**STUDY TITLE:**
THE VALENTINES II TRIAL

**STUDY OBJECTIVE(S):**
The primary objective of this multi-center, international registry is to assess clinical success and efficacy of the paclitaxel eluting balloon treatment for *de novo* lesions at 6-9 months follow up. Clinical success defined as freedom from major adverse cardiac events (MACE: death, myocardial infarction [MI], target lesion revascularization [TLR]) and target vessel revascularization [TVR]) and stent thrombosis, both early and late occurrences will be assessed (as defined by the ARC definite and probable definitions).

In addition, a cohort of the registry will undergo angiographic follow up at 6-9 months to assess in-lesion and in-segment late loss and binary restenosis subsequent to paclitaxel eluting balloon treatment.

**BACKGROUND AND RATIONALE FOR STUDY:**
Thirty years ago, the emergence of balloon angioplasty revolutionized coronary revascularization, establishing itself as the main modality for percutaneous coronary intervention. However, abrupt closure and restenosis caused by elastic recoil, along with cellular proliferation and late remodeling became major drawbacks of balloon angioplasty. Intracoronary stenting, which could tackle dissections and eliminate elastic recoil, became the next dominant mode of intervention but was limited by stent thrombosis and increased neointimal hyperplasia, and consequently in-stent restenosis. Drug-eluting stents (DES) significantly attenuate healing and the cellularity post stenting and reduce the need for repeat revascularization. However, late stent thrombosis, and the dependency on prolonged dual antiplatelet therapy with DES, and continued restenosis in complex subset of lesions with DES, led to a quest for new treatment modalities that will curtail in stent restenosis without the limitations associated with DES. In recent years, a new technology of drug eluting balloons (DEB) is emerging as a potential alternative to combat restenosis. Paclitaxel was identified as the primary drug for DEB with the ability to retain in the vessel all for nearly a week. The DEB technology demonstrated safety and efficacy in the porcine model of restenosis and in randomized clinical trials for patients with in-stent restenosis. Further studies for de-novo lesions in small vessels and bifurcations and for lesions in the superficial femoral artery and below the knee continue to signal safety and efficacy of the technology for broader indications. Nevertheless, the technology carries challenges in release kinetics, its ability to overcome elastic recoil, and concerns whether it can be coupled successfully to bare metal stents.

The recent advances in the field of intravascular medicine have seen the emergence of drug eluting balloon (DEB) technologies as a viable alternative for treating stenosed arterial vessels. Although stents including drug eluting stents emerged as the default device for treatment of coronary stenosis not all lesions are suitable to accommodate stent implantation small vessels, bifurcation, and calcified lesions, and not all patients can be committed for prolonged dual antiplatelet therapy. The question is whether DEB as adjunct therapy to POBA can be a viable alternative to stenting of de-novo lesions in coronary arteries has not been determined. Further it is not clear whether DEB will be disruptive to currently available treatments, including stents.
The Valentines II Trial

The Dior balloon demonstrated efficacy in preclinical trials and effectiveness for the \textit{de novo} lesions in small vessel and bifurcation as well as in-stent restenosis application in several clinical trials. The purpose of the present study is to determine the safety and efficacy of the Dior balloon as adjunct to POBA for non-stented \textit{de novo} coronary artery lesions.

In the Spanish Multicenter Registry patients with small vessel (< 2.5 mm) and in-stent restenosis were treated with Dior to assess the efficacy and safety of the Paclitaxel-eluting balloon in these settings. 222 patients were included in this registry. Mid-term results indicate the safety and efficacy of Dior treatment in this real world setting. The TLR rate was 8\% and the MACE rate was 11\% in ISR subgroup. In small vessel subgroup the TLR rate was 1.1\% and MACE rate was 2.2\% (Serra et al., EuroPCR 2010; Vaquerizo et al., EuroPCR 2010).

The DEBIUT trial, a prospective, controlled, randomized, multicentre study, compared the outcome of DEB Dior treatment in main and side branch with subsequent BMS implantation in the main branch with two control groups, either with plain old balloon angioplasty (POBA) instead of DEB or POBA and drug-eluting stent implantation in the main branch. In all three arms only bail-out stenting was allowed. Balloon dilatation was performed with kissing-balloon technique. 120 patients have been included in the trial. The patients are followed with repeated angiography at 6 month and clinical follow-up up to 5 years.

The intermediate results of the DEBIUT trial show strong trends for a favorable outcome of combining DEB with a BMS in the main branch (MB) and DEB in the side branch (SB) versus POBA instead of DEB with regards to late lumen loss (0.3mm/0.26mm in MB and -0.01mm in SB vs. 0.48mm/0.25mm in MB and 0.11mm in SB), binary restenosis rate (0 \%/9.1 \% in MB and 9.1\% in SB vs. 2.9 \%/8.6 \% in MB and 22.9\% in SB) and target lesion revascularization (15\% vs. 27\%). The DEB arm showed a comparable rate of target lesion revascularization to the POBA/DES arm. The use of DEB combined with BMS and only 3 months dual antiplatelet therapy seem to be safe for treatment of bifurcations with 0\% occurrence of stent thrombosis.

Also other drug-eluting balloons have proven there safety and efficacy in clinical trials. In the randomized, double-blind, multicenter Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR I) trial Scheller et al. enrolled 52 patients who had clinical evidence of stable or unstable angina and who had a single restenotic lesion in a stented coronary artery. The main inclusion criteria were a diameter stenosis of \leq 70\% and <30 mm length with a vessel diameter of 2.5-3.5 mm. The primary endpoint was angiographic late lumen loss in-segment. Secondary endpoints included binary restenosis rate and major adverse cardiovascular events (MACE). Patients were randomly assigned to undergo balloon angioplasty of the target lesion with either a paclitaxel-coated balloon (3 \(\mu\)g of paclitaxel per square millimeter of balloon surface area) or an uncoated catheter. At six months, the in-segment late luminal loss was 0.74\pm0.86 mm in the uncoated-balloon group versus 0.03\pm0.48 mm in the coated-balloon group (\(p = 0.002\)). Ten of 23 patients (43\%) in the uncoated-balloon group had binary restenosis, as compared with 1 of 22 patients (5\%) in the coated-balloon group (\(p = 0.002\)). At 12 months, the rate of major adverse cardiac events was 31\% in the uncoated balloon group and 4\% in the coated balloon group, essentially driven by less need for target lesion revascularization (\(p = 0.02\)). PACCOCATH ISR I and II pooled data after a complete follow-up of 2 years confirmed these results.
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PEPCAD II was a prospective, randomized, multi-center, two-arm phase-II pilot study conducted in Germany. The objectives of the study were to examine the safety and efficacy of the Sequent Please™ DEB in the treatment of ISR in native coronary arteries (reference diameter 2.5mm, 3.5mm; lesion length: ≤22mm) for procedural success and preservation of vessel patency in comparison to the Taxus™ DES. The primary endpoint was angiographic late loss at 6 months and the secondary endpoints were procedural success (≤30%) 6-month binary restenosis rate, 6-month MACE, and MACE at 1 and 3 years. The paclitaxel-eluting balloon catheter was safe and was associated with a high procedural success rate, and significant reduction in 6-month lumen loss 0.19± 0.38 for the DEB versus 0.47 ± 0.71 for the Taxus stent. The TLR rate was 3.1% for the DEB versus 16.7% for the Taxus stent p 0.02. At 1 year, the event-free survival was significantly improved in patients treated with the paclitaxel-coated balloon (P=0.01), while in the period between 6 and 12 months, there were no new MACE events in either group. Why Taxus did worse when compared to the Taxus ISR study is not clear. Nevertheless, these encouraging results confirm the efficacy and the safety of DEB for the treatment of in-stent restenosis.

Dr. Unverdorben evaluated the PEPCAD I study on the use of drug eluting balloons for the treatment of small vessel disease in 120 patients. This trial will investigate the use of drug eluting balloons in native lesions, not previously treated by DES or bare metal stents. These data further supported the above data at six months, native lesions treated solely with SeQuent Please DEB showed only a 5.5 percent binary restenosis rate and 6.1 percent MACE, as compared with previously published results using DES for the treatment of small vessel disease with 31.2 percent restenosis and 18.9 percent MACE.

STUDY METHODOLOGY:
The Valentines II trial is a multi-center, international registry of patients who present electively with de novo lesion ≤ 24 mm in length in the native coronary system. Patients will be recruited from up to 50 centers around the globe within a period starting February 14, 2011 and completing upon adjournment of the CRT 2011 conference (February 27-March 1, 2011) or upon recruitment of 100 patients, whatever comes first. Patients will be followed with a clinical follow up at 6-9 months. A cohort of the trial will undergo angiographic follow up at 6-9 months. Baseline data includes clinical and angiographic characteristics.

MAJOR INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:
✓ Patients, male or female, ≥ 18 years of age;
✓ Patients who present electively with one or two de novo lesion(s) within the native coronary system;
✓ The patient has stable or unstable angina, and/or clinical evidence of ischemia (ECG, exercise test, etc.);
✓ The target lesion(s) is (are) in a native vessel;
✓ One or two lesions per patient;
✓ Target lesion(s) stenosis is ≥50%.
Specific Exclusion Criteria:

- The patient has had an acute myocardial infarction within the last 48 hours;
- Lesions in the Left main coronary artery (proximal to the LAD/LCX bifurcation);
- The patient has a co-morbid illness (i.e. any illness likely to limit his/her life expectancy to <8 months);
- Lesion(s) > 24mm in length
- Lesion(s) requiring additional stenting either bare metal or drug eluting (prior to DEB treatment, non bail-out indications);
- Lesions in saphenous vein grafts
- The patient is intolerant to antiplatelet therapy;
- Restenotic or in-stent restenosis lesions
- Bifurcational lesions and lesions in small vessels (< 2.5mm)
- Patients with more than two lesions requiring treatment

Pre-dilation with POBA is required. If the angiographic result is good (defined as 30% residual stenosis or less without flow-limiting dissection or the clinical need for stent implantation), then proceed to the DEB treatment with the DIOR® balloon.

In the event that a good angiographic result is not obtained post DIOR® inflation, bail-out stenting will be allowed, but those patients requiring bail-out stenting will be excluded from the final endpoint analysis. The recommendation is to ONLY use bare metal stents for bail-out purposes. These patients’ data will be collected in the eCRF.

**DURATION OF FOLLOW-UP AND DESCRIPTION:**

This multi-center registry of patients who present with one or two de novo lesions will evaluate 6-9-month clinical outcome of these patients treated with paclitaxel eluting balloon (DIOR®). All patients will be followed for 6-9 months to evaluate clinical MACE with a cohort of patients undergoing 6-9 month angiographic follow-up to evaluate angiographic late lumen loss in-stent and in-segment.

**Table 1: Schedule of Contacts**

<table>
<thead>
<tr>
<th>At time of DEB</th>
<th>Prior to Discharge</th>
<th>6-9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Demographics &amp; Medical History</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication Review</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Catheterization</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Patients will be followed via telephone or survey for 6-9 months following the paclitaxel eluting balloon treatment.
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DATA ANALYSES:
INDEX DATA ELEMENTS:
✓ Select clinical variables, risk factors, and medical history.
✓ In-hospital clinical outcomes
  o Identification of presentation with positive functional exams or stable or recurrent angina
  o Medication at admission, periprocedure and at discharge
  o Cardiac enzymes

FOLLOW-UP DATA ELEMENTS:
Follow-up data will be collected at 6-9 months post paclitaxel eluting balloon treatment.
✓ Clinical outcomes (MACE: death, MI, and target vessel and lesion revascularization) and stent thrombosis (both early and late occurrences)
  o The Academic Research Consortium (ARC) definite and probable definitions of stent thrombosis will be evaluated.

STATISTICAL ANALYSIS:
Statistical analysis will be done by the Cardiovascular Research Institute Data Coordinating Center of the Washington Hospital Center.
Categorical variables will be reported as numbers and frequencies and compared using chi-square and Fischer exact statistics. Continuous variables will be reported as mean ± SEM and compared using Wilcoxon test. For categorical data, the chi-square or Fisher exact test will be performed. Stepwise logistic regression to determine the independent predictors of current events will be used for univariate and multivariate analyses, clinical characteristics (age, gender, clinical risk factors, medication etc), and angiographic data. A two-tailed probability value < 0.05 will be considered statistically significant.

DATA COLLECTION AND ANALYSIS:
All data for analysis will be collected via an electronic data capture system and analyzed within the Cardiovascular Research Institute Data Coordinating Center of the Washington Hospital Center.

ALTERNATIVE TREATMENT(S):
Alternative treatments include standard stent implantation, DES or BMS implantation, balloon angioplasty, cutting balloon angioplasty, atherectomy, laser angioplasty or coronary artery bypass surgery.

EXPENSE – REIMBURSEMENT TO SUBJECT:
No additional expenses will be generated to the subject.