Beyond DES: Peripheral Vascular Disease, TAVR, and Hypertension

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City
Presenter Disclosure Information for TCTAP 2011; April 27-29, 2011

Martin B. Leon, M.D.

**NON-PAID Consultant:** Abbott, Boston Scientific, Edwards Lifesciences, Medtronic

**Consultant:** Neovasc, Symetis,

**Equity Relationship:** Coherex, GDS, Medinol, Mitralign, Sadra
Interventional Opportunities

FUTURE!

- Structural Heart Disease
- Hypertension
- Novel (new) Anti-restenosis Therapy
- Out-of-the-box Concepts
Interventional Opportunities

**FUTURE!**

Structural Heart Disease
STRUCTURAL Heart Disease

What is it?

STRUCTURAL heart disease… “wastebasket” term referring to…

All catheter-based interventional therapies which are not associated with vascular pathology requiring “endoluminal” endovascular treatment.
 STRUCTURAL Heart Disease

Why the excitement?

- **New patient care treatment alternatives for “common” diseases (e.g. hypertension, migraines)**
- **Completely “additive” to current cath lab procedural activities**
- **Crosses sub-specialty territorial boundaries (e.g. imaging, surgery)**
- **Requires new training and educational initiatives (e.g. simulation)**
- **Extra-ordinary economic market potential!!!**
The Future Growth of IC Markets

Driven by New Segments

Boston Scientific Internal Estimates

- PAVR (aortic)
- PMVR (mitral)
- LAA Occlusion
- PFO Closure
- Hypertension

$0.4B
$2.5B
$8B

2009
2014
2019
Transcatheter Valve Therapy (TVT)

Predicting the Future

TVT is the MOST EXCITING new procedure in interventional cardiovascular therapeutics!!!
Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis
First Human Case Description
Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; Francois Laborde, MD; Martin B. Leon, MD

Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

April 16, 2002
TAVR Technologies

Current Generation Devices

~ 25,000 patients treated thru 2010 in > 450 interventional centers around the world!

Edwards Lifesciences
The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Parneela C. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

On behalf of the Executive Committee, the Investigator Sites, and the courageous patients who participated in the PARTNER trial!
PARTNER Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High Risk AVR Candidate
3105 Total Patients Screened
Total = 1057 patients

n= 699
High Risk

ASSESSMENT: Transfemoral Access

High Risk TF
1:1 Randomization
TAVI Transfemoral
VS Surgical AVR
Primary Endpoint: All Cause Mortality (1 yr) (Non-inferiority)

High Risk TA
1:1 Randomization
TAVI Transapical
VS Surgical AVR

n=358
Inoperable

ASSESSMENT: Transfemoral Access

High Risk TF
1:1 Randomization
TAVI Transfemoral
VS Standard Therapy (usually BAV)
Primary Endpoint: All Cause Mortality over length of trial (Superiority)

High Risk TA
1:1 Randomization
TAVI Transapical
VS Surgical AVR

2 Parallel Trials: Individually Powered

Total = 1057 patients

1:1 Randomization
VSVS

Standard Therapy (usually BAV)
Not In Study

1:1 Randomization
VSVS

1:1 Randomization
VSVS

Primary Endpoint: All Cause Mortality (1 yr) (Non-inferiority)
Primary Endpoint: All Cause Mortality over length of trial (Superiority)
1\textsuperscript{st} EP: All Cause Mortality

HR [95% CI] = 0.54 [0.38, 0.78]
P (log rank) < 0.0001

\[ \Delta \text{ at 1 yr} = 20.0\% \]

NNT = 5.0 pts

<table>
<thead>
<tr>
<th>Numbers at Risk</th>
<th>TAVI</th>
<th>Standard Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVI</td>
<td>179</td>
<td>138</td>
</tr>
<tr>
<td>Standard Rx</td>
<td>179</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>122</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>12</td>
</tr>
</tbody>
</table>
PARTNER: Quality of Life
KCCQ Overall Summary

MCID = 5 points

Δ = 13.9
P<0.001

Δ = 20.7
P<0.001

Δ = 24.5
P<0.001

MCID = minimum clinically important difference
Cost-Effectiveness of TAVR vs. Control Lifetime Results

Cost = $79,837
LE = 1.59 years
ICER = $50,212/LYG

$100,000 per LY

$50,000 per LY

ΔCost = $79,837
Δ LE = 1.59 years
ICER = $50,212/LYG
Primary Endpoint: All-Cause Mortality at 1 Year

HR [95% CI] = 0.93 [0.71, 1.22]
P (log rank) = 0.62
P non-inferiority = 0.001
All-Cause Mortality
Transfemoral (N=492)

HR [95% CI] = 0.83 [0.60, 1.15]
P (log rank) = 0.25
P non-inferiority = 0.002
Patients Will Always Come First!

Patient #1

92 yo man with critical AS…
TAVI at CUMC on 2/8/06…
Playing golf in Palm Springs on 3/8/06!!!
Catheter-Based Mitral Valve Repair
MitraClip® System

Investigational Device only in the US;
Not available for sale in the US
EVEREST II Randomized Clinical Trial

Study Design

279 Patients enrolled at 37 sites

- Significant MR (3+-4+)
- Specific Anatomical Criteria

Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair or Replacement
N=95

Echocardiography Core Lab and Clinical Follow-Up:
- Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years
EVEREST II RCT: Primary Endpoints
Per Protocol Cohort

Safety Major Adverse Events
30 days

- Device Group, n=136: 9.6%
- Control Group, n=79: 57.0%

\[ p_{SUP} < 0.0001 \]

Met superiority hypothesis
- Pre-specified margin = 6%
- Observed difference = 47.4%
- 97.5% LCB = 34.4%

Effectiveness Clinical Success Rate*
12 months

- Device Group, n=134: 72.4%
- Control Group, n=74: 87.8%

\[ p_{NI} = 0.0012 \]

Met non-inferiority hypothesis
- Pre-specified margin = 31%
- Observed difference = 15.4%
- 95% UCB = 25.4%

* Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR >2+ at 12 months

LCB = lower confidence bound
UCB = upper confidence bound
November 20, 2010 | Frankfurt, Germany

LAA 2010 – How to Close the Left Atrial Appendage

www.csi-congress.org/laa-workshop
WATCHMAN LAA Filter System

- **Nitinol**
  - Contour shape accommodates most LAA anatomy
  - Barbs engage the LAA tissue
- **PET Filter**
  - Prevents embolization
  - Reduces the pressure on the peripheral seal until endothelialization has occurred
- **Available in 4 sizes**
Primary Efficacy Over Time

Event-free probability vs. Days from randomization for Watchman and Control groups.

- Watchman: 244, 207, 115, 33, 7
- Control: 463, 377, 230, 82, 14
Interventional Opportunities

FUTURE!

- Structural Heart Disease
- Hypertension
Chronic Hypertension

Significant Unmet Clinical Need

- Astonishing prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6B by 2025
- Single largest contributor to death
- Every 20 mmHG increase in systolic BP doubles 10-year cardiovascular mortality
- Dramatically increases risk of heart attack, stroke, heart failure, kidney failure & insulin resistance
- Only half of all treated hypertensives are controlled to established BP targets
  - Physician Inertia
  - Patient Compliance
  - Resistant HTN

Hypertension medications work, but not as well as you may think

Renal Sympathetic Efferent Nerve Activity

Kidney as Recipient of Sympathetic Signals

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
Renal Sympathetic Afferent Nerves

Kidney as Origin of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis
- Insulin Resistance
- Sleep Disturbances
- Hypertrophy
- Arrhythmia
- Oxygen Consumption
- Sodium Retention
- Renin Release → RAAS activation
- Renal Blood Flow
Renal Nerve Anatomy Allows a Catheter-Based Approach

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms

In the United States: Caution: Investigational Device. Limited by U.S. law to investigational use.
Staged Clinical Evaluation

First-in-Man ✓
Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA
Symplicity HTN-3
US Randomized Clinical Trial (upcoming)

EU/AU
Other Areas of Research:
Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More
Initial Cohort – Reported in the Lancet, 2009:

- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

Expanded Cohort – This Report (Symplicity HTN-1):

- Expanded cohort of patients (n=153)
- 24-month follow-up
Significant, Sustained BP Reduction

<table>
<thead>
<tr>
<th>Time (M)</th>
<th>BP Change (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=138)</td>
<td>-20, -10</td>
</tr>
<tr>
<td>3 (n=135)</td>
<td>-24, -11</td>
</tr>
<tr>
<td>6 (n=86)</td>
<td>-25, -11</td>
</tr>
<tr>
<td>12 (n=64)</td>
<td>-23, -11</td>
</tr>
<tr>
<td>18 (n=36)</td>
<td>-26, -14</td>
</tr>
<tr>
<td>24 (n=18)</td>
<td>-32, -14</td>
</tr>
</tbody>
</table>

Systolic and Diastolic BP changes over time.
• **PURPOSE:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial

• **PATIENTS:** 106 patients randomized 1:1 to treatment with renal denervation vs. control

• **CLINICAL SITES:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)
Primary Endpoint: 6-Month Office BP

- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Interventional Opportunities

FUTURE!

Structural Heart Disease

Novel (new) Anti-restenosis Therapy

Hypertension
Rationale for the Clinical Use of DEB for the Prevention of Restenosis

- Shown to be efficacious in reducing restenosis in humans in specific clinical situations (ISR).
- Easy concept, rapid adoption, no learning curve…balloon-based technology.
- Cost-effective strategy…if used alone or with BMS…
- Potential for improved safety: no chronic polymer effects + “shorter” drug exposure = potential for enhanced biocompatibility.
- Complements DES= use in situations where DES problematic or less effective, e.g. ISR, bifurcations, small vessels, diffuse disease.
DEB Technology: How Does It Work?

**DEB Components**

**The Drug - Paclitaxel:**
- Provides appropriate anti-restenotic drug therapy for an acute delivery system such as a DEB.
- Facilitates acute delivery due to hydrophobicity and tight binding to the microtubule subunit.
- Allows for increased potency for single-shot therapy.
- Limits drug toxicity with DEB delivery.

**Drug Components:**
- Balloon catheter (standard PTCA or PTA)
- Drug
- Matrix
The In.Pact products use urea as an excipient.

**The excipient:**
- Separates paclitaxel molecules to increase drug solubility and balance hydrophobicity.
- Provides drug transfer time in 30–60 seconds.
- Remains in the artery post-procedure along with the anti-restenotic drug.

The In.Pact products use urea as an excipient.
As the balloon unwraps, the drug-excipient coating is fully exposed to the vessel wall.

Paclitaxel’s hydrophobicity along with the increased solubility conferred by the excipient allows for rapid drug diffusion across the vessel wall.
Invatec FreePac™ DEB Technology

- Proprietary hydrophilic coating formulation
- Paclitaxel (3 μg/mm² balloon surface)
- Urea
  - Hydrophilic additive
  - Natural degradation product of protein synthesized in the liver
  - One of the most common substances in human serum (100-500 mg/liter)
  - Low toxicity, no hypersensitivity reactions
- Undisclosed solvents
• Dose of 3 µg/mm² was determined to be the optimal dose, with significant activity 1 µg/mm²
The majority of paclitaxel is cleared from the media at 24 hours, but retention of therapeutically relevant drug levels in the media are maintained for at least 28 days.

IN.PACT BTK Registry Leipzig (LINC 2010)

- Prospective registry of patients with BTK-lesions
- In.Pact Amphirion paclitaxel-coated balloon
- Angiography after 3 months
- Clinical FU 3, 6 and 12 months
- 102 pts. treated with In.Pact Amphirion
  - 3 months FU available in 64 pts.
  - 2 pts. died
    - 1 cardiac death, 1 major amputation
  - 15 pts. did not come to the 3-months FU

Schmidt A, LINC 2010
IN.PACT BTK Registry Leipzig (LINC 2010)

- Angiographic FU in 48 pts
- Diabetes mellitus 41 / 48 (85 %)
- Lesions treated with In.Pact Amphirion
  - De-novo 28 (58 %)
  - Restenosis 15 (31 %)
  - In-stent restenosis 5 (11 %)
  - Mean lesion-length 170 ± 76 mm
  - Total occlusion 28 (58 %)

Schmidt A, LINC 2010
The Leipzig Experience with Drug-Eluting Balloons in BTK

A. Schmidt, MD
Department of Angiology
Heart Center & Park Hospital
Leipzig, Germany

Schmidt A, LINC 2010

3 months angiographic FU

- Restenosis >50%
  - POBA: 69%
  - InPact: 31%

- Restenosis whole segment
  - POBA: 56%
  - InPact: 15%
Interventional Opportunities

*FUTURE*

- Structural Heart Disease
- Hypertension
- Novel (new) Anti-restenosis Therapy
- Out-of-the-box Concepts
Erectile Dysfunction is Prevalent

- ~25 million men in the United States
- >300 million men worldwide

Causes of Erectile Dysfunction

- **Etiology**
  - 80% *Vasculogenic*
  - Traumatic
  - Post-surgical
  - Hormonal
  - Chronic disease- DM, CRI
  - Medication
  - Psychological

Lue. NEJM 2000;342:1803
Medtronic ZEN Trial

Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Suboptimal Response to PDE5 Inhibitors

• Prospective, single arm trial
• Endpoints: 1° Safety, 2° Efficacy
• Enrolling 50 patients, 15 U.S. centers
Left Internal Pudendal Stenosis and Rx

LEFT INTERNAL PUDENDAL STENOSIS

AFTER 3.0 X 18 MM STENT
Over more than three decades, interventional cardiology has evolved in stages, challenging conventional wisdom and overcoming biologic obstacles.

Innovation combined with a commitment to rigorous scientific principles and a dedicated global collaboration has resulted in a vibrant medical subspecialty.

BUT, during challenging times, interventional cardiology is at a crossroads – the re-emergence of medical therapy (post-COURAGE) and CABG (post-SYNTAX) coupled with financial pressures threaten to limit future vascular interventional growth.
Now is the time to rediscover past success by extending the interventional model to other unmet cardiovascular needs.

The breakthrough emergence of TAVI is the first step as interventional cardiology enters a new phase of striking diversity and creativity.

The interventional community must respond by embracing change and providing the milieu future growth.
Interventional Opportunities

The FUTURE!

There’s never been a better time to be an interventional cardiologist!
Interventional Opportunities

The FUTURE!

Our Message: ADAPT and EVOLVE!