A Scientific and Rational Approach To Delineate Future Stent Platform

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Disclosure Statement of Financial Interest

I, Stephen WL Lee DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
THE NEXT ERA: COMBO DUAL THERAPY STENT

COMBO™

A Safe, No Compromise Solution for You and Your Patients
OrbusNeich Lunch Symposium
Wednesday, 25th April, 2012

THE NEXT ERA: COMBO DUAL THERAPY STENT
Endovascular Arena, Level 1
The Convention Center of Sheraton Grande Walkerhill Hotel, Seoul, Korea
Chairpersons: Seung Jung Park and Harry Suryapranata

12:45 - 12:50 Opening address - Seung Jung Park
12:50 - 13:00 The Next Era: COMBO Dual Therapy Stent - Roxana Mehran
13:00 - 13:15 COMBO - a combination sirolimus eluting and anti-CD34 antibody coated stent: technology, development, and clinical data - Stephen M Rowland
13:35 - 13:45 Q & A followed by Closing Remarks - Harry Suryapranata

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Any better choice? ...... achieving

1. Neointimal suppression without non-healing (e.g. Dual Therapy Combo Stent)
2. Scientifically predicting future stent thrombosis in new stent platform
Bern – Rotterdam cohort study
Angiographic DES Stent Thrombosis

Days after PCI | Days after stenting
--- | --- | --- | --- | --- | --- | --- |
9 | 30 | 365 | 730 | 1095 |
Incidence SES (%) | 1.0 | 1.1 | 1.3 | 1.9 | 2.5 |
Incidence PES (%) | 1.2 | 1.3 | 2.0 | 2.7 | 3.2 |
Pts at risk | 8146 | 7162 | 7002 | 2841 | 971 |

**PES** $P = 0.06$

3.2% vs 2.5%
2 first generation DES implanted 3 years ago. Completed dual anti-platelet therapy for 1 year.

Acute MI 3 years later.
Porcine overlapping model
14 days explants

Distal DES – still uncovered
Mid EPC GENOUS – covered
Prox. DES – still uncovered

**OCT** is an invaluable tool to assess stent healing in-vivo. EPC capturing is likely to be pro-healing.
Vascular Healing following Stent (especially DES) implantation

- Most powerful histological predictor of stent thrombosis = endothelial coverage
- Most powerful surrogate indicator of endothelialization = neointimal coverage
- Best morphometric predictor of LST = ratio of uncovered to total stent struts
Coronary angiogram (quantitative coronary analysis) remains the gold standard in detecting coronary atherosclerotic disease & assessment of treatment results.

Totally impossible to reveal the composition of atherosclerotic plaque. Totally incapable to show the healing responses after stenting (DES).
Identical frames in a “newly implanted” COMBO stent

IVUS resolution (100um) versus OCT resolution (10um)

IVUS has never been useful in detecting early stent coverage (healing)

FD-OCT is an invaluable tool assessing treatment results & vascular healing
Frequency Domain OCT

- Measure interference pattern: spectrum + Fourier transform
- Signal generated from all depths simultaneously
- Fixed mirror & fast image acquisition without loss of quality
- Takes only 3 seconds
C7-XR FD-OCT Image Resolution

Measure echo delay of reflected light waves

- 1 frame = 500 axial lines
- 1 axial line = 1024 pixels
- 1 pixel = 5 x 19 μm

Optical resolution:

- **axial** = 10 - 15 μm
- transverse = 20 to 40 μm

An invaluable tool for very thin neointimal tissue, strut coverage and stent healing
Usefulness of OCT

Baseline Information
- Tissue and plaque characterization
  (fibrous, lipid core, calcium, cap thickness, thrombus)
- Aiding PCI strategy (stent size & length, vulnerable plaque)

During and After PCI
- Stent strut apposition / mal-apposition, dissection, thrombus

Follow-Up Assessment
- Neointimal coverage, neointimal thickness & area, restenosis
- Late thrombosis

Research  Next Generation stent development, DAPT duration
Bio-absorbability, polymer, optimal drug dosages, eluting kinetics
Tissue Characterization & Fibroatheroma

- **Lipid**
  - low back scattering
  - high attenuation
  - top is bright
  - body is black
  - diffuse border

- **Thick Cap Fibroatheroma**

- **Fibrous tissue**
  - bright signal
  - homogenous
  - inner lumen

- **Lipid Plaque**
Tissue Characterization & Calcification

Calcified Plaque
- low backscattering (dark signal)
- low attenuation
- sharp border
- heterogeneous
Lipid plaque with thin cap
Understanding of ACS

Vulnerable Plaque

Thin-cap fibroatheroma
Large lipid core

Fibrous Cap
Lipid Core

- Large lipid pool + thin fibrous cap ≤ 65 μm
- Necrotic core > 10%.
Red and White Thrombus

White Thrombus
Low attenuation

Red Thrombus
High attenuation

Kume et al. Am J Cardiol 2006;97:1713
Circumferential mixed plaque

Already ruptured with spontaneous dissection
Stent with white thrombi
Covered stent struts
Poor healing of DES with necrotic tissue / fibrin
DES healing with positive remodeling (toxicity.....)
Bioresorbable Vascular Scaffold (BVS)

In 2 years’ time, OCT will definitely discern any residual non-absorption, with 100% accuracy.
Usefulness of OCT

Baseline Information
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Research
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Validation of OCT (Terumo) on Stent Coverage / Healing Comparing to Light and Electronic Microscopy

Validated in porcine model ......

...... clinical practice, problems ?!

...... especially in very early phases ?!

No consensus on definition of OCT stent coverage especially in very early phases (stent healing)

partially covered / uncovered ?!

uncovered

Templin C et al. Euro Heart J 2010; 31:1792–1801
The EGO-Genous Study

Evaluation of Early Healing of **Endothelial Progenitor Cell Capturing** (GENOUS) Stent by **Optical Coherence Tomography**

**Design:** Prospective, single centre study
- Treatment by GENOUS stent for stable angina or ACS/AMI
- 50 patients randomly assigned to 5 groups (10 patients each)
- Restudy OCT evaluation at 2, 3, 4, 5, 6 weeks
- Core laboratory OCT analysis *(blinded to clinical data)*
- **Endpoints:** % Strut Coverage, NIT, and NIA

**Status:** Study completed; 53 patients enrolled altogether; pending Core Lab OCT Analyses
- **Stable angina** 11 (37%), **NSTEMI** 6 (20%), **STEMI** 13 (43%)
Genous Healing Approach

Coronary blood flow

CD34 EPC Capture Technology

EPCs circulate in the bloodstream

Immobilized antibodies on the stent surface

EPCs are captured by antibodies → EPCs differentiate into endothelial cells → A mature, functional endothelium is formed

Genous stent strut
Core Laboratory (Dr. Harry Suryapranata)

(1) Malapposed Frames
(2) Frames over Side-branches
(3) Properly Apposed Frames

The EGO-Genous Study

Definitely Uncovered
Uncovered / Fibrin
Partially Covered

Uncovered

Covered

Covered (corrugated)
Covered (embedded)
Covered (proliferative)
The EGO-Genous Study (interim results)

Approaching 70% strut coverage by 15 days, & 100% by 6 weeks

6 weeks DAPT could be more than adequate for EPC stent

For the first time the healing profile of an intra-coronary stent was established, supporting possible pro-healing benefits of EPC-capturing GENOUS Stent, as already been shown by other studies.
**Genous Stent**:- a pro-healing EPC capturing stent
But similar to a bare metal stent ........ still with some late lost .......... !!

Same patient in REMEDEE Study:
2 lesions treated

Pre-Genous stenting | Post-Genous stenting | 9 months FU

Pre-Combo stenting | Post-Combo stenting | 9 months FU

**REMEDEE Study**
Late Loss = 0.39mm

**Dual Therapy COMBO Stent**:- a DES with EPC capturing + sirolimus coating
Benefits of pro-healing + neointimal suppression & less late loss like DES.
Same Patient in REMEDEE Study: OCT at 9 months

Benefits of Dual Therapy COMBO
- Fully covered struts by 9 months
- Low neointimal hyperplasia as a DES
Methods: Prospective, single center study, 60 patients treated by COMBO stent randomly assigned to 4 monthly groups. FD-OCT performed serially at baseline post-stenting, at early follow-ups in 4 groups at 2\(^{nd}\), 3\(^{rd}\), 4\(^{th}\), and 5\(^{th}\) month (for early neointimal healing), and at 9 months (for OCT late loss). Independent OCT core laboratory (blinded to the clinical data) performed the covered strut % and neointima analyses, while in-house analysis further classified the early strut coverage into 6 categories (A to F).

Status: Study completed (61 patients), 100% FU rate, pending Core Lab.
CRF Core Laboratory (Drs. Akiko Maehara & Roxana Mehran)

1. Malaposed Frames
2. Frames over Side-branches
3. Properly Apposed Frames

The EGO-Combo Study

Uncovered

Covered

Definitely Uncovered
Uncovered / Fibrin
Partially Covered

Covered (corrugated)
Covered (embedded)
Covered (proliferative)
The EGO-COMBO Study

Interim Results: As of the date of abstract submission, all 60 patients (30% diabetic, 87 COMBO stents) were enrolled and 40 had the first OCT restudy. A total of 7,004 frames and 60,069 struts were analyzed. The mean percentages of covered struts (with properly apposition) were 74.4%, 84.0%, 87.4%, & 95.6%, $p = 0.014, 0.226, & 0.046$, between 2$^{nd}$ to 5$^{th}$ month, respectively. No MACE was recorded.

Approaching 70% coverage in <50 days
Near 100% by 140 days
The EGO-COMBO Study (exponential plot)

Approaching 70% coverage in <50 days
Near 100% by 140 days

Over 12 months follow-up:
- only 1 patient has **non-ischemic** (angiographic) driven TLR treated by simple ballooning.
- no stent thrombosis / MI / death
- **9-months late loss = 0.32mm**
- **Overall 12-months TVF = 1/61 patients = 1.6%**

**COMBO Stent = quite likely a novel device**

**More results**: EuroPRC2012
Conclusions

Pure Ballooning

BMS

DES

Acute Closure

Bail-out + BMS

Restenosis 30-50%

25-35%

3-10% !!

All current DES = can achieved neointimal suppression

PCI objective = purely for achieving revascularization = without complicated issues of

But many DES still show poor Stent Healing = drug cytotoxicity, polymer hypersensitivity, local inflammatory reactions, loss endothelial and vasomotor functions

• Acute failure
• Restenosis
• Stent thrombosis
• Prolonged DAPT

• Stent thrombosis
• MACE
Sequential longitudinal OCT FU with a very stringent strut coverage classification should be adopted as a vigorous & novel step for guiding any new stent platform.

Proper stent apposition

Degree of early coverage (healing profile)

Guiding appropriate DAPT duration

9 to 12 months OCT (late loss NIH)

Little late loss as a DES

Reduced stent thrombosis

Very stringent strut coverage classification

May predict / prevent late stent thrombosis, rather than waiting for years to observe for adverse effects.