Biolimus A9: A New Generation Rapamycin Analogue

3.1±0.5

NS

94±22

NS

Optimal Geometry Is Still Important With Sirolimus-

2.8±0.3

The Long-Term Clinical Results of a Platelet

dial infarction and revascularization during hospital stay in control stent group. During clinical follow-up, there were two myocardial infarctions in control group. Follow-up coronary angiogram was done 62.3% (48/77) in coated and 65.4% (51/78) in control groups. A first-in man clinical trial has been initiated. We performed a prospective randomized trial to compare two types of stents. Methods: Nine bare metal(B) and 9 Biolimus A9(B9) coated stents were evaluated in 28 day overlap stent model. The drug delivery polymer was thin layer bio-resorbable Poly-lactic acid. The average balloon artery ratio was 1.18±0.03. At sacrifice coronary angiography and histologic analysis was performed for each stented vessel. Results: The results are tabulated in Table 1. There was no difference of injury in both groups. There was 50% reduction of area stenosis by the B9 coated stent(p=0.001). Histology, showed near complete endothelialization in both control and A9 groups with a only a slight increase in fibrin content in the B9 group.Conclusions: Biolimus A9 delivered via bioresorbable polymer coated stent inhibits intimal hyperplasia in a porcine model. There is normal healing of treated arteries at 28days and no inflammation as compared to controls. A first-in man clinical trial has been initiated.

Histomorphometric Analysis of the Bare and Biolimus A9 stents

<table>
<thead>
<tr>
<th>Injury Score</th>
<th>0.30±0.10</th>
<th>0.30±0.12</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal Hyperplasia(Um)</td>
<td>238±24</td>
<td>152±14</td>
<td>0.004</td>
</tr>
<tr>
<td>Area Stenosis(%)</td>
<td>38</td>
<td>20</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The Long-Term Clinical Results of a Platelet Glycoprotein Ib/IIa Receptor Blocker (Abciximab; ReoPro®)-Coated Stent in Patients With Coronary Artery Disease

Weon Kim, Myung Ho Jeong, Young Keun Ahn, Ju Han Kim, Young Joon Hong, Jeong Gwan Cho, Jong Chun Park, Jung Chae Kang, Chonnam National University Hospital, Gwangju, South Korea

Background: Previously we reported the inhibition of coronary restenosis with Abciximab (ReoPro®)-coated stent in a porcine model. ReoPro® inhibits platelet aggregation, the proliferation of vascular smooth muscle cells and inflammatory reaction.

Methods: We performed a prospective randomized trial to compare two types of stents for the revascularization in native coronary artery. The primary effective end points were major adverse coronary events (MACE): cardiac death, acute myocardial infarction, target vessel revascularization (TVR), restenosis at 6-month clinical and angiographic follow-up.

Results: One hundred fifty-five patients were enrolled between Aug, 2001 and Jun, 2003. Mean ages (56±10.0 V. 56±10.8 years), baseline diameter stenosis and minimal lumen diameter were not different between the two groups. There was one myocardial infarction and revascularization during hospital stay in control stent group. During clinical follow-up, there were two myocardial infarctions in control group. Follow-up coronary angiogram was done 62.3% (48/77) in coated and 65.4% (51/78) in control groups. Diameter stenosis and late loss were significantly less in the ReoPro®-coated stent group compared with controls (16±4.5±8.9% vs. 34±6±5.1%, p=0.009; and 0.33±0.28 mm vs. 0.88±0.41 mm; p=0.002). The restenosis and TVR rates of ReoPro®-coated stent were relatively lower compared with control stent (14%±7(48)/vs. 29.4%±15(51), p=0.062; and 9.2%±7(76) vs. 14.7%±17(55); p=0.327).

Conclusion: A ReoPro®-coated stent is safe and may be effective in the prevention of coronary restenosis.

Nitric Oxide Through Biodegradable Layer Elective Study for Safety and Efficacy (NOBLESSE): Final Results From the South American Study Arm

Xiaoshun Liu, Costantino Costantini, Hugo Londero, Hans Bonnier, Ivan De Scheeunr, The NOBLESSE Investigators, University Hospitals Leuven, Leuven, Belgium

Background: Oxygen free radical scavengers may play a significant role in preventing neointimal hyperplasia after stent implantation. The Blue Medical TEMPO coronary stent is characterized by its particular biodegradable PEA coating conjugated with tempamine, a potent antioxidant substance. Pre-clinical work showed a similar tissue response and reduced intimal hyperplasia in a porcine coronary stent model using this stent. The aim of this study was to evaluate the acute safety and efficacy of the TEMPO loaded Blue Medical stent implanted in patients with de-novo single vessel disease.

Methods: This is a multinational, multicenter, 2 armed phase III trial. 45 patients treated with an intermediate dose (50%) of temparine loaded on the Blue Medical stent from 2 South American study sites are presented here (44% were male, average age 61 (range 37 - 86) 38% had lesion type B2 or C. One 14 mm or 18mm long stent was used. Minimal lumen diameter (MLD) and % diameter stenosis (DS) were measured. The primary end points are 4m in-stent %DS and late loss determined by QCA. The secondary endpoints are binary restenosis rate at 4m follow-up and 30 days, 60 days and one year major adverse cardiac events (MACE) defined as death, MI, CABG & target vessel revascularization.

Results: All the stent implantations were successful except one that resulted in a distal dissection, treated by an additional coated stent implantation. Two patients were excluded because of violation of the inclusion and/or exclusion criteria. There was no MACE at 30 days and 60 days f-up. TLR occurred in 2 patients during the 4m f-up. 4m angiographic f-up rate was obtained in 98%. QCA: mean reference diameter: 3.01±0.29 mm, % DS was 64.0±15.20% before, 8.4±0.1% after. Angiographic lesion and 30.3±17.03 % at 4m. Late loss was 0.69±0.52. Four patients developed an in-stent restenosis at 4m in a binary restenosis rate of 9.52%. Final 12m clinical f-up will be presented.

Conclusion: This short term and 4 month results show that implantation of a temparine loaded Blue Medical stent is feasible and safe. QCA data showed a low late loss and binary restenosis rate, therefore suggesting a beneficial effect on neointimal hyperplasia and in-stent restenosis.

Optimal Geometry Is Still Important With Sirolimus-Eluting Stents: Incomplete Stent Expansion as a Risk for Target Lesion Revascularization

Junya Ake, Yoshio Morino, Mitsuaysi Terashima, Yasuhiro Honda, Shinjiro Sonoda, Martin B. Leon, Jeffrey W. Moses, Paul G. Yock, Peter J. Fitzgerald, The SIRIUS Investigators, Stanford University, Stanford, CA, Lenox Hill Hospital, New York, NY

Background: Despite the striking reduction in neointimal hyperplasia seen with sirolimus eluting stents (SES), target lesion revascularization (TLR) has not been completely eliminated. The aim of this IVUS substudy was to clarify procedure-related risk factors for TLR in sirolimus-eluting stents.

Methods and Results: Angiographic and IVUS data were obtained from SIRIUS, a prospective, randomized, multicenter clinical trial comparing SES (sirolimus-eluting Bx VELOCITY, Cordis) and bare metal stent (BMS). Post-procedure IVUS measurements in SES were available in 108 cases. TLR expanded was defined as minimum stent area (MSA) divided by reference LA. There were 6 TLR cases in SES in this patient cohort. Table summarizes comparisons between TLR and non-TLR cases. Angiographic lesion length was longer in TLR cases. With respect to procedure-related factors, TLR cases had lower maximal pressure, smaller % expansion, and a trend toward smaller MSA.

Conclusion: Incomplete stent expansion may be a risk factor for TLR in sirolimus-eluting stents. Proper mechanical stent deployment to achieve adequate lumen geometry may further improve the clinical success of this technology.
Impact of Coronary Artery Bending at Stent Edges on Neointima Formation

Methods: Eight month follow-up volumetric IVUS analyses were performed in 35 patients treated with single SES. Patients were categorized in the edge group when average NI area, located 1mm inside the stent from either edge, was greater than average NI area of the non-edge segment. The impact of procedural aggressiveness was evaluated by assessment of procedural demographics including maximum pressure, balloon:artery ratio and the previously described artery injury index (product of maximum pressure and balloon:artery ratio).

Results: Average NI areas, within 1mm from both edges, were 0.67 ± 0.53 and 0.04 ± 0.09 mm² in the edge and the non-edge group, respectively. Clinical demographics including age and diabetes mellitus were not different in the two groups. IVUS and procedural data are presented in the Table.

Conclusions: These results suggest that aggressive stent deployment strategy and smaller vessel size are risk factors for stent edge neointimal formation following sirolimus-eluting stent implantation. A less aggressive strategy, particularly in small vessels, may be important to optimize the long-term durability of this procedure.

---

Impact of Coronary Artery Bending at Stent Edges on Subsequent Plaque Proliferation: A Serial Volumetric Intravascular Ultrasound Analysis

Hiroshi Yamauchi, Hideaki Kaneda, Fumiake Ikeno, Brian K. Coughney, Shinjo Sonoda, Ryouta Sakurai, Yoshishita Shimada, Paul G. Yock, Peter J. Fitzgerald, Yasuhiro Honda, Stanford University Medical Center, Stanford, CA

Background: The significant anti-proliferative effect of drug-eluting stents will encourage the use of longer stents to treat diffuse coronary lesions as well as to ensure the full coverage of diseased segment. This strategy, however, potentially leads to chronic stent edge injury by straightening effect of rigid metal stents. The aim of this study was to investigate the possibility associated between vessel bending at stent edges and peri-stent plaque increase following bare metal stenting.

Methods: Serial (baseline and 6 months) angiographic and 3D IVUS images were obtained in 24 cases treated with an identical bare metal stent (3.0-3.5 mm, 18 mm length). By quantitative angiography at baseline, vessel bending at the stent edge (defined as the angle between the tangents of two adjacent segments 5 mm inside/outside the stent edge) was evaluated by two independent observers. Volumetric IVUS analyses were also independently performed to obtain serial changes in plaque volume at the proximal and distal reference segments within 2 mm outside the stent edges.

Results: Overall, vessel bending was 17 ± 11° and 14 ± 8° at the proximal and distal stent edges, respectively. At 6 months, plaque volume significantly increased by 0.98 ± 1.4 (proximal) and 1.04 ± 1.08 mm³ (distal). Plaque increase at both the proximal and distal edge significantly correlated with the degree of vessel bending at baseline (p=0.048, r=0.492, p=0.05, respectively).

Conclusions: Significant vessel bending due to stent implantation may be associated with increased plaque proliferation at stent edges. Enhanced stent conformability to minimize chronic stent edge injury may be important in the era of drug-eluting stents.

---

A Randomized Study Comparing a Titanium-Nitride-Oxide Coated With an Uncoated Stent for Coronary Revascularization

Stephan Windische, The TINOX Study Investigators, Swiss Cardiovascular Center Bern, Bern, Switzerland

Background: Experimental data have shown reduced neointimal hyperplasia following implantation of a titanium-nitride-oxide (TINOX) coated stents. The objective of the present study is to evaluate safety and efficacy of TINOX coated stents for treatment of de novo coronary artery lesions compared with an uncoated, bare metal stent in a randomized, single-blind, multi-center trial.

Methods: Ninety-two patients (lesion diameter 2.5-3.5 mm, lesion length ≤ 15 mm) were randomly assigned to a TINOX coated (n=45) or bare metal stent (n=47) of identical design (slotted tube stent: Omega, AMG, Germany). TINOX coating was performed by physical vapor deposition in the vacuum chamber. All stents were manually crimped on a standard balloon catheter after predilation of the lesion. Dual antiplatelet therapy consisting of acetylsalicylic acid (100 mg qd) and clopidogrel (300mg loading dose, followed by 75 mg qd) was administered for 3 months. Clinical follow-up was performed at 1 and 6 months. Pre-, post- and follow-up angiograms were analyzed by quantitative coronary angiography (QCA).

Results: Baseline characteristics were similar in the 2 groups. Lesion length (TINOX: 13.3 ± 4.0 mm, Control: 12.4 ± 3.3 mm, p=ns) and reference vessel diameter (TINOX: 2.91 ± 0.40 mm, Control: 2.82 ± 0.31 mm, p=ns) were not different. Device success was 100% in both groups. No stent thrombosis was observed in either group. MACE at 30 days (2% in TINOX group and 4% in the control group) were not different. QCA showed a significantly reduced late loss (TINOX: 0.59 ± 0.64, Control: 0.94 ± 0.74, p=0.03). Binary restenosis was 15.8% in the TINOX and 34.1% in the control group (p=0.06). Target lesion revascularization (TINOX: 9.1, Control: 27%; p=0.03) and MACE (TINOX: 9.1, Control: 31.1%; p=0.01) at 6 months were significantly lower in the TINOX than control group.

Conclusions: Coronary revascularization with TINOX coated stents is feasible and safe in patients with de novo coronary artery lesions. TINOX coated stents significantly reduce late loss and thus restenosis. TINOX coated stents were associated with significantly fewer MACE mainly driven by a decreased need for target lesion revascularization.

---

Intravascular Ultrasound Analysis of the New ABT-578 Eluting Phosphorylcholine-Coated Stent Implantation to De Novo Human Coronary Lesions: The ENDEAVOR I Trial

Yoichiro Hongo, Ryoza Sakurai, Ian Meredith, Robert J. Whitbourn, John Ormiston, Patrick Key, David Muller, Mark Pinney, Con Aroony, Mark Adams, Ali Hassan, Yasuhiro Honda, Paul G. Yock, Peter J. Fitzgerald, The ENDEAVOR I Trial Investigators, Stanford University, Stanford, CA, Monash Medical Centre, Clayton, Australia

Background: ABT-578, a sirolimus analogue, is a new anti-proliferative agent with promising preclinical study results. ENDEAVOR I is a multicenter, single-arm trial of the ABT-578 eluting phosphorylcholine (PC)-coated cobalt-chromium alloy Driver® (Medtronic Vascular, Santa Rosa, CA) stent in de novo human coronary lesions. The aim of this substudy was to evaluate short-term safety of this new drug-eluting stent and its impact on neointimal proliferation using IVUS.

Methods: IVUS analysis (baseline and 4-month follow-up) was available in 95 out of 100 patients. Seven patients had two stents placed. All stents were 18 mm long and 3.0 / 3.5 mm in diameter.

Results: At baseline, no major plaque protrusion or thrombus was detected over the stented segment. At 4 months, no late incomplete stent apposition was observed. No significant change in minimum luminal area within stented segments was observed between baseline and 4-month follow-up (6.23 ± 1.51 vs. 6.02 ± 1.71 mm², NS). Volumetric IVUS analysis showed that neointimal volume index (neointimal volume / stent length) was 0.32 ± 0.39 mm³/mm (Figure) and percent neointimal volume (neointimal volume * 100 / stent volume) was 4.5 ± 5.9 %.

Conclusion: Early results of the initial human experience with the ABT-578 eluting PC-coated stent showed a minimum amount of neointimal proliferation with no apparent adverse vessel response in the stented segment. Further studies will be warranted to confirm these favorable observations.

---

An Intravascular Ultrasound Analysis From FUTURE I, the First Human Experience Using Everolimus-Eluting Stents: Six- and 12-Month Results

Shinjo Sonoda, Eberhard Grube, Yoshishita Shimada, Ali H.M Hassan, Paul G. Yock, Charles Chan, Hidehiko Honda, Saibai Kar, Alexandra J. Larsky, Peter J. Fitzgerald, Yasuhiro Honda, Stanford University Medical Center, Stanford, CA, Heart Center Siegburg, Siegburg, Germany

Background: FUTURE I is a prospective, randomized trial to evaluate safety and efficacy of everolimus-eluting stents (EES), coated with a unique bioabsorbable polymer, compared to conventional metallic stents (MS) in the treatment of de novo coronary lesions. The purpose of this IVUS substudy was to investigate the long-term antiproliferative effectiveness of EES compared to MS.

Methods and Results: A total of 36 patients completed the angiographic follow-up at 6 months. To date, IVUS images are available in 35 patients (EES 24; MS 11) at 6 months and 9 patients (all EES) at 12 months. At baseline, EES achieved stent expansion similar to MS. No significant differences were observed between groups for minimum stent area (EES 7.0 ± 2.2 vs. MS 6.4 ± 1.2 mm², P=NS). However, at 6 months follow-up, minimum lumen area was significantly larger in EES than in MS (EES 6.9 ± 2.6 vs. MS 4.6 ± 1.5 mm²; P<0.01). EES showed 87% volume reduction in neointimal formation compared to MS. No significant differences were observed between groups for minimum stent area (EES 7.0 ± 2.2 vs. MS 6.4 ± 1.2 mm², P=NS). However, at 6 months follow-up, minimum lumen area was significantly larger in EES than in MS (EES 6.9 ± 2.6 vs. MS 4.6 ± 1.5 mm²; P<0.01). EES showed 87% volume reduction in neointimal formation compared to MS (See figure). There was no significant difference in vessel volume post procedure, or at 6 months follow-up between groups. In 6 patients, neointimal hyperplasia was still significantly suppressed at 12 months follow-up. Qualitative analysis showed no evidence of healed dissections or late stent malapposition in either group.

Conclusion: Everolimus-eluting stents, utilizing a unique bioabsorbable polymer, are effective in preventing neointimal hyperplasia with no evidence of IVUS-detected adverse effects.