DES in Diabetic Patients

Charles Chan, M.D., FACC
Gleneagles Hospital
Singapore

TCT ASIA PACIFIC 2007
Why do diabetics have worse outcome after PCI?

- More extensive atherosclerosis and diffuse disease
- Increase prevalence of multivessel disease
- Smaller vessel and longer lesions
- More highly stenotic lesions and higher plaque burden
- Higher incidence of left main disease
Why does Diabetes increase restenosis after PCI?

- Increase insulin
- Increase oxidative stress and inflammation (Fibrinogen and C reactive protein expression)
- Impaired vasomotor activity and increase smooth muscle cell proliferation
- Proatherogenic protein glycation
- Altered coagulation / fibrinolysis (Prothrombotic and increased PAI-1)
- Increased IIa / IIIb receptor numbers
Impact of DES vs BMS in Diabetic Patients
Issues concerning DES in Diabetic Patients

Diabetic patients: Heterogenous population i.e insulin/non-insulin, large / small vessels, focal / diffuse disease

None of the randomized Cypher & Taxus trials were designed or powered to prospectively assess the comparative efficacy of DES in DM and non-DM patients
Randomized Controlled Trials Designed To Evaluate Efficacy in Patients with Diabetes

- RCTs – CYPHER® Stent vs. BMS
  - DIABETES Trial
  - DECODE Trial
  - SCORPIUS Trial

- RCTs – Taxus Stent vs. BMS
  - None currently exist

- RCTs and Meta-Analysis – CYPHER® Stent vs. Taxus Stent
  - ISAR-DIABETES
  - SIRTAX Trial (Pre-specified sub-analysis)
The DECODE Study: 12-Month Analysis

A RANDOMIZED STUDY WITH THE SIROLIMUS-ELUTING BX VELOCITY™ BALLOON-EXPANDABLE STENT IN THE TREATMENT OF DIABETIC PATIENTS WITH NATIVE CORONARY ARTERY LESIONS

Charles Chan, Robaayah Zambahari, Upendra Kaul, Sidney A. Cohen, Maurice Buchbinder, on behalf of the DECODE Study Investigators

AHA 2005
Multi-center, Open-label, Prospective, randomized controlled trial
200 diabetic patients (100 in US and 100 in Asia/Pacific) undergoing
multi-lesion/multi-vessel PCI

Randomize 2:1
(Stratification by pre-PCI prediction of IIb/IIla use)

Sirolimus-eluting Stent (SES)
Bare-Metal Stent (BMS)

Clinical Evaluations at 30 days, 6 months and 1 year post-PCI
Repeat angiography at 6 months post-PCI
Primary Endpoint: Angiographic In-stent Late Loss at 6 months
There was no stent thrombosis in either treatment group.
Freedom From MACE Through 12 Months (N=120)

Intent-to-Treat Analyses

DECODE

Event-free Survival (%)

Days of Follow-up

SES

Bare-Metal Stent

P = 0.006

AHA 2005; Oral Presentation.
MACE at 24 Month Follow-up
The DIABETES Trial (N=160)

The CYPHER® Stent Demonstrated Comparable Safety and Superior Efficacy in Diabetic Patients vs. BMS

J Am Coll Cardiol 2006;47:2172–9
MACE at 8 Month Follow-up
The SCORPIUS Trial (N=190)

The CYPHER® Stent Demonstrated Comparable Safety and Superior Efficacy in Diabetic Patients vs. BMS

TCT 2006, Oral Presentation
RCTs Designed To Compare the Taxus Stent vs. BMS in Diabetic Patients (N=0)

The Taxus Stent Has Not Been Tested in RCTs Designed To Compare Taxus Stent vs. BMS in Diabetic Patients
Meta-analysis of Randomized Cypher & Taxus Trials

- Diabetics subgroup analysis
- Long-term safety data
CYPHER Trials – Late Loss in DM pts

- **In Stent**
  - Control: 1.19 mm
  - Sirolimus: 0.26 mm
  - P < 0.0001

- **In Segment**
  - Control: 0.96 mm
  - Sirolimus: 0.32 mm
  - P = 0.0006

Control = 158, Sirolimus = 211
## Sirolimus-Eluting stents in Diabetics with Multivessel disease – 1 Yr. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>SES 100 pts</th>
<th>BMS 122 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death %</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Myocardial infarction %</td>
<td>10</td>
<td>9.8</td>
</tr>
<tr>
<td>CVA %</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Revascularization %</td>
<td>17</td>
<td>41 *</td>
</tr>
<tr>
<td>CABG %</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>PCI %</td>
<td>15</td>
<td>35 *</td>
</tr>
<tr>
<td>MACCE %</td>
<td>25</td>
<td>44 *</td>
</tr>
</tbody>
</table>
# Events Through 4 Years: Diabetic Subgroups

<table>
<thead>
<tr>
<th>Diabetic Subgroups</th>
<th>CYPHER® Stent</th>
<th>BMS</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL (n=44)</td>
<td>6</td>
<td>2</td>
<td>0.056</td>
</tr>
<tr>
<td>SIRIUS (n=279)</td>
<td>14</td>
<td>6</td>
<td>0.037</td>
</tr>
<tr>
<td>E–SIRIUS (n=81)</td>
<td>2</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>C–SIRIUS (n=24)</td>
<td>1</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Mortality</td>
<td>11.8% (23 / 195)</td>
<td>4.3% (10 / 233)</td>
<td>0.006</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>6.2% (12 / 195)</td>
<td>8.2% (19 / 233)</td>
<td>0.460</td>
</tr>
</tbody>
</table>

Limitation: Results are derived from post-hoc analyses of non-randomized subgroups

*Fisher’s Exact Test p-value

All data are adjudicated by an independent Clinical Events Committee (CEC)

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, Mi and stent thrombosis
Cypher™ Stent all-cause mortality to 4 years in Diabetic sub-group vs total population

The Difference in Diabetic Mortality is More Apparent in Cardiac Death

RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>195</td>
<td>233</td>
</tr>
<tr>
<td>All Death</td>
<td>23 (11.8%)</td>
<td>9 (3.9%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>14 (7.2%)</td>
<td>5 (2.1%)</td>
</tr>
<tr>
<td>Non-Cardiac</td>
<td>9 (4.6%)</td>
<td>4 (1.7%)</td>
</tr>
</tbody>
</table>

Adapted from Dr. Patrick Serruys independent meta-analysis of RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS, TCT 2006. Control is Bx Velocity™. Cypher and Bx Velocity are trademarks of J&J Cordis Corporation.
Published data suggest the 5-year mortality rate for the treatment of diabetics with single vessel de novo lesions should be twice as high as that seen in the BMS treatment group in the SIRIUS, E-SIRIUS, C-SIRIUS & RAVEL Trials.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>BMS 4RCTs (n=233)</th>
<th>BMS (5 yrs F/U) n=263</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4.3%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

* Lee T et al., AJC, 2006; 98:718-721

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, MI and stent thrombosis.
SIRIUS and RAVEL Kaplan–Meier Curve

Pooled Data from SIRIUS, RAVEL (Diabetic Patients)

Cumulative Incidence of Death: 0 – 1,980 Days

Catch-up occurs between 4 and 5 years.

<table>
<thead>
<tr>
<th># Entered</th>
<th>0 D</th>
<th>180 D</th>
<th>360 D</th>
<th>720 D</th>
<th>1080 D</th>
<th>1440 D</th>
<th>1800 D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>150</td>
<td>147</td>
<td>145</td>
<td>142</td>
<td>134</td>
<td>124</td>
<td>110</td>
</tr>
<tr>
<td>Bx Velocity</td>
<td>173</td>
<td>172</td>
<td>171</td>
<td>169</td>
<td>164</td>
<td>157</td>
<td>136</td>
</tr>
</tbody>
</table>

* Data from RAVEL and SIRIUS

Internal Data, Cordis.
No Significant Difference in Mortality Rates Across Trials Designed To Assess The Efficacy of the CYPHER® Stent vs. BMS Patients With Diabetes

Studies, individually or collectively, were not powered to assess differences in the rates of rare events, such as death, MI and stent thrombosis.
**TAXUS Trials – Late Loss in NIDDM pts**

- **In Stent**
  - Control: 1.03 ± 0.58 (N=80)
  - TAXUS: 0.36 ± 0.51 (N=91)
  - P<0.0001

- **In Segment**
  - Control: 0.74 ± 0.58 (N=80)
  - TAXUS: 0.22 ± 0.41 (N=91)
  - P<0.0001
TAXUS™ Stent: Significantly lower TLR and as safe -- or safer -- than a BMS in diabetics

TAXUS Stent 4 yr meta-analysis: All Diabetics
TAXUS II¹ (4 yr), IV² (4 yr), V³ (2yr), VI⁴ (3 yr) studies (N=814)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Bare Metal Stent (N=415)</th>
<th>TAXUS Stent (N=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>25.5%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Death</td>
<td>1.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>3.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>QWMI</td>
<td>1.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Death or QWMI</td>
<td>12.6%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

TLR = Target Lesion Revascularization

Δ = 3.0%

TAXUS™ Stent 4-Year Meta-Analysis
Diabetic Sub-Group

TAXUS All-Cause Mortality to 4 Years by Diabetic Sub-Group

**Total Population**

n=3441

**No Statistical Difference**

**All Diabetics**

n=814

Impact of DES in Diabetics Subgroups
Diabetic Patients in TAXUS Trials
3-year Target Lesion Revascularization

Diabetic Patients in TAXUS Trials

Non Diabetics ORAL Agents Only Diabetics Insulin-treated Diabetics

TLR (%) Control TAXUS

18.5% 25.2% 23.4%
8.9% 11.8% 9.2%

P<0.0001 P<0.0001 P=0.0052

N=1,312 N=1,319 N=279 N=279 N=136 N=120

Equal benefit across patients
DES in Insulin–Requiring Diabetics

TAXUS metaanalysis including TAXUS II, IV, V, VI
N=256
16.9%
P=0.006
5.8%

Cypher integrated analysis including RAVEL, SIRIUS, E- and C-SIRIUS, DIRECT, SVELTE
N=131
19.4%
P=n.s.
10.1%

TAXUS metaanalysis including TAXUS II, IV, V, VI
Cypher integrated analysis including RAVEL, SIRIUS, E- and C-SIRIUS, DIRECT, SVELTE
presented at ACC 2005 by Dr. W. Wijns.
The Cypher Stent vs the Taxus Stent: RCT’s in diabetic patients

There is one trial (ISAR–Diabetes) designed to compare the Cypher Stent vs the Taxus stent in diabetics and one pre-specified sub-analysis of diabetic patients in the Sirtax Trial.
In-segment Late Loss

In-stent Late Loss

CYPHER® Stent

Taxus Stent

P=0.002

P<0.001

% of Patients

P=0.03

P=0.13

Significantly Less Late Lumen Loss

Almost Half the TLR (Difference Is Not Statistically Significant)

Summary of Outcomes Through 9 Months: The ISAR-DIABETES Trial

<table>
<thead>
<tr>
<th></th>
<th>CYPHER® Stent (N=125)</th>
<th>Taxus Stent (N=125)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>4 (3.2%)</td>
<td>6 (4.8%)</td>
<td>0.52</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>5 (4.0%)</td>
<td>3 (2.4%)</td>
<td>0.72</td>
</tr>
<tr>
<td>TLR, n (%)</td>
<td>8 (6.4%)</td>
<td>15 (12.0%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Limitation: Results are from a randomized, controlled trial powered for binary angiographic restenosis
All patients completed clinical follow-up

Summary of MACE* Through 1 Year:
Pre-specified SIRTAx Trial Diabetic Subgroup

Results are from a pre-specified subgroup analysis of a randomized, controlled trial powered for MACE.
Limitation: RCT was not powered for comparisons among diabetic patients on insulin or oral hypoglycemic agents.

* Cardiac Death, Myocardial Infarction, or Ischemia-driven Target Lesion Revascularization

Windecker S., et al., ESC 2006; Poster Presentation.
Individual Patient Data Meta-Analysis
Risk of TLR and Diabetes

Target Lesion Revascularization

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Risk Ratio &amp; 95% CI</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Diabetes</td>
<td>1,928</td>
<td>0.60 (0.42, 0.86)</td>
<td>0.006</td>
<td>0%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>887</td>
<td>0.54 (0.22, 1.33)</td>
<td>0.18</td>
<td>65%</td>
</tr>
<tr>
<td>NIDDM</td>
<td>602</td>
<td>0.78 (0.43, 1.38)</td>
<td>0.39</td>
<td>0%</td>
</tr>
<tr>
<td>Insulin dependent Diabetes</td>
<td>256</td>
<td>0.61 (0.06, 6.46)</td>
<td>0.68</td>
<td>71%</td>
</tr>
<tr>
<td>Pooled</td>
<td>2,786</td>
<td>0.20 (0.06, 6.46)</td>
<td>0.18</td>
<td>85%</td>
</tr>
</tbody>
</table>

Data from ISAR-DESIRE, ISAR-DIABETES, REALITY, SIRTAX
The safety and efficacy of the TAXUS® Express2™ Stent have not been established in patients with diabetics. Data from trials that are not head-to-head are not intended to be comparative.
Real World Diabetic Patients

Data from Cypher & Taxus Registries
Comparative Real World Studies & Registries
In Diabetics (3,000+ Patients with Clinical Follow-up Only)

**S.T.E.N.T Registry**
- 9 Month TVR
- Non-Insulin Requiring
  - Dr. Simonton
  - P=0.28
- Insulin Requiring
  - Dr. Simonton
  - P=0.08

**SOLACI**
- 9 Month TVR
- (Diabetics)
- Dr. Sousa
- No P-value Reported

**RESEARCH/T-SEARCH**
- 12 Month TLR
- (Diabetics)
- Dr. Serruys
  - P=0.08

**Milan Experience**
- 9 Month TLR
- (Diabetics)
  - Dr. Colombo
  - P=0.2

<table>
<thead>
<tr>
<th>Re-intervention %</th>
<th>Cypher® Stent</th>
<th>TAXUS™ Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>3.1%</td>
<td>3.4%</td>
</tr>
<tr>
<td>5%</td>
<td>4.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>10%</td>
<td>5.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>15%</td>
<td>8.8%</td>
<td>8.8%</td>
</tr>
<tr>
<td>20%</td>
<td>14.3%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

**Non-Insulin Requiring**
P=0.28

**Insulin Requiring**
P=0.08

**Increasing Lesion Length**
New registries confirm that the TAXUS™ Stent is Superior in Diabetics

TC WYRE Registry

12-Month TVR

N=247

8.5%

TAXUS Stent: Clinically Superior

p=0.004

2.5%

N=289

8.5%

TAXUS Stent: Clinically Superior

Kaiser Permanente Registry

12-Month Death, MI, TVR

N=272

9.0%

TAXUS Stent: Clinically Superior

p=0.02*

4.0%

Prairie Heart Institute Registry

9-Month TLR

p=n.s.

N=928

11.1%

Trend favors TAXUS Stent

N=201

8.5%

T-SEARCH/RESEARCH Registry

24-Month TVR

p=0.06

N=171

15.3%

Trend favors TAXUS Stent

N=171

9.7%

TAXUS Stent: Clinically Superior

Cypher™ Stent

TAXUS™ Stent: Mortality rates better in Diabetic patients

**S.T.E.N.T. Registry**
- Insulin-Treated Diabetics
- 9-months
  - Mortality Rate: 5.7%
  - p=0.07

**Prairie Heart Institute Registry**
- All Diabetics
- 9-months
  - Mortality Rate: 9.5%
  - p=0.005

**MILAN II Registry**
- All Diabetics
- 12-months
  - Mortality Rate: 6.4%
  - p=0.32

**TAXUS Stent Clinically Superior**
- Trend favors TAXUS Stent

Cypher™ Stent

TAXUS Stent

Cypher is a registered trademark of J&J Cordis Corp.

S.T.E.N.T. Registry presented at ACC 2006 by Dr. Simonton. Prairie Heart Institute study presented by Dr. Mishkel et al. TCT 2006. Centro Cuore Colombus (Milan II) data presented by Dr. Cosgrave at TCT 2006.
Conclusions

- Does DES improve outcome of PCI in DM? → Yes
- Is there a difference in response to DES between insulin and non-insulin required DM? → Perhaps
- Does DES eliminate DM as a predictor of restenosis? → No
- Is there compelling evidence to establish the comparative efficacy of Sirolimus vs Paclitaxel stent in DM? → There is no significant difference in clinical outcomes and neither in NIDDM which are hypothesized to be better off with PES although there is a trend in more favourable outcome in PES especially in Real World Registries