

THE DIRECTOR TRIAL

DIRECT STENTING STUDY WITH THE **ORBUS R** STENT

A Controlled, Prospective, Multicenter Registry Trial

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DIRECTOR: DIRECT Stenting Study with the Orbus R stent Trial Six Month Angiographic and Clinical Follow Up Results

Orbus Medical Technologies (Orbus) has concluded its DIRECTOR – **DIRECT** Stenting Study with the **Orbus R** stent Trial. As the name implies, the DIRECTOR Trial has been designed to clinically and angiographically evaluate the performance of the R stent when implanted using the direct stenting technique. Direct coronary stenting without predilatation is a therapeutic approach with both potential healthcare as well as health economic benefits. Potential benefits are the avoidance of abrupt vessel closure after balloon angioplasty, reduction of debris embolization, and lessening of the restenosis rate due to reduced arterial wall injury¹. The results from this trial demonstrate that direct stenting with the R stent is safe and effective with a high angiographic success rate, a low conversion to predilatation, and favorable long term angiographic and clinical results.

The primary endpoint for the DIRECTOR trial is the occurrence of any of the following composite endpoints: MACCE (Major Adverse Cardiac and Cerebrovascular Events) within 30 days and angina pectoris at one month follow up visit. MACCE includes cardiac death, stroke, myocardial infarction (MI), coronary artery bypass graft (CABG), and target lesion revascularization (TLR). The secondary endpoints include post procedure in-stent percent diameter stenosis, angiographic success, percentage diameter stenosis (%DS), minimal lumen diameter (MLD) and restenosis rate at six months, and major bleeding and/or major vascular complications up to nine months.

The management of all aspects of this study and the evaluation of the data was conducted by Cardialysis B.V., an independent Clinical Research Organization (CRO) and Quantitative Coronary Angiography (QCA) core laboratory.

During the course of this trial, 128 patients were enrolled in 17 clinical sites located in nine countries. Patients were followed clinically after hospital discharge at one month, six months (including an exercise test), and nine months. In addition, angiography was performed and analyzed by offline QCA preprocedure, post procedure, and at six months.

All patients presented with angina pectoris or objective evidence of ischemia and a stenotic lesion in a native coronary artery. Patients were required to have one single de novo lesion which could be entirely covered by one single 18 mm R stent in coronary arteries ranging from 2.75 to 4.0 mm in diameter. Patients who met the eligibility criteria were enrolled in the trial and then treated utilizing the direct stenting technique. 93% of the patients enrolled returned for their six months angiographic follow up and a nine month clinical follow up was performed on 95% of the patients.

The DIRECTOR population consists of 71.1% male patients with an average age of 59.8 years, 64.4% had hypercholesterolemia, 45.3% had hypertension, and 40.6% had a family

history of coronary artery disease. In addition, 53% of the patients presented with stable angina, 24.3% had multivessel disease, 12.5% were diabetic, and 43% had previously experienced a myocardial infarction. The index lesions had an average reference diameter (RD) of 2.88 mm, a minimal lumen diameter (MLD) of 0.98 mm, and an average lesion length of 10.8 mm. 60.6% of all lesions were Type B2 and 38.6% were Type B1. Most patients had single vessel disease (75%). Triple vessel disease was present in 8%.

The deliverability and acute performance of the R stent was clearly demonstrated with high rates of clinical angiographic and procedural success. After stent implantation a clinical angiographic success rate (defined as post procedure diameter stenosis < 30% and TIMI flow 3) of 99.2% was obtained, yielding an average post procedural MLD of 2.64 mm and percent diameter stenosis of 13.2% within the stent. While a procedural success rate (angiographic success and freedom of MACCE prior to discharge) of 96.1% was achieved.

The stent delivery system performed well in this patient population that was comprised of predominantly type B2 (60%) lesions. In 5.4% of the cases operators had to revert to predilatation. In each of these cases the R stent was successfully withdrawn without any incidence of balloon rupture, stent migration, or clinical incident. This compares favorably to the crossover rates reported in recent randomized direct stenting trials. In these trials predilatation was necessary in 8-14% of lesions^{2,4}. Only in the DISCO trial⁵ was a comparable predilatation rate of 3% found⁴. In this trial, which was a direct stenting trial in Spain, generally less challenging lesions were treated with only 40% of B2 lesions in the patient population. Severe calcification and tortuosity were exclusion criteria in all these studies but were not in DIRECTOR.

The low 30 day MACCE rate of 3.9% (five events) in DIRECTOR is comparable to other studies with second and third generation coronary stents. Four non-Q wave myocardial infarctions occurred and one repeat PTCA was necessary because of subacute stent thrombosis. This stent thrombosis did not lead to myonecrosis.

Patient compliance was remarkably good in DIRECTOR. 119 of 128 patients (93%) returned for a follow up angiogram. Quantitative Coronary Angiographic (QCA) assessment of the data yielded a six months binary angiographic restenosis rate of 19% (23 of 119 patients). Target lesion revascularization during seven months of follow up was carried out nine times in eight patients (7%). All nine TLRs were ischemia driven. In other direct stenting studies, using a Medtronic AVE S670 stent, Baim et al⁴ found an ischemia driven TLR of 12% and IJsselmuiden et al³ reported a rate of 6.5% at six months follow up.

To put DIRECTOR in perspective, the results were compared with those obtained from other Cardialysis monitored coronary stent studies that were analysed using the same QCA technology, the same endpoint definitions, and the same adjudication procedure (RAVEL, DUET, and SOPHOS trials in Tables 1-3). Results from the bare metal stent arms (control) of the TAXUS II and IV trials are also included for comparative purposes.

Table 1: Comparable Cardialysis Monitored Coronary Stent Studies

| Study Name | Device | Sponsor | Lengths Utilized | Comments |
|------------------------|----------------|-----------------------------------|------------------------|---|
| RAVEL* Control | BX Velocity | J&J | 18 mm | The bare metal stent control group of the RAVEL trial. All lesions predilated prior to stent implantation. |
| TAXUS II** Control | NIR conformer | Boston Scientific Corporation | 15 mm | The bare metal stent control group of the TAXUS II trial. 270 patients treated with bare stents and followed for up to 24 months. |
| TAXUS IV*** Control | Express | Boston Scientific Corporation | 16, 24, & 32 mm | The bare metal stent control group of the TAXUS IV trial. 652 patients treated with bare stents and followed for up to nine months. |
| DUET* | Multilink | Guidant | 8, 13, 18, & 28 mm | More than 90% of the stents implanted were < or = to 18 mm in length. |
| SOPHOS* | BiodivYsio | Biocompatibles | 15 mm | 200 patients treated with 15 mm phosphorylcholine coated stent with six months angiographic follow up. |
| RESTOR* | R stent | Orbus Medical Technologies | 9, 13, 18, 23, & 28 mm | 67% of stents were > or = 18 mm. |
| DIRECTOR* | R stent | Orbus Medical Technologies | 18 mm | 128 patient direct stenting registry trial. |

*Cardialysis Monitored Coronary Stent Studies

**Colombo, A. TAXUS II. Transcatheter Cardiovascular Therapeutics (TCT) 2002, Expert Slide Presentation 2002 Scientific Session. www.TCTMD.com

***Stone, G.W., TAXUS IV RESULTS. Transcatheter Cardiovascular Therapeutics (TCT) 2003, Expert Slide Presentation 2003 Scientific Session.

www.TCTMD.com

Table 2: MACE/TLR Comparison

| Study Name | MACE (1 month) | MACE (6-7 months) | TLR (6-7 months) |
|------------------|----------------|-------------------|------------------|
| RAVEL Control | - | 27.1% | 23% |
| TAXUS II Control | 4.0% | 19.8% | 13% |
| TAXUS IV Control | 2.5% | 15.0% (9 months) | 11% (9 months) |
| DUET | 5.1% | 17.2% | 14% |
| SOPHOS | 4.0% | 16.0% | 9% |
| RESTOR | 3.3% | 12.4% | 10% |
| DIRECTOR | 3.9% | 10.2% | 7% |

Table 3: QCA Comparison

| Study Name | RD (mm) | Restenosis Rate (%) |
|------------------|-------------|---------------------|
| RAVEL Control | 2.64 | 26 |
| TAXUS II Control | 2.75 | 19 |
| TAXUS IV Control | 2.75 | 27 (9 months) |
| DUET | 2.91 | 16 |
| SOPHOS | 2.94 | 18 |
| RESTOR | 2.84 | 20 |
| DIRECTOR | 2.88 | 19 |

*RD= reference diameter or vessel size

Conclusion

The data on the R stent collected in the DIRECTOR study are encouraging when compared to other clinical studies using competitive coronary stent designs. The safety and efficacy of the R stent for the treatment of single de novo coronary lesions in patients with angina pectoris has clearly been demonstrated by the high event free (MACCE) survival and angiographic and procedural success rates. In addition, this study demonstrates that the R stent may be effectively used with the direct stenting technique for the treatment of single de novo coronary lesions with a high angiographic success rate, a low conversion to predilatation, and good long term angiographic and clinical results.

The low TLR rate in DIRECTOR comes close to TLR rates reported in drug eluting stent trials (Table 4). Not an unimportant finding in this era of healthcare cost containment.

Table 4: MACE and TLR in Drug Eluting Stent Trials

| Trial | Drug | MACE | TLR |
|------------------------------------|-------------|-----------------|----------------------------------|
| RAVEL ⁶ | Rapamycin | 5.8% (1 year) | 0.0% (1 year) |
| SIRIUS ⁷ | Rapamycin | 7.1% (9 months) | 4.1% (9 months) |
| E-SIRIUS ⁸ | Rapamycin | 8.0% (9 months) | 4.0% (9 months) |
| TAXUS II Slow Release ⁹ | Paclitaxel | 8.5% (9 months) | 4.6% (9 months) |
| Taxus IV ¹⁰ | Paclitaxel | 8.5% (9 months) | 4.7% (9 months, ischemia driven) |

Endnotes

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