Late Breaking Clinical Trials

Ted Feldman, M.D., FSCAI, FACC

Angioplasty Summit
April 25-27th 2007
Seoul, Korea
Ted Feldman MD, FACC, FSCAI

Disclosure Information

The following relationships exist:

**Grant support:** Abbott, Atritech, BSC, Cardiac Dimensions, Cordis, Evolve, St Jude
**Consultant:** BSC, Cardiac Dimensions, Cordis, Edwards, Myocor
**Speaker:** Boston Scientific

*Off label use of products and investigational devices will be discussed in this presentation*
Our findings reinforce existing clinical practice guidelines, which state that PCI can be safely deferred in patients with stable coronary artery disease, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, multifaceted medical therapy is instituted and maintained. As an initial management approach, optimal medical therapy without routine PCI can be implemented safely in the majority of patients with stable coronary artery disease. However, approximately one third of these patients may subsequently require revascularization.


March 27, 2007

Medicine enough for pain in chest?

Study sees way to avoid angioplasty

By Steve Sternberg
USA TODAY

NEW ORLEANS — Thousands of people with crushing chest pain who once opted for angioplasty as a quick fix may change their minds based on a landmark study out Monday showing that medication costs less, poses fewer risks and works just as well.

“I think this will change the discussion between the patient and doctor,” says Raymond Gibbons of the

```Angioplasty vs. medication
A landmark trial of 2,287 patients pitted angioplasty and medication vs. medication alone.

- Angioplasty group
  - Rate of deaths, heart attacks and strokes: 20%, 19.5%

- Drug group
  - Rate of deaths, heart attacks and strokes: 12.4%, 11.8%

Hospitalization rate for heart attacks and worsening chest pain

- Angioplasty group: 13.2%, 12.3%

Source: The New England Journal of Medicine
```
COURAGE Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Favors PCI</th>
<th>Favors Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death &amp; non-fatal MI</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>Hosp for ACS</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)
Design and rationale of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial: Veterans Affairs Cooperative Studies Program no. 424

<table>
<thead>
<tr>
<th></th>
<th>Death &amp; MI</th>
<th>PCI</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Projected</td>
<td></td>
<td>16.4%</td>
<td>21%</td>
</tr>
<tr>
<td>Actual</td>
<td></td>
<td>19%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

Background
Most patients with coronary artery disease have occult myocardial ischemia, including clinical end points of death or MI. Aggressive multifaceted medical therapy (OMT) may increase the “hard” end points and does not consistently improve QOL.

Methods
The COURAGE trial randomized 2287 patients to PCI or OMT. PCI plus OMT included: aspirin, clopidogrel, atorvastatin (low-density lipoprotein cholesterol target 50–80 mg/dL), long-acting metoprolol and/or amlodipine, lisinopril or losartan, and long-acting nitrates, as well as lifestyle interventions. The primary end point was the composite of all-cause mortality or acute myocardial infarction, and there will be 85% power to detect an absolute 4.6% (relative 22%) difference between strategies. The principal hypothesis is that PCI plus aggressive medical therapy (projected event rate 16.4%) will be superior to aggressive medical therapy alone (projected event rate 21%) during a 2.5- to 7-year (median of 5 years) follow-up.

Conclusions
COURAGE is the largest prospective randomized trial of PCI versus intensive medical therapy to date and will define the incremental benefits of PCI in the setting of contemporary optimal medical therapy for chronic coronary heart disease. A total of 2287 patients have been enrolled, and follow-up will conclude in June 2006. (Am Heart J 2006; 151:1173-9.)
Incomplete Revascularization

POBA 14.5% - DES 1.8%

- Diseased vessels
- Number of stents

21% Re-PCI due to incomplete revascularization?
40% started with minimal or no angina
30% crossed over
72% angina free at 5 years
# Long-Term Improvement in Treatment Targets

*Group Median ± SE Data*

<table>
<thead>
<tr>
<th>Treatment Targets</th>
<th>Baseline</th>
<th>60 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI +OMT</td>
<td>OMT</td>
</tr>
<tr>
<td>SBP</td>
<td>131 ± 0.77</td>
<td>130 ± 0.66</td>
</tr>
<tr>
<td>DBP</td>
<td>74 ± 0.33</td>
<td>74 ± 0.33</td>
</tr>
<tr>
<td>Total Cholesterol mg/dL</td>
<td>172 ± 1.37</td>
<td>177 ± 1.41</td>
</tr>
<tr>
<td>LDL mg/dL</td>
<td>100 ± 1.17</td>
<td>102 ± 1.22</td>
</tr>
<tr>
<td>HDL mg/dL</td>
<td>39 ± 0.39</td>
<td>39 ± 0.37</td>
</tr>
<tr>
<td>TG mg/dL</td>
<td>143 ± 2.96</td>
<td>149 ± 3.03</td>
</tr>
<tr>
<td>BMI Kg/M²</td>
<td>28.7 ± 0.18</td>
<td>28.9 ±</td>
</tr>
<tr>
<td>Moderate Activity (5x/wk)</td>
<td>25%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Anti-Anginal Therapy after 5 Years

Ca Blocker
- PCI: 42%
- Medical Rx: 52%

Nitrate
- PCI: 40%
- Medical Rx: 57%

PCI or CABG
- PCI: 20%
- Medical Rx: 32%
CRUSADE Registry
Compliance with Medical Therapy in Patients with CAD

- Selected population
- Rigorous optimal medical therapy (OMT) regimen
- Incomplete revascularization
  - BMS & POBA
  - procedure success 89%
  - device success 93%
- Trend toward less mortality with PCI
- High rate of cross-over in OMT arm
- Reinforces existing guidelines
A Randomized Controlled Trial for the Prevention of Contrast Induced Nephropathy with Sodium Bicarbonate in Persons Undergoing Coronary Angiography (MEENA)

Somjot S. Brar, MD
Kaiser Permanente
Los Angeles Medical Center
Study Flow

353 Patients Undergoing Coronary Angiography, GFR ≤ 60

Sodium Chloride

178 Patients

22 Excluded*
6 Had early CABG
3 Had Early PCI
11 Had Incomplete Follow Up Lab Data
2 Had the Coronary Angiogram Canceled

156 Patients

Sodium Bicarbonate

175 Patients

28 Excluded*
8 Had Early CABG
3 Had Early PCI
16 Had Incomplete Follow Up Lab Data
1 Had the Coronary Angiogram Canceled

147 Patients

* p=0.33

(1:1)
GFR & Creatinine Endpoints

**Primary Endpoint**

(≥ 25% Decrease in GFR)

**Secondary Endpoint**

(≥ 25% Increase in Creatinine)

**Incidence of Contrast Induced Nephropathy (%)**

- **GFR**
  - NaCl: 13.5
  - NaHCO₃: 13.6
  - p = 0.97

- **Creatinine**
  - p = 0.82
  - NaCl: 15.4
  - NaHCO₃: 16.3
Conclusion

Hydration with Sodium Bicarbonate or Sodium Chloride in patients undergoing coronary angiography with a GFR ≤ 60 resulted in very similar rates of Contrast Induced Nephropathy.
DISCLOSURE INFORMATION:
The following relationships exist related to this presentation:
None

UNLABELED/UNAPPROVED USE:
The following products are not labeled for the use under discussion or are still investigational:
Sodium Bicarbonate for the Prevention of Contrast Induced Nephropathy
Low REsponsiveness to CLOpidogrel and Sirolimus- or Paclitaxel-Eluting StEnt Thrombosis (RE-CLOSE) Trial

Department of Cardiology, Careggi Hospital, Florence, Italy


David Antoniucci, MD, ACC 2007
Primary End Point

Definite/Probable Thrombosis

<table>
<thead>
<tr>
<th>% at 6 Months</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>8.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>n=699</td>
<td>n=105</td>
</tr>
</tbody>
</table>

Late Stent Thrombosis

<table>
<thead>
<tr>
<th>%</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>0.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>n=699</td>
<td>n=105</td>
</tr>
</tbody>
</table>

P<.001
Long-Term Safety of DES in Off-Label Use: Results of the MATRIX Registry

George D. Dangas, MD, PhD, FACC
On Behalf of the Matrix Investigators

Cardiovascular Research Foundation
Columbia University Medical Center
MATRIX: Goals and Design

- Prospective single arm study initiated in 2004 as a 3,500 patient trial under an investigator-initiated IDE

- Both on- and off-label SES use

- Clinical follow-up at 1 month, 6 months, 1 year and 2 years thus far
## Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of stents per procedure</td>
<td>2.0 ± 1.2</td>
</tr>
<tr>
<td>No. of stents per lesion</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>16.0%</td>
</tr>
<tr>
<td>Bivalirudin used</td>
<td>84.9%</td>
</tr>
<tr>
<td>IIb/IIIa inhibitors administered</td>
<td>8.1%</td>
</tr>
<tr>
<td>Procedure success</td>
<td>95.6%</td>
</tr>
<tr>
<td>Device success (N=2608 Lesions)</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

N = 1,522 patients
On-Label Use of Cypher Stent

- The CYPHER Sirolimus-eluting Coronary Stent is indicated in patients with symptomatic ischemic disease due to discrete de novo lesions of length < 30 mm in native coronary arteries with a reference vessel diameter of > 2.5 to < 3.5 mm (http://www.fda.gov/cdrh/PDF2/p020026c.pdf).

- On-label definition in MATRIX: De novo lesion; 1 lesion; 1 vessel; Lesion length < 30mm; RVD 2.5-3.5mm; Also excluding:
  - Diffuse disease
  - Multivessel PCI; PCI with 3 of more SES
  - Use of rotablator, atherectomy or laser
  - Use of thrombectomy or intracoronary thrombus
  - Acute ST elevation MI within 72 hours before the procedure
  - ACS with positive CKMB prePCI
  - Ostial lesions
  - Bifurcation lesions
  - Chronic occlusions, baseline TIMI flow 0 or 1
  - Vein grafts, LIMA/RIMA, radial or GEA grafts
  - Angioplasty restenosis or in-stent restenosis
  - Severe calcification; Severe tortuosity

14% Of Patients in MATRIX w/o any of above
Stent Thrombosis (K-M analysis)

* Stent thrombosis included the definite and probable thromboses by ARC

P=0.829

P=0.826

P=0.826

P=0.649

* On-label
* Off-label

MATRIX Registry
# Prediction of 2-Year Adverse Outcomes

## Multivariate Predictors Using Cox Model

<table>
<thead>
<tr>
<th>2-Year Events</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (32 events)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.09</td>
<td>1.05 - 1.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>4.03</td>
<td>1.94 - 8.38</td>
<td>0.0002</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6.69</td>
<td>1.58 - 28.34</td>
<td>0.0099</td>
</tr>
<tr>
<td><strong>Cardiac death (11 events)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.11</td>
<td>1.04 - 1.18</td>
<td>0.0028</td>
</tr>
<tr>
<td>DM</td>
<td>3.81</td>
<td>1.11 - 13.08</td>
<td>0.0334</td>
</tr>
<tr>
<td><strong>Definite or probable stent thrombosis (12 events)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Renal Insufficiency</td>
<td>4.45</td>
<td>1.34 - 14.79</td>
<td>0.0148</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>1.03</td>
<td>0.99 - 1.07</td>
<td>0.0977</td>
</tr>
</tbody>
</table>

Candidate predictors included on-label use, ACS, multivessel/stent PCI, RVD, clopidogrel.
## Prediction of 2-Year Adverse Outcomes

### Multivariate Predictors Using Cox Model

<table>
<thead>
<tr>
<th>2-Year Events</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (43 events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.03</td>
<td>1.00 to 1.06</td>
<td>0.0325</td>
</tr>
<tr>
<td>Male</td>
<td>0.50</td>
<td>0.27 to 0.93</td>
<td>0.0273</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.83</td>
<td>1.42 to 5.64</td>
<td>0.0031</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>1.03</td>
<td>1.01 to 1.06</td>
<td>0.0024</td>
</tr>
<tr>
<td>TVR (107 events)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-label</td>
<td>0.53</td>
<td>0.26 to 1.10</td>
<td>0.0870</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.98</td>
<td>0.96 to 0.99</td>
<td>0.0156</td>
</tr>
<tr>
<td>DM</td>
<td>1.72</td>
<td>1.18 to 2.52</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

Candidate predictors included on-label use, ACS, multivessel/stent PCI, RVD, clopidogrel.

**MATRIX Registry**
In 1,522 patients with complex CAD treated with SES, off-label use of SES using a strict definition was evident in 86% of patients.

In Matrix, we found:

- Low frequency of early and late adverse events considering the complexity of patients and lesions treated
  - 2-year death 3.3%, death/MI 6.8%, death/MI/TVR 15.6%
- 2-year stent thrombosis rate 1.1%
  - ARC definite/probable definitions
  - Independent event adjudication
- Similar mortality in on- vs off-label use
  - MI and TVR were higher with off-label application
  - Independent predictors of mortality, stent thrombosis and MI included baseline patient and lesion characteristics (i.e. Age, DM, Renal failure, lesion length) as opposed to off-label application and procedure factors.
Clinical Evaluation of the Abbott Vascular BVS Bioabsorbable Everolimus Eluting Coronary Stent System in the Treatment of Subjects with de novo Native Coronary Artery Lesions

Patrick Serruys, MD, PhD
Co-Principal Investigator of the ABSORB Trial
Bioabsorbable Polymer

Everolimus/PLA Matrix Coating
- Thin coating layer
- Amorphous (non-crystalline)
- 1:1 ratio of Everolimus/PLA matrix
- Conformal Coating
- Controlled drug release

PLA Stent Backbone
- Highly crystalline
- Provides stent integrity
- Processed for increased radial strength

Product currently in development at Abbott Vascular. Not available for sale.
QCA/IVUS Patient inclusion

- 30 patients
  - n = 4 excluded*
    - 3 bailout stenting
    - 1 device failure
  - 26 patients
    - 6 months QCA
  - 24 patients
    - n = 2 IVUS not analyzable
    - 6 months IVUS

* Per treatment evaluable population. Four patients were excluded who received a non-BVS bailout stent, including one patient who did not receive a BVS stent at the target lesion.

Product currently in development at Abbott Vascular. Not available for sale.
What is Contributing to Late Loss?

**SPIRIT-First ML Vision Stent**
- Δ Vessel Area (mm²) = -0.29 (-1.9%)
- Δ Stent Area (mm²) = -0.14 (-2.0%)
- Δ Lumen Area (mm²) = -2.12 (-29.4%)
- NIH Area (mm²) = 1.98
- % VO = 28.1%
- Late Loss = 0.87mm

**SPIRIT-First Xience V Stent**
- Δ Vessel Area (mm²) = 0.19 (+1.2%)
- Δ Stent Area (mm²) = -0.02 (-0.3%)
- Δ Lumen Area (mm²) = -0.51 (-7.2%)
- NIH Area (mm²) = 0.50
- % VO = 8.0%
- Late Loss = 0.10mm

**ABSORB BVS Stent**
- Δ Vessel Area (mm²) = -0.06 (-0.4%)
- Δ Stent Area (mm²) = -0.71 (-11.7%)
- Δ Lumen Area (mm²) = -1.01 (-16.6%)
- NIH Area (mm²) = 0.30
- % VO = 5.5%
- Late Loss = 0.44mm
Randomized Comparison of the Effect of Distal Protection and Drug Eluting Stent versus Bare Metal Stent Implantation during Percutaneous Coronary Intervention for ST-elevation Myocardial Infarction

The DEDICATION study


Rigshospitalet, Copenhagen
Aarhus University Hospital, Skejby
Denmark
Patients with Acute ST-elevation Myocardial Infarction
n=626

Randomization

Primary PCI + Distal Protection (n: 312)

Primary PCI - Distal Protection (n: 314)

Primary end point

ECG ST-resolution at 30-90 min

Secondary endpoints

Post procedure TIMI flow
Wall motion index at discharge
Cardiac biomarker release
Major adverse cardiac and cerebral events at 30 days
Primary Endpoint: ST-Segment Resolution

- Distal protection: 76%
- Conventional treatment: 72%

Log Rank, P=0.27

Graph showing time from 1.wire (minutes) versus patients achieving >70% ST-resolution.
EVEREST Registry

Significant Reduction in Mitral Regurgitation Twelve Months Following Percutaneous Mitral Valve Repair: Initial Experience With the MitraClip Device

Ted Feldman, M.D., FSCAI, FACC
for the EVEREST Investigators

ACC - New Orleans
March 26th 2007
Percutaneous Mitral Repair

Caution: Investigational Device. Limited by Federal (US) Law to Investigational Use
Event Free Clinical Success Kaplan-Meier
Patients with Acute Procedural Success
n = 79

Freedom from death, mitral valve surgery, & MR>2
The MONARC system
Delayed Release-\textit{in situ}
EVOLUTION study interim performance data

**Mean MR Value**

- **Baseline Grade 3-4+**
  - Baseline: 3.4 (n = 22)
  - 30 Days: 2.7 (n = 42)
  - 90 Days: 2.6 (n = 30)
  - 180 Days: 2.3 (n = 27)

- **Baseline Grade 2-4+**
  - Baseline: 2.1 (n = 30)
  - 30 Days: 2.0 (n = 27)
  - 90 Days: 1.6 (n = 13)
  - 180 Days: 1.4 (n = 13)

**Mean MR Reduction over Time**

- **Sustained Device Tension**
  - Active Device Foreshortening (6 Weeks)

*Echo Core Lab data*