Indian TUXEDO Trial In Medically Treated Diabetics

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TCTAP 2012
Disclosure Statement of Financial Interest

Investigator Sponsored Research

Study funded by Boston Scientific Corporation

No other Financial Relations
Taxus Element vs. Xience Prime in a Diabetic population in India

TUXEDO-INDIA
Diabetic patients tend to present with more complexity

WHY?

Smaller vessels
Higher rate of calcified lesions
More multi-vessel disease
In-stent restenosis
Higher incidence of AHA/ACC class “C” lesions
More hypertensive patients
More hyperlipidemia
More CKD
CHOICE OF DES IN A DIABETIC
Paclitaxel Stent seems to work differently in diabetic Patients

TCT 2006 - TC WYRE Registry
12-Month TVR
- Cypher™ Stent: 8.5% (N=247)
- TAXUS Stent: 2.8% (N=289)

TCT 2006 - Kaiser Permanente Registry
12-Month Death, MI, TVR
- Cypher™ Stent: 9.0% (N=272)
- TAXUS Stent: 4.0% (N=227)

AHA 2006 - T-SEARCH/RESEARCH Registry
24-Month TLR
- Cypher™ Stent: 13.2% (N=206)
- TAXUS Stent: 5.3% (N=252)

P-values:
- 12-Month TVR: p=0.004
- 12-Month TVR: p=0.02*
- 24-Month TLR: p=0.004

PSSST# 4011C
What About Randomized Trials
# REALITY

## Clinical Events at 8 Months

<table>
<thead>
<tr>
<th>Event</th>
<th>CYPHER® (684 patients; 970 lesions)</th>
<th>TAXUS™ (669 patients; 941 lesions)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (%) (n)</td>
<td>9.2% (63)</td>
<td>10.6% (71)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death (%) (n)</td>
<td>1.8% (12)</td>
<td>1.2% (8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>1.0% (7)</td>
<td>0.9% (6)</td>
<td>0.99</td>
</tr>
<tr>
<td>MI (all) (%) (n)</td>
<td>4.8% (33)</td>
<td>5.5% (37)</td>
<td>0.62</td>
</tr>
<tr>
<td>Q-Wave</td>
<td>0.15% (1)</td>
<td>0.90% (6)</td>
<td>0.067</td>
</tr>
<tr>
<td>Non Q-Wave</td>
<td>4.7% (32)</td>
<td>4.6% (31)</td>
<td>0.99</td>
</tr>
<tr>
<td>TLR (all) (%) (n)</td>
<td>5.0% (34)</td>
<td>5.4% (36)</td>
<td>0.81</td>
</tr>
<tr>
<td>TVR (non-TL)</td>
<td>1.6% (11)</td>
<td>1.2% (8)</td>
<td>0.65</td>
</tr>
<tr>
<td>TVF (%) (n)</td>
<td>10.4% (71)</td>
<td>11.5% (77)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
REALITY – Diabetic Subgroup Analysis
Moric MC et al. JAMA 2006;295:895-904

No Diabetes

Diabetes

\[ \uparrow \text{RR}=30\% \]
\[ \text{HR}=0.70 \]
\[ (0.49-1.01) \]
\[ P=0.06 \]

\[ \uparrow \text{RR}=20\% \]
\[ \text{HR}=1.20 \]
\[ (0.78-1.85) \]
\[ P=0.20 \]

Restenosis %

- SES
- PES

Restenosis %

- SES
- PES
ISAR-DIABETES: Randomized Comparison of CYPHER vs TAXUS in Diabetic Patients

Dibra A et al. NEJM 2005;27:260-66

Late Loss

P=0.002

Restenosis

P=0.02

TLR

P=0.13

In-segment

SES  PES
N=102 N=103

In-segment

SES  PES
N=102 N=103

TLR

SES  PES
N=125 N=125
Differential Clinical Responses to Everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus

• The databases of 6780 patients recruited in SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE was analyzed
• 1869 patients (27.6%) had diabetes
• Death, MI and TLR rates up to 24 months were compared in non diabetic and diabetic subsets.

Stone et al, Circulation 2011;124 :893-900
Differential Clinical Responses to everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus

Stone et al, Circulation 2011;124:893-900
Differential Clinical Responses to everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus

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Differential Clinical Responses to everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus

Stone et al, Circulation 2011;124 :893-900
Results from Randomized studies

- Despite various efforts from randomized studies to compare TAXUS and Limus DES in diabetes mellitus patients, it is difficult to draw any conclusion due to their inconsistent findings.

- No dedicated trial with sufficient power to study the clinical outcomes with Limus vs Paclitaxel stents.
**Taxus Element vs. Xience Prime in a Diabetic population in India**

**TUXEDO-INDIA**

**Diabetic RCT Study Flow**

1,830 Diabetic Mellitus patients undergoing PCI enrolled up to 50 clinical sites in India

- TAXUS Element (N=915)
- Xience Prime (N=915)

- 30-Day f/u
- 180-Day f/u
- 12-Month f/u
- 24-Month f/u
Primary Endpoint – Sample Size

• Statistical Method
  – A one-group Z-test (normal approximation to binomial) will be used to test whether the 12-month TVF for TAXUS Element is less than or equal to a pre-specified performance goal.

• Sample Size Parameters
  – Expected TAXUS Element (test) rate = 8.4%
  – Expected Xience Prime (test) rate = 8.4% based on the XIENCE V (PROMUS) results from the SPIRIT trials
  – Non-inferiority margin (Δ) = 4.0%
  – Test significance level (α) = 0.025 (1-sided)
  – Power (1−β) = approximately 0.80
  – Expected rate of attrition = 10%
  – \textbf{N=1,830 patients}
OBJECTIVE: Compare the safety and performance of the TAXUS Element™ against the Xience Prime™ in medically treated diabetic patients.

DESIGN: A Prospective, Single Blind, Multi-center, Randomized Trial

PRIMARY ENDPOINT: composite efficacy and safety endpoint of target vessel failure (TVF) rate at 12 months post-index procedure:
## Stent Comparison TE vs XP

<table>
<thead>
<tr>
<th>Element Stent Series</th>
<th>XIENCE Prime Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Alloy</strong></td>
<td>Platinum Chromium</td>
</tr>
<tr>
<td>Cobalt Chromium</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>Paclitaxel (TAXUS)</td>
</tr>
<tr>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td><strong>Polymer / Release Rate</strong></td>
<td>Translute™ Polymer (SIBS) (TAXUS)</td>
</tr>
<tr>
<td>Flourinated Co-Polymer (PROMUS)</td>
<td></td>
</tr>
<tr>
<td>Flourinated Co-Polymer</td>
<td></td>
</tr>
<tr>
<td><strong>Delivery System</strong></td>
<td>• Now catheter technology</td>
</tr>
<tr>
<td>• Bi-Segment™ Inner for greater track and push</td>
<td></td>
</tr>
<tr>
<td>• Balloon material designed for optimal performance</td>
<td></td>
</tr>
<tr>
<td>• Shorter balloon tapers</td>
<td></td>
</tr>
<tr>
<td>• Higher RBP</td>
<td></td>
</tr>
<tr>
<td>• Softer tip flexibility</td>
<td></td>
</tr>
<tr>
<td>• “Significantly” lower deflation times</td>
<td></td>
</tr>
<tr>
<td><strong>Stent Design</strong></td>
<td><img src="image1.jpg" alt="Stent Design" /></td>
</tr>
<tr>
<td><img src="image2.jpg" alt="Stent Design" /></td>
<td></td>
</tr>
<tr>
<td><strong>Sizes Available</strong></td>
<td>TAXUS™ Element™ – 53 codes</td>
</tr>
<tr>
<td>PROMUS™ Element™ – 47 codes</td>
<td></td>
</tr>
<tr>
<td>XIENCE Prime—46 codes</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Endpoints
Measured at 30, 180 days, and 1 and 2 years post index procedure:

Primary End Point: TVF rate at 1 year
   Cardiac Death, MI and TVR

Secondary End Points
- Target Vessel Revascularization (TVR) rate
- Target Lesion Revascularization (TLR)
- Composite of cardiac death or target vessel MI
- Composite of all deaths, all MI, all revascularizations
- Major Adverse Cardiac Events (MACE) which is the composite endpoint of cardiac death, all myocardial infarction, and TLR
Clinical Endpoints…..contd

- MI (Q-wave and non–Q-wave) rate
- Cardiac death rate
- Non-cardiac death rate
- All death rate
- Cardiac death or MI rate
- All death or MI rate
- Stent thrombosis rate (definite or probable by Academic Research Consortium [ARC] definitions)
Clinical Inclusion Criteria

• Patients with a diagnosis of diabetes mellitus (Type 1 or Type 2) on drug treatment.

• 1. Two hour plasma glucose >200 mg/dL (11.1 mmol/L) following a 75g oral glucose tolerance test
   2. Random plasma glucose >200 mg/dL in individuals with symptoms of hyperglycemia
   3. A fasting plasma glucose level >126 mg/dL (7.0 mmol/L)
   4. Elevated HbA1c level ≥ 6.5 and currently on treatment
   5. Patients admitted with ACS NSTEMI and Hb A1c> 7% can be included even if not on treatment for diabetes with drugs.

• Patient (or legal guardian) understands the trial requirements and provides written informed consent
Clinical Inclusion Criteria (cont)

- Patient is eligible for PCI
- Patient has symptomatic coronary artery disease or documented silent ischemia.
- Patient is willing to comply with all protocol-required follow-up evaluations.
Angiographic Inclusion Criteria

• Target lesion must be a de novo lesion located in a native coronary artery with reference vessel diameter ≥2.25 mm & ≤4.00 mm, lesion length ≤30 mm by visual estimate
• Up to 3 target lesions can be taken.
• A maximum of 2 lesions in one target vessel.
• Target lesion must be in a major coronary artery or branch with visually estimated stenosis ≥50% & <100% with TIMI flow >1.
Clinical Exclusion Criteria

• Patient has known allergy to the study stent system or protocol-required concomitant medications (e.g., stainless steel, platinum, chromium, nickel, iron, thienopyridines, aspirin, contrast) that cannot be adequately pre-medicated.
• Patient has any other serious medical illness (e.g., cancer, congestive heart failure) that may reduce life expectancy to less than 12 months
• LVEF < 30%
• Serum Creatinine > 2 mgs/dl.
Angiographic Exclusion Criteria

• **Target lesions in located in**
  - Left main including left main ostial location
  - Within 2 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCX) coronary artery by visual estimate
  - Within a saphenous vein graft or an arterial graft or distal to a diseased arterial or saphenous vein graft. Diseased graft defined as irregularity per angiogram and any visually estimated diameter stenosis > 20%.
  - A bifurcation in which the side branch ≥2.0 mm in diameter AND the ostium of the side branch is > 50% stenosed by visual estimate.
  - A side branch requiring pre-dilatation
  - TIMI flow 0 (total occlusion) prior to guide wire crossing
Post PCI Management

- Medical management of diabetes mellitus according to the American Diabetes Association (ADA) guidelines
  - HbA1c < 7
  - B P treated to target of < 140/90
  - LDL cholesterol < 70 mgs
  - Triglycerides < 150 mgs

Dual Anti platelet therapy for at least 1 year
Total Patients Recruited as of April 24th, 2012
N= 738
Study Overview

- Total number of patients to be enrolled in this study: 1830
- Total number of patients recruited up to 24th-Apr-12: 738
- Total number of patients considered till 05-Mar-12: 500*
  - Visits completed till Discharge visit: 498 patients
    - Visits not completed till Discharge visit: 02 patients
  - Patients continuing the study: 492
    - Visits completed till 30 days: 453 patients
    - Visits completed till 6 months: 60 patients

* 2nd DSMB meeting
Patient Disposition First 500 Patients

- Out of 500 patients, 492 are ongoing the protocol
  - Group A (N=248): 243 (98.0%) patients
  - Group B (N=252): 249 (98.8%) patients

- Eight (1.6%) patients discontinued the study due to
  - Withdrawal of consent (n=3): Group A 2 (0.8%) patients
    - Group B 1 (0.4%) patient
  - Death (n=5): Group A 3 (1.2%) patients
    - Group B 2 (0.8%) patients
**Total Patients Analysed**

N= 500

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (N=248)</th>
<th>Group B (N=252)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>58.0 ± 9.21</td>
<td>58.9 ± 9.34</td>
<td>0.2933</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>191 (77.0)</td>
<td>186 (73.8)</td>
<td>0.4052</td>
</tr>
<tr>
<td>Number of patients on pharmacological treatment, n (%)</td>
<td>224 (90.3)</td>
<td>226 (89.7)</td>
<td>0.8115</td>
</tr>
<tr>
<td><strong>Total Number of Treated Lesions</strong></td>
<td>319</td>
<td>344</td>
<td></td>
</tr>
<tr>
<td>Target-lesion location, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending, n (%)</td>
<td>156 (62.9)</td>
<td>154 (61.1)</td>
<td>0.2768</td>
</tr>
<tr>
<td>Left circumflex, n (%)</td>
<td>70 (28.2)</td>
<td>86 (34.1)</td>
<td>0.4098</td>
</tr>
<tr>
<td>Right, n (%)</td>
<td>90 (36.3)</td>
<td>98 (38.9)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Ramus Intermediate, n (%)</td>
<td>3 (1.2)</td>
<td>7 (2.8)</td>
<td>0.3438</td>
</tr>
</tbody>
</table>
Total Patients Analysed
N= 500

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (N=248) n (%)[1]</th>
<th>Group B (N=252) n (%)[1]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Diabetes Mellitus Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>248 (100.0)</td>
<td>250 (99.2)</td>
<td></td>
</tr>
<tr>
<td>Insulin requiring</td>
<td>72 (29.0)</td>
<td>86 (34.1)</td>
<td>0.2205</td>
</tr>
<tr>
<td>Risk Factors for CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History of CVD</td>
<td>36 (14.5)</td>
<td>27 (10.7)</td>
<td>0.178</td>
</tr>
<tr>
<td>History of Smoking</td>
<td>36 (14.5)</td>
<td>34 (13.5)</td>
<td>0.698</td>
</tr>
<tr>
<td>Hypertension</td>
<td>170 (68.5)</td>
<td>176 (69.8)</td>
<td>0.771</td>
</tr>
<tr>
<td>Dyslipidemia as per site</td>
<td>57 (23.0)</td>
<td>54 (21.4)</td>
<td>0.746</td>
</tr>
<tr>
<td>Dyslipidemia as per NCEP criteria*</td>
<td>180 (72.6)</td>
<td>186 (73.8)</td>
<td>0.7630</td>
</tr>
<tr>
<td>Bleeding Disorder</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

\[1\] Percentages were calculated taking N of corresponding column header group as denominator

*Patients were said to be dyslipidemic if had triglycerides >150; LDL > 130; and HDL <40 in both genders
Anginal status at Randomization
N= 500
Indications

- Objective evidence of ischemia- positive

51% patients had ACS
## Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (N=248) n (%)[1]</th>
<th>Group B (N=252) n (%)[1]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>97 (39.1)</td>
<td>95 (37.7)</td>
<td>0.854</td>
</tr>
<tr>
<td>Silent Ischemia</td>
<td>15 (6.0)</td>
<td>18 (7.1)</td>
<td>0.720</td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention</td>
<td>25 (10.1)</td>
<td>23 (9.1)</td>
<td>0.763</td>
</tr>
<tr>
<td>Coronary Artery Bypass Graft (CABG) surgery</td>
<td>9 (3.6)</td>
<td>8 (3.2)</td>
<td>0.810</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (LVEF) measured</td>
<td>237 (95.6)</td>
<td>243 (96.4)</td>
<td>0.655</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction (LVEF) measured, mean ± SD</td>
<td>53.4 ± 12.64</td>
<td>54.9 ± 12.14</td>
<td>0.2082</td>
</tr>
<tr>
<td>Known Left Main Disease (&gt;50% stenosis)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Known Multi-vessel disease (50% stenosis) in 2 or 3 major epicardial coronary vessels</td>
<td>110 (44.4)</td>
<td>130 (51.6)</td>
<td>0.106</td>
</tr>
</tbody>
</table>

[1] Percentages were calculated taking N of corresponding column header group as denominator
## Use of Stents \( n=500 \)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A ( n=248 ) n(%)</th>
<th>Group B ( N=252 ) n (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated Lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>181 (73.0)</td>
<td>174 (69.0)</td>
<td>0.2938</td>
</tr>
<tr>
<td>2</td>
<td>57 (23.0)</td>
<td>61 (24.2)</td>
<td>0.8331</td>
</tr>
<tr>
<td>3</td>
<td>8 (3.2)</td>
<td>16 (6.3)</td>
<td>0.1421</td>
</tr>
<tr>
<td><strong>Implanted Stents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>178 (71.8)</td>
<td>171 (67.9)</td>
<td>0.3272</td>
</tr>
<tr>
<td>2</td>
<td>55 (22.2)</td>
<td>63 (25.0)</td>
<td>0.5272</td>
</tr>
<tr>
<td>3</td>
<td>13 (5.2)</td>
<td>14 (5.6)</td>
<td>1.0000</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>3 (1.2)</td>
<td>0.2486</td>
</tr>
</tbody>
</table>
Use of Stents in 2 Groups
N=500

Mean ± SD number of stents implanted per patient: 1.4 ± 0.64

- Mean ± SD number of stents implanted per patient in Group A: 1.3 ± 0.64

- Mean ± SD number of stents implanted per patient in Group B: 1.4 ± 0.65
Use of Stents in 2 Groups

N = 500

- Stent Diameter, mean ± SD: 2.91 ± 0.35
  - Stent Diameter in Stent A, mean ± SD: 2.93 ± 0.36
  - Stent Diameter in Stent B, mean ± SD: 2.89 ± 0.33

- Stent Length, mean ± SD: 23.75 ± 7.19
  - Stent length in Stent A, mean ± SD: 23.56 ± 7.12
  - Stent length in Stent B, mean ± SD: 23.95 ± 7.28
A dedicated study in medically treated patients with diabetes mellitus comparing Taxus Element with Xience Prime. Insulin requiring diabetics = 32%.

Demographic data of first 500 patients available.

Multi vessel disease with long lesions being included. Av stent length = 23.75 ± 7.19, Av stent diameter 2.91 ± 0.35. Average no of stents used= 1.4±0.64.

ACS in 51% patients.

Primary end point TVF at 1 year.

Recruitment of 1830 patients estimated to be completed by February 2013.
<table>
<thead>
<tr>
<th>Study Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal Investigator</strong></td>
</tr>
<tr>
<td><strong>Steering Committee</strong></td>
</tr>
<tr>
<td><strong>Clinical Events Committee</strong></td>
</tr>
<tr>
<td><strong>Data Safety Monitoring Committee</strong></td>
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<td></td>
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</tbody>
</table>