Why Should Diabetics be Treated Differently?

Keith Dawkins MD FRCP FACC FSCAI
Associate Chief Medical Officer
Senior Vice President
Boston Scientific Corporation
Conflicts of Interest

- Employee & Stockholder: Boston Scientific Corporation
- I intend to reference unlabeled/unapproved uses of products in my presentation
Prevalence of Diabetes Mellitus

Worldwide Prevalence (%)

2000: 2.8% 171 million

2030: 4.4% 366 million

Diabetes Care 2004:27:1047–1053
Prevalence of Diabetes Mellitus
Diabetes: Collateral Damage in Europe

- Every 2 minutes a **Stroke**
- Every 4 minutes a **Myocardial Infarction**
- Every 4 minutes an **Amputation**
- Every 12 minutes a **Loss of Kidney Function**
- Every 18 minutes a **Loss of Eye Sight**

Influence of Glucose Status on Adjusted Mortality Risk

Long-term Effects of Intensive Medical Management in Diabetes Mellitus

Cumulative Incidence of Cardiovascular Events

Follow-Up (Years)

Conventional Treatment

Intensive Treatment

Risk Reduction 42% (CI: 9–63%, p=0.02)

Percutaneous Coronary Intervention
Multivariante correlates of cumulative late mortality

- Advanced age
- Current smoker
- Elevated cholesterol
- Left main PCI
- Unstable angina
- Prior MI
- Saphenous vein graft
- CK elevation (8x)
- Diabetes mellitus
- Renal Impairment

Hazard Ratio ± 95% CI (p<0.05)

Circ 2001;104:642-647
Percutaneous Coronary Intervention
Multivariate correlates of cumulative late mortality

Advanced age
Current smoker
Elevated cholesterol
Left main PCI
Unstable angina
Prior MI
Saphenous vein graft
CK elevation (8x)
Diabetes mellitus
Renal Impairment

Hazard Ratio ± 95% CI (p<0.05)

Circ 2001;104:642–647
POBA and Diabetes

Restenosis Rate (%)

Holmes (1984)
Vandormael (1987)
Lambert (1988)
Quigley (1989)
Ellis (1989)
Macdonald (1990)
Bourassa (1991)
Weintraub (1993)
Rabbini (1994)
Lefevre (1994)
Van Belle (1997)
Levine (1997)
Van Belle (1998)

J Am Coll Cardiol 1999;34:476–485
Outcomes in Diabetics following BMS

**Event-Free Survival (%)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>73.0%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Restenosis</td>
<td>37.5%</td>
<td>28.3%</td>
</tr>
<tr>
<td>TV Occlusion</td>
<td>5.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

**Statistical Significance**

- p < 0.001
- p = 0.037

*J Am Coll Cardiol 1998;32:1866–1873*
Why are Diabetics different?

- Increased oxidative stress and inflammation (Fibrinogen and C-reactive protein expression)
- Impaired vasomotor activity, increased smooth muscle cell proliferation
- Proatherogenic protein glycation
- Altered coagulation/fibrinolysis (prothrombotic and increased PAI-1)
- Increased platelet IIb/IIIa receptor numbers
Is there a Specific Role for Paclitaxel Elution in the Diabetic Patient?
Insulin & Restenosis

Non-Diabetic

- cell membrane
- insulin receptor
- insulin

IRS1/2
- PI3-Kinase pathway
- Sirolimus
- Paclitaxel
- mTOR
- P70 S6K
- protein synthesis
- cell cycle progression
- cell growth

promotes restenosis

IRS - insulin receptor substrate
PI3-K - phosphatidylinositol-3-kinase
mTOR - mammalian target of rapamycin
Insulin & Restenosis

Early type II diabetes

Insulin receptor

IRS1/2

mTOR

P70 S6K

protein synthesis

cell cycle progression

cell growth

PI3-Kinase Pathway

Sirolimus

Paclitaxel

promotes restenosis

IRS – insulin receptor substrate
PI3-K – phosphatidylinositol-3-kinase
mTOR – mammalian target of rapamycin
**Insulin & Restenosis**

- Advanced type II diabetes
- cell membrane
- insulin receptor
- insulin

**MAPK Pathway**
- Paclitaxel
- MEK
- ERK1/2
- cell migration
- cell proliferation
- promotes restenosis

**PI3K Pathway**
- IRS1/2
- mTOR
- P70 S6K

**IRS1/2**
- promotes restenosis

**MEK** - MAPK/ERK kinase
**ERK** - extracellular signal–related kinase
Comparative Effects of Paclitaxel and Rapamycin on Smooth Muscle Migration and Survival
Role of Akt-Dependent Signaling

Cam Patterson, Sabeen Mapera, Hui-Hua Li, Nageswara Madamanchi, Eleanor Hilliard, Rob Lineberger, Robert Herrmann, Peter Charles

Objective—Advances in stent technology have enabled the delivery of drugs to improve outcomes after stent deployment. However, the optimal payloads for stents are not clear, and the appropriate stent-based therapies for high-risk patients, such as diabetics, have not been clearly established.

Methods and Results—We used smooth muscle cell culture models to compare the activities of rapamycin and paclitaxel. Smooth muscle cells were grown in normal or high glucose to induce insulin resistance. Both paclitaxel and rapamycin activate mitogen-activated protein kinase pathways similarly. However, rapamycin potently activates AKT-dependent signaling, an effect that overrides the downregulation of this pathway by insulin resistance and that causes phosphorylation of the AKT-dependent transcription factor FOXO1. This effect is associated with attenuation of the anti-migratory effects of rapamycin under high glucose conditions that are not observed with paclitaxel, as well as with increased protection against ceramide-induced cytotoxicity, both of which are dependent on FOXO1 phosphorylation.

Conclusions—Differences between the ability of rapamycin and paclitaxel to activate AKT may account for their differential cell survival and antichemotactic activities. These observations may provide a basis for understanding clinical differences between rapamycin- and paclitaxel-coated stents. The approaches used in these studies can be expanded to other candidate stent payloads as a method for triage in preclinical studies. (Arterioscler Thromb Vasc Biol, 2006;26:1473-1480.)
Comparable efficacy and safety results between TAXUS and CYPHER
REALITY: Subgroup Analysis
In-Lesion Restenosis (8 months)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cypher Better</th>
<th>Taxus Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Stents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Vessel (≥2.5mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Vessel (&lt;2.5mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Lesion (≥20mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Lesion (&lt;20mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True Bifurcation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values:
- Overall: P=0.31, P=0.64, P=0.30
- Diabetes: P=0.44
- Male: P=0.06, P=0.15, P=0.19, P=0.84, P=0.23, P=0.82, P=0.20, P=0.64, P=0.99, P=0.22, P=0.48

Morice M-C. ACC 2005
REALITY Trial
Diabetic Cohort (n=466)

Event Rate (%)

<table>
<thead>
<tr>
<th></th>
<th>TAXUS</th>
<th>CYPHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary Restenosis</td>
<td>13.2%</td>
<td>15.9%</td>
</tr>
<tr>
<td>TLR</td>
<td>5.2%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

p=0.20

Kastrati TCT 2006
Diabetic Meta-Analysis

Total Patients
N=3445

Non Diabetics
N=2631

Medically Treated Diabetics
N=814

Insulin-Requiring Diabetics
N=256

Oral Agents Only Diabetics
N=558

Control
N=1312

TAXUS
N=1319

Control
N=279

TAXUS
N=279

Control
N=136

TAXUS
N=120

*TAXUS II, IV, V, VI

EuroInterv 2006;2:61–68
Target Lesion Revascularisation (12 months)

- **Non Diabetics**: 13.6% (Control) vs. 5.4% (TAXUS), p<0.0001
- **Oral Agents Only Diabetics**: 19.4% (Control) vs. 7.9% (TAXUS), p=0.0001
- **Insulin-Requiring Diabetics**: 16.9% (Control) vs. 5.8% (TAXUS), p=0.0063
In–Stent Late Loss

Late Loss (mm)

<table>
<thead>
<tr>
<th>Group</th>
<th>Late Loss (mm)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Diabetics</td>
<td>0.40 ± 0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oral Agents Only Diabetics</td>
<td>0.43 ± 0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin–Requiring Diabetics</td>
<td>0.41 ± 0.63</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Control

TAXUS
Diabetics: Four Year Event Rates (n=715)
TAXUS I (5y), II–SR (4y), IV (4y), V (2y) Meta–Analysis

Cumulative Events (4 years) (%)

All AMI  Q–AMI  Primary ARC ST (Definite/Probable)  All Death  TLR

- All AMI: 7.4% (N=24) vs. 7.2% (N=20), p=0.57
- Q–AMI: 1.1% (N=3) vs. 0.3% (N=1), p=0.34
- Primary ARC ST: 1.4% (N=5) vs. 2.2% (N=5), p=0.96
- All Death: 10.7% (N=28) vs. 9.2% (N=25), p=0.78
- TLR: 24.9% (N=81) vs. 13.4% (N=40), p<0.0001

Event rates based on Kaplan Meier Estimate & P–Values from Log Rank
Surgical Revascularisation (CABG) in Diabetics following treatment with the Taxus SR* Stent vs. BMS Control (5 Years)

5 Year CABG-TLR (%)

Diabetics

Non-Diabetics

18/355 3/349 33/1012 15/1020

6.0% 1.0% 3.5% 1.6%

p<0.01

*TAXUS SR II, IV, V Trials (n=2,736)
Diabetes Mellitus: PES vs. SES vs. BMS (Thoraxcenter)

- **PES**: 90.3% (n=708)
- **SES**: 84.7% (n=708)
- **BMS**: 80.5% (n=708)

*P-value (Log-rank test)*
- SES vs. PES: p=0.06
- SES vs. BMS: p=0.35
- PES vs. BMS: p=0.0034

Eur Heart J 2007;28:26–32
Diabetes Mellitus: PES vs. SES vs. BMS (Thoraxcenter)

P-value (Log-rank test)
- SES vs. PES: p=0.057
- SES vs. BMS: p=0.97
- PES vs. BMS: p=0.04

MACE Free (%)

Months

PES: 78.8%
SES 71.1%
BMS 70.3%
n=708

Eur Heart J 2007;28:26–32
Patients with Diabetes

- BMS (95.6%)
- SES (87.8%)

P = 0.004

Days: 0, 360, 720, 1080, 1440

Overall Survival (%)

100 – 95 – 90 – 85 – 80

Patients without Diabetes

- BMS (94.2%)
- SES (94.9%)

P = 0.59

Days: 0, 360, 720, 1080, 1440

TAXUS IV & SIRIUS
Target Lesion Revascularization (12 months)

**TAXUS IV**

<table>
<thead>
<tr>
<th></th>
<th>Non-DM</th>
<th>All DM</th>
<th>IDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>3.4%</td>
<td>7.1%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Population</td>
<td>505</td>
<td>155</td>
<td>51</td>
</tr>
</tbody>
</table>

**SIRIUS**

<table>
<thead>
<tr>
<th></th>
<th>Non-DM</th>
<th>All DM</th>
<th>IDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>3.7%</td>
<td>7.1%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Population</td>
<td>462</td>
<td>131</td>
<td>38</td>
</tr>
</tbody>
</table>
Comparative TLR Reduction with DES
Insulin–treated Diabetic Patients

- **TAXUS Stent Meta–Analysis**: 16.9%, N=136, p=0.0063
- **CYPHER Stent Integrated Analysis**: 19.4%, N=62, 10.1%, N=69, p=0.46
- **ENDEAVOR Stent ENDEAVOR II Study**: 13.6%, N=70, 11.5%

p=1.00
ARRIVE I & II, E-CYPHER Registries
Stent Related Revascularization (12 months)

### Pooled ARRIVE I & II

<table>
<thead>
<tr>
<th>Category</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>5.1%</td>
</tr>
<tr>
<td>All DM</td>
<td>4.6%</td>
</tr>
<tr>
<td>IDDM</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7307</td>
<td>5.1%</td>
</tr>
<tr>
<td>2305</td>
<td>4.6%</td>
</tr>
<tr>
<td>746</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

### E-CYPHER

<table>
<thead>
<tr>
<th>Category</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>3.7%</td>
</tr>
<tr>
<td>All DM</td>
<td>7.1%</td>
</tr>
<tr>
<td>IDDM</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2067</td>
<td>3.7%</td>
</tr>
<tr>
<td>640</td>
<td>7.1%</td>
</tr>
<tr>
<td>200</td>
<td>13.9%</td>
</tr>
</tbody>
</table>
TAXUS IV and V Diabetic Subset 8–Month Angiographic Results

Late Loss (mm)

<table>
<thead>
<tr>
<th></th>
<th>Non DM</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare Metal Stent</td>
<td>0.45</td>
<td>0.94</td>
</tr>
<tr>
<td>TAXUS Express Stent</td>
<td>0.48</td>
<td>0.45</td>
</tr>
<tr>
<td>TAXUS Express (Non DM)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>TAXUS Express (DM)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001
p<0.57

ACC 2008
## ENDEAVOR IV
Diabetic Subset Analysis

<table>
<thead>
<tr>
<th>TLR Rate – 12 Months (%)</th>
<th>Overall</th>
<th>No DM</th>
<th>DM</th>
<th>NIDDM</th>
<th>IDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.2%</td>
<td>2.7%</td>
<td>2.1%</td>
<td>5.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td></td>
<td>34/749</td>
<td>24/741</td>
<td>18/516</td>
<td>16/233</td>
<td>10/164</td>
</tr>
<tr>
<td></td>
<td>11/518</td>
<td></td>
<td></td>
<td>13/223</td>
<td>3/78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13/155</td>
<td>3/59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p-values**:
- Overall: 0.154
- No DM: 0.19
- DM: 0.70
- NIDDM: 0.518
- IDDM: 1.00

**ACC 2008**
## TAXUS Stent Diabetic CE Mark
**Diabetic Evidence Base**

<table>
<thead>
<tr>
<th>Study</th>
<th>TAXUS (n)</th>
<th>Control (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAXUS IV</td>
<td>155</td>
<td>163</td>
</tr>
<tr>
<td>TAXUS V de novo</td>
<td>183</td>
<td>173</td>
</tr>
<tr>
<td>TAXUS V ISR</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>ATLAS WH, DS, SV, LL</td>
<td>413</td>
<td>517</td>
</tr>
<tr>
<td>ARRIVE I</td>
<td>756</td>
<td>–</td>
</tr>
<tr>
<td>ARRIVE 2</td>
<td>1549</td>
<td>–</td>
</tr>
<tr>
<td>OLYMPIA IC Transitional</td>
<td>264</td>
<td>–</td>
</tr>
<tr>
<td><strong>Total Diabetic Patients (n)</strong></td>
<td><strong>3398</strong></td>
<td><strong>914</strong></td>
</tr>
</tbody>
</table>

*Medically treated Diabetics*
Conclusions:

- The worldwide prevalence of diabetes is increasing.
- Patients with diabetic coronary disease present a therapeutic challenge.
- Signal pathways confirm the unique effect of paclitaxel in inhibiting smooth muscle cell migration, proliferation and restenosis.
- Data from randomized controlled trials, meta-analyses and registries have confirmed the safety, efficacy and superiority of the TAXUS stent in the diabetic patient.