands). Restenosis was defined as a stenosis of 50% or more at the follow-up angiogram. Late luminal loss was defined as the difference between the minimal luminal diameter (MLD) after the procedure and at 6 months.

**Endpoints and definitions.** The primary endpoint of the study was the incidence of major adverse cardiac events (MACE) at 210 days post-procedure. MACE were defined as cardiac death, MI (Q-wave and non-Q wave, CK levels > 2 times normal), CABG and TLR. The secondary endpoints were MACE at 30 days post-procedure, major bleeding and vascular complications, and angiographic parameters (percentage diameter stenosis, minimal luminal diameter and restenosis rate) by means of central core laboratory analysis. Angiographic success was defined as a diameter stenosis post-procedure of < 30%. Procedural success was defined as angiographic success and the absence of MACE during hospital stay.

**Statistical methods.** The statistical and safety analysis were performed according to the intention-to-treat principle. Statisti-

**Table 3.** Principle effectiveness and safety measures of all patients treated.

| Effectiveness Measures | R Stent™ | 95% Confidence Interval |
|---|---|---|
| Angiographic success | 85.0% (102/120) | {77.3%, 90.9%} |
| Procedural success | 82.6% (100/121) | {74.7%, 88.9%) |
| Minimal luminal diameter after device in-stent (mm) (min.–max.) | 2.64 ± 0.38 (N = 120) (1.82 – 3.52) | {2.57, 2.71} |
| Min. luminal diameter at 6-mo. follow-up in-stent (mm) (min.–max.) | 1.85 ± 0.68 (N = 101) (0.00 – 3.67) | {1.72, 1.99} |
| % Diameter stenosis after device in-stent (min.–max.) | 13.1 ± 5.9 (N = 120) (1.0 – 29.0) | {12.0, 14.1} |
| % Diameter stenosis at 6-month follow-up in-stent (min.–max.) | 35.9 ± 17.6 (N = 101) (7.0 – 100.0) | {32.5, 39.4} |
| Binary restenosis rate | 20.8% (21/101) | {13.4%, 30.0%} |
| TLR–free at 210 days | 89.8% | {84.2%, 95.3%} |
| TVR-free at 210 days | 88.9% | {83.2%, 94.6%} |
| MACE-free at 210 days | 87.3% | {81.2%, 93.4%} |
| **Safety meaures** | | |
| In-hospital clinical events | 3.3% (4/121) | {0.9%, 8.2%} |
| Out-of-hospital clinical events to 210 days | 9.1% (11/121) | {4.6%, 15.7%} |
| MACE to 210 days | 12.4% (15/121) | {7.1%, 19.6%} |
| Non-cardiac death to 210 days | 0.8% (1/121) | {0.0%, 4.5%} |
| Stroke to 210 days | 0.0% (0/121) | {0.0%, 3.0%} |
| Major bleeding | 0.0% (0/121) | {0.0%, 3.0%} |
| Total occlusion at follow-up | 2.0% (2/121) | {0.2%, 7.0%} |

cal significance testing was not performed because this was an observational, non-randomized study. Descriptive statistics were performed for all relevant variables. For categorized variables the data were collected as counts and incidence rates, for continuous variables as mean, standard deviation, median, minimum and maximum. The occurrences of major clinical events and target lesion revascularization were analyzed using the actuarial life table method.

## Results

**Acute results.** The diameters and lengths of the R Stents used in this study are shown in Table 2. A single study stent was implanted in 102/121 patients (84.3%), 2 study stents in 16/121 patients (13.2%), and 3 study stents in 1 patient (0.8%). In one patient (0.8%) a non-study stent was implanted as well as a study stent because of non-availability of the appropriate size of the study stent at that moment. There was 1 case of emergency CABG because of guidewire-induced spiral dissection in a severely diseased RCA before stent implantation could be attempted. Thus, the angiographic success rate of R Stent implantation, defined as < 30% diameter residual stenosis was 98.3% (119/121 patients). Procedural success, defined as angiographic success and absence of MACE prior to hospital discharge as determined by the independent Endpoint Review Committee, was reached in 116/121 patients (95.9%). As described above, there was 1 case of emergency CABG. Another patient, who inadvertently had not received clopidogrel before PCI, suffered a subacute stent occlusion 4 hours after implantation and underwent repeat PCI and IIb/IIIa inhibitor treatment. Including these 2 cases, 4 patients had non-Q-wave myocardial infarctions. There were no deaths, re-PCIs or non-Q wave myocardial infarctions during hospitalization. There have been no incidences of device failure of the R Stent in this study.

Table 3 shows the principal effectiveness and safety measures of all patients after treatment and during the follow-up period of 7 months. One patient underwent CABG at 12 weeks post PCI because of progression of disease in non-target coronary segments and 11 patients underwent re-PCI of the stented lesion either before or after their scheduled 6 months control angiogram. Thus, the overall 7 months MACE rate of this trial was 12.4% (Figure 2). The QCA data of this study are presented in Table 4. Of the 121 included patients, 101 underwent repeat coronary angiography either at 6 months as scheduled or earlier because of recurrent angina. The binary restenosis rate with a > 50% diameter stenosis at angiographic follow-up was 20.8%

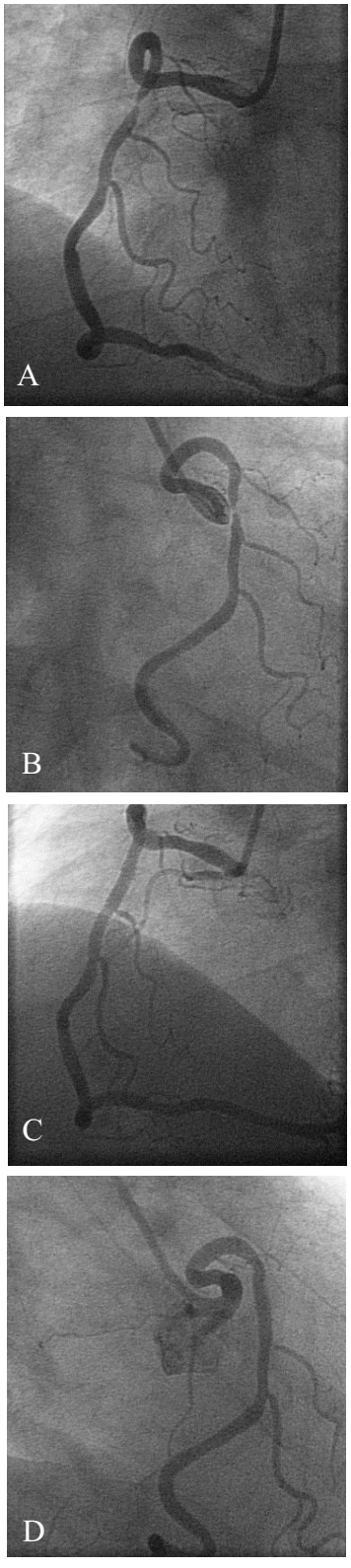


**Figure 3.** *Angiograms of R stent implantation in study patient with tortuous RCA* **(A)** *LAO view pre-PCI.* **(B)** *RAO view pre-PCI.* **(C)** *LAO view post-PCI.* **(D)** *RAO view post-PCI.*

(21/101 patients). Figure 4 shows the cumulative distribution of diameter stenosis pre- and post-PCI and at follow-up angiography.

With numerous new coronary stents becoming available on the market the attention of investigators in this field is shifting towards coating these stents with antiproliferative and other drugs. It is in our opinion however still mandatory to investigate the safety and efficacy of a new design on its mechanical, clinical and angiographic merits using a well established prospective study method and core lab. This is especially true if such a stent will be further developed as a carrier of such drugs in the near future. The RESTOR trial demonstrates that the R Stent as a bare, non-coated stent, is a safe and effective device. It is associated with a high primary success rate and a MACE rate comparable to other modern stainless steel coronary stents.[7,12–16] The binary restenosis rate of 20.8% found in this trial is in the expected range for a study with an average stented length of treated segments of 15.7 mm per patient, using more than 1 stent in 19/121 patients (15.7%) (Table 2).[17,18]

The R Stent has special mechanical properties because of its unique dual helix design. The resulting flexibility can be seen from Figure 4: A single R Stent was implanted easily in a study patient with an extremely tortuous RCA. Other potential advantages such as the suitability of the R Stent for direct stenting and sidebranch/bifurcation treatment will be addressed in future, more specific studies.

## Conclusions

The R Stent is a new coronary stent with a dual helix design, which offers the flexibility, conformability and sidebranch access of a coil stent in combination with the radial strength and scaffolding properties of a tubular stent. The RESTOR study has established its safety and efficacy in an open, prospective clinical endpoint and quantitative angiography trial. Its angiographic restenosis rate lies within the expected range for a bare, non-coated stent. The R Stent is well suited as a platform for the further development of drug-eluting stents.

**Acknowledgement.** The authors wish to acknowledge the helpful support of Cardialysis, Rotterdam, the Netherlands, for their data and manuscript review.

**Table 4.** Quantitative coronary angiography data (mean ± standard deviation).

| | Pre-PCI (n = 119) | Post-PCI (n = 120) | Follow-up (n = 101) |
|---|---|---|---|
| Reference diameter (mm) | 2.84 ± 0.54 | 3.04 ± 0.43 | 2.87 ± 0.58 |
| Minimal luminal diameter (mm) | 0.98 ± 0.37 | 2.64 ± 0.38 | 1.85 ± 0.68 |
| Diameter stenosis (%) | 65.2 ± 11.5 | 13.1 ± 5.9 | 35.9 ± 17.6 |
| Late loss (mm) | | | 0.78 ± 0.48 |
| Late loss index | | | 0.51 ± 0.36 |
| Binary restenosis rate (> 50% DS) | | | 20.8% |

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