Indian TUXEDO Trial In Medically Treated Diabetics

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No other Financial Relations

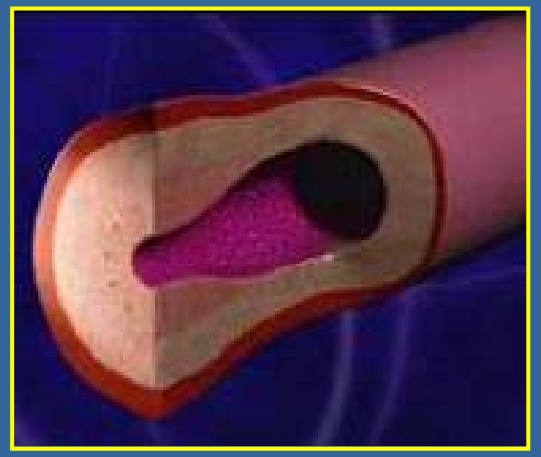
*T*ax*u*s Element vs. *X*i*e*nce Prime in a *D*iabetic p*o*pulati*o*n in *India*

TUXEDO-INDIA

Diabetic patients tend to present with more complexity

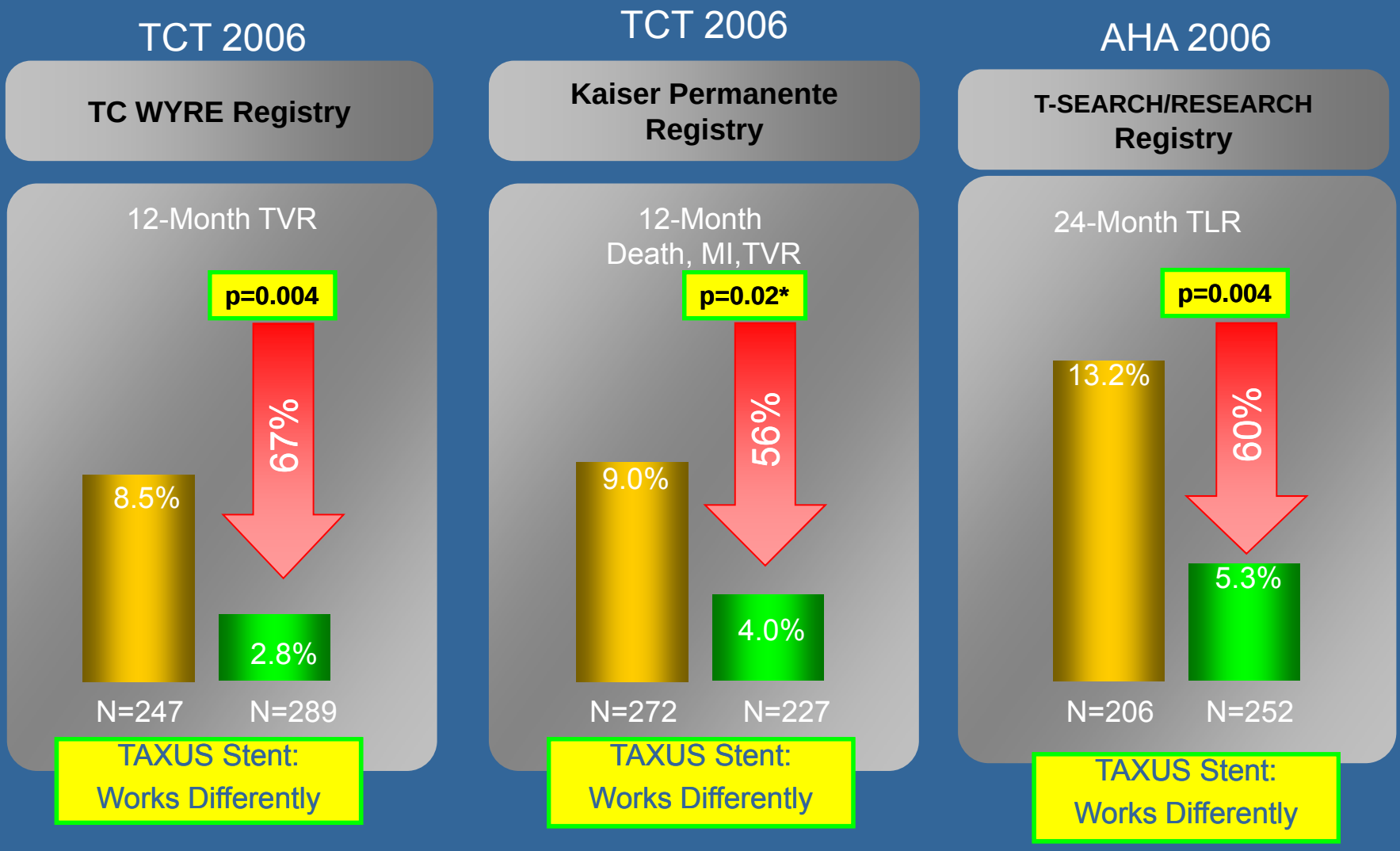
WHY?

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 hyperlipidimia
More CKD



CHOICE OF DES IN A DIABETIC

Paclitaxel Stent seems to work differently in diabetic Patients



What About Randomized Trials

REALITY

Intention-to-Treat Analyses

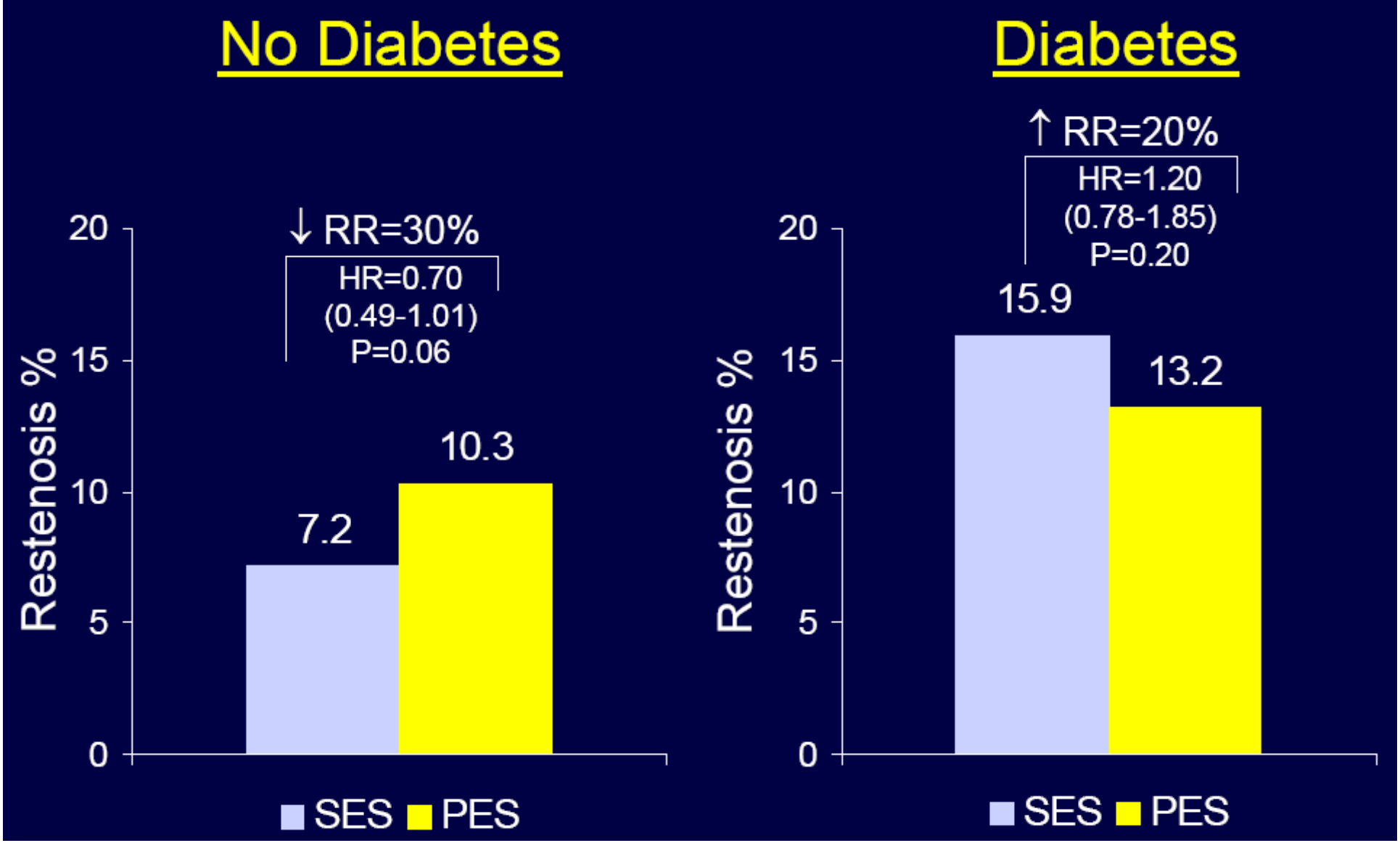
REALITY

Clinical Events at 8 Months

	CYPHER® (684 patients; 970 lesions)	TAXUS™ (669 patients; 941 lesions)	*P*-Value
MACE (%) (n)	9.2% (63)	10.6% (71)	0.41
Death (%) (n)	1.8% (12)	1.2% (8)	0.50
Cardiac Death	1.0% (7)	0.9% (6)	0.99
MI (all) (%) (n)	4.8% (33)	5.5% (37)	0.62
Q-Wave	0.15% (1)	0.90% (6)	0.067
Non Q-Wave	4.7% (32)	4.6% (31)	0.99
TLR (all) (%) (n)	5.0% (34)	5.4% (36)	0.81
TVR (non-TL)	1.6% (11)	1.2% (8)	0.65
TVF (%) (n)	10.4% (71)	11.5% (77)	0.54

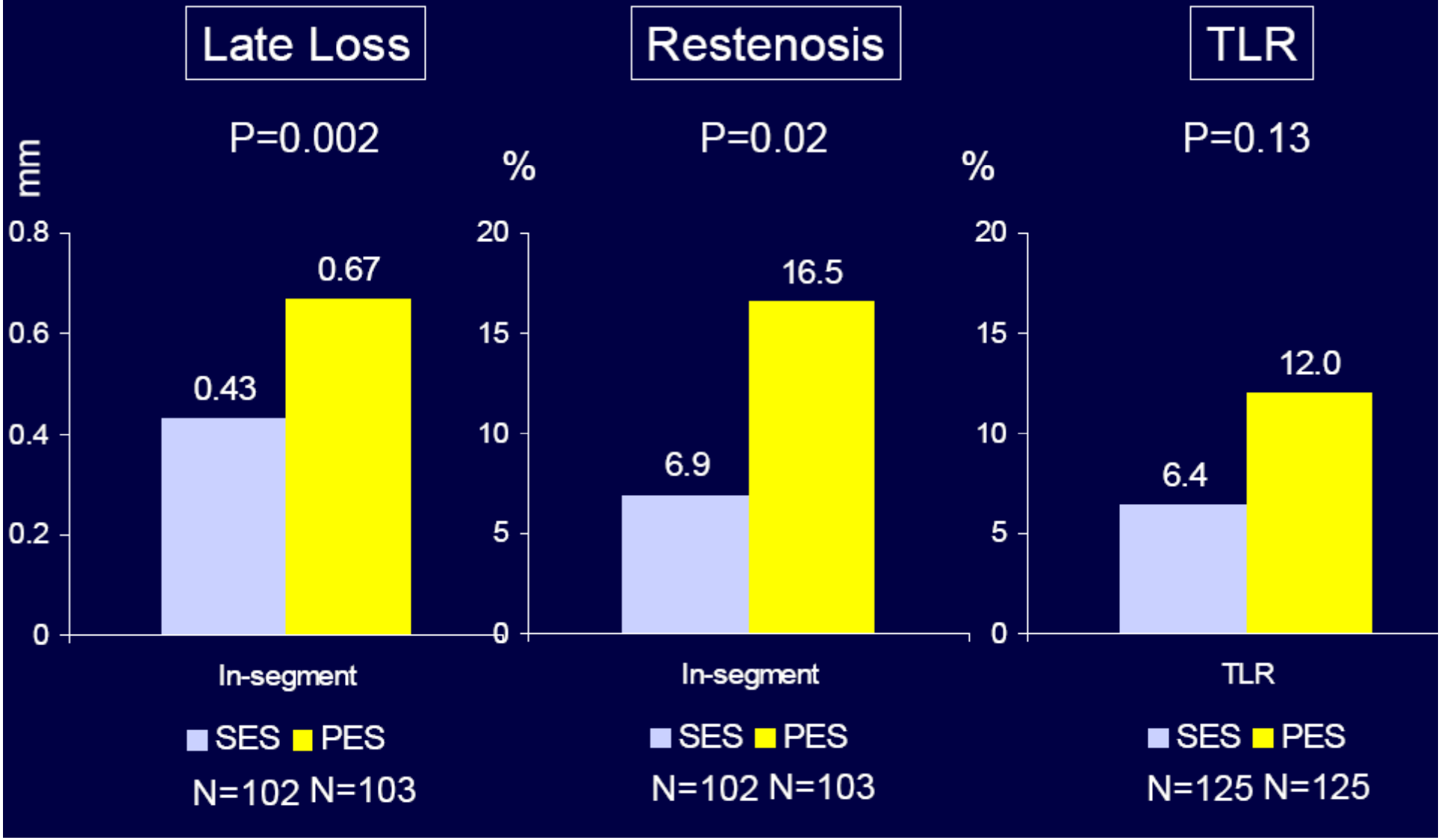
REALITY – Diabetic Subgroup Analysis

Morice MC et al. *JAMA* 2006;295:895-904



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

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

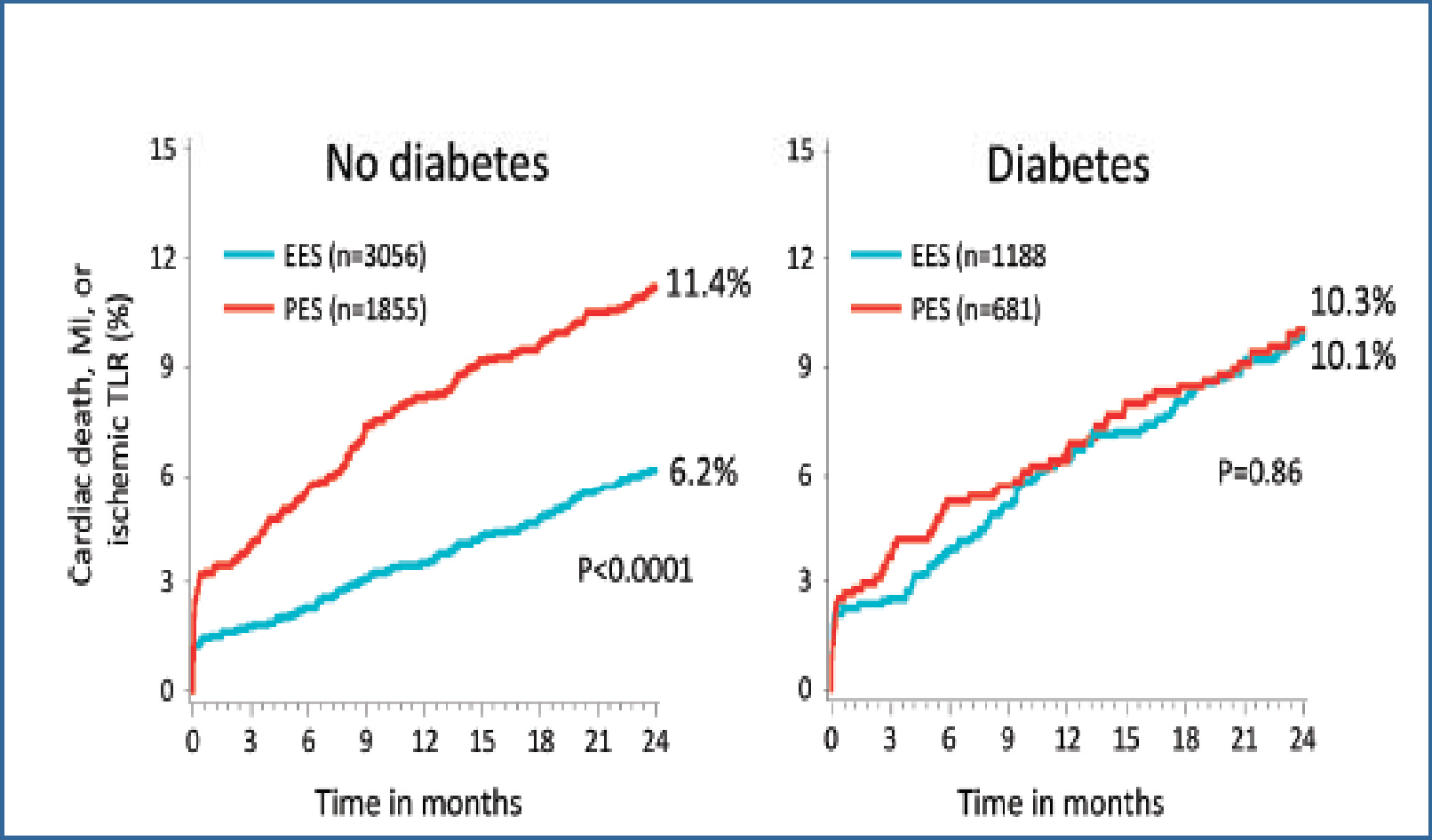


Differential Clinical Responses to Everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus

- 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



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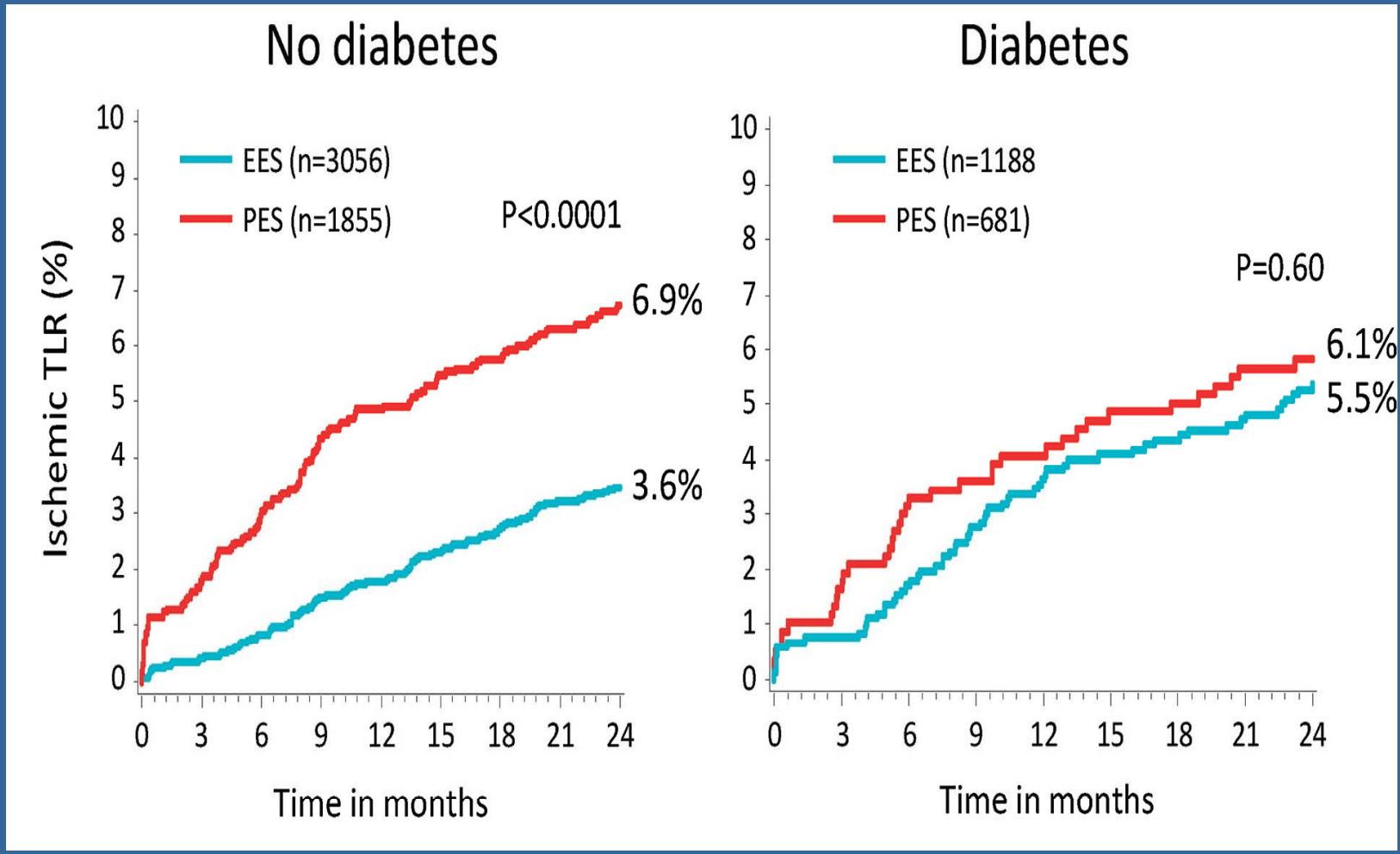

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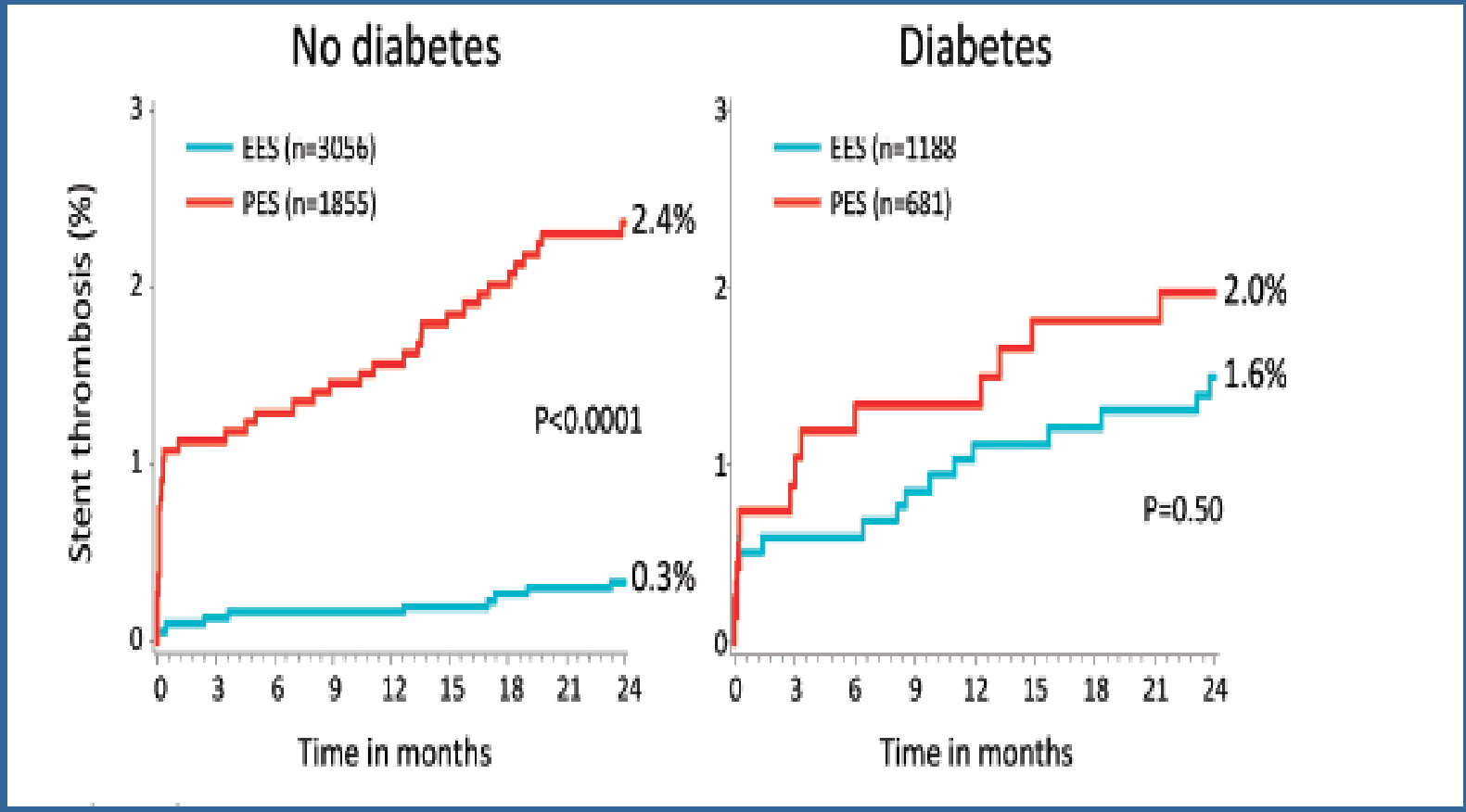
Differential Clinical Responses to everolimus eluting and Paclitaxel Eluting Coronary Stent in Patients with and without diabetes Mellitus



Stone et al , Circulation 2011;124 :893-900

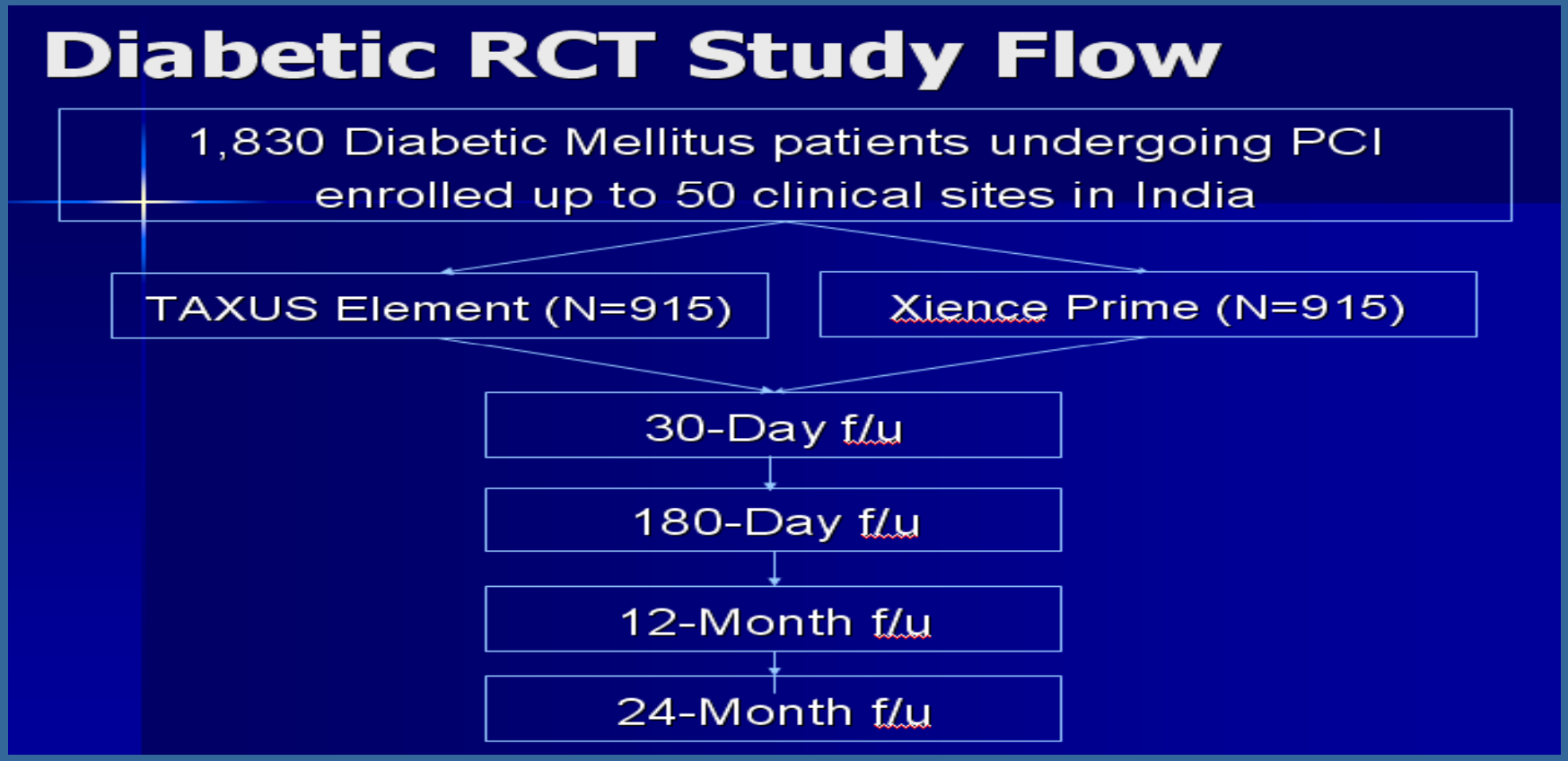
Results from Randomized studies

- 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

*T*ax*u*s Element vs. *X*i*e*nc*e* Prime in a *D*iabetic populati*o*n in *India*

TUXEDO-INDIA



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 ($1-\beta$) = approximately 0.80
  - Expected rate of attrition = 10%
  - **N=1,830 patients**

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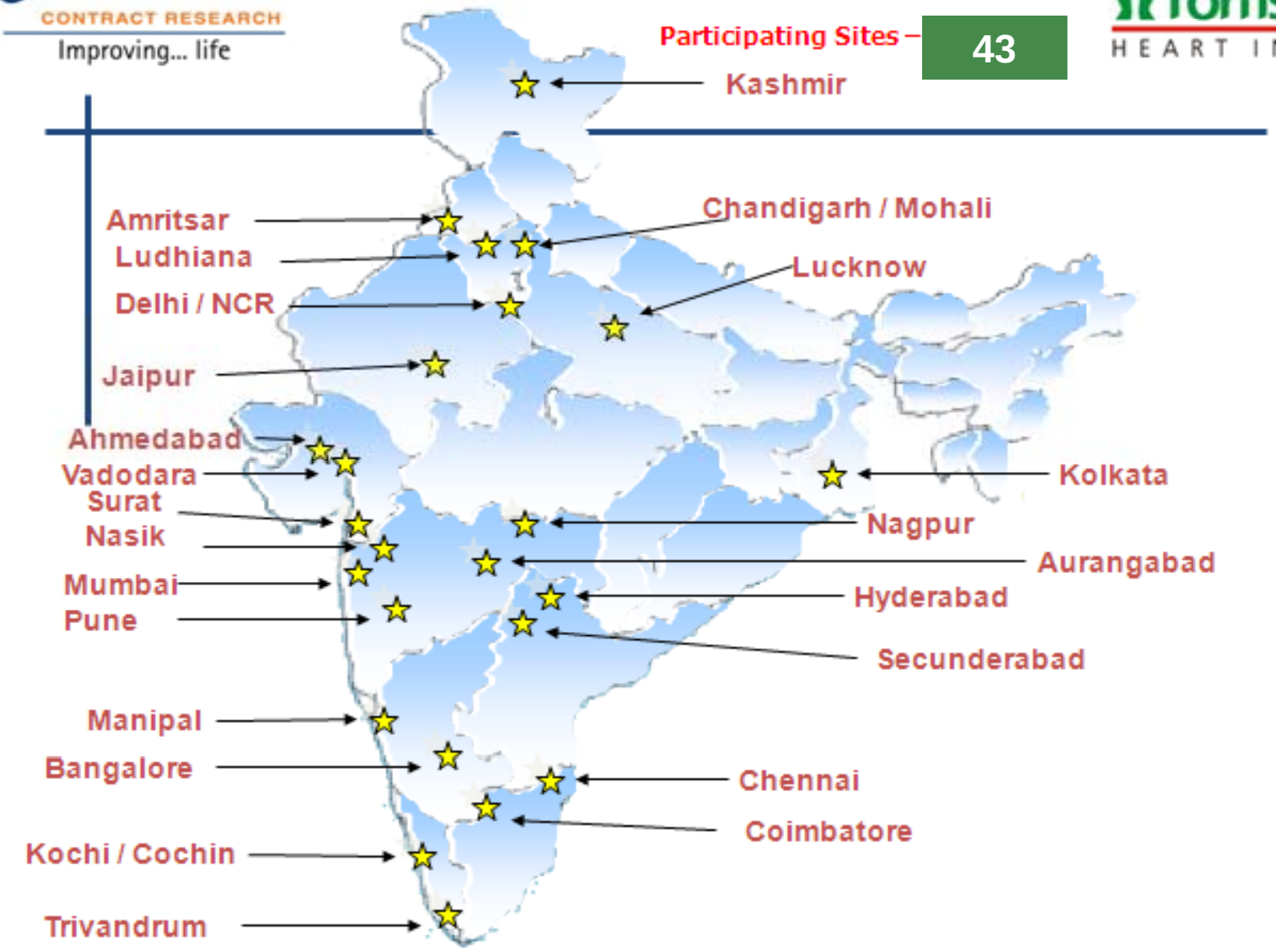


TUXEDO-India : RCT Design

- 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

	Element Stent Series	XIENCE Prime Stent
Stent Alloy	Platinum Chromium	Cobalt Chromium
Drug	Paclitaxel (TAXUS) Everolimus (PROMUS)	Everolimus
Polymer / Release Rate	Translute™ Polymer (SIBS) (TAXUS) Flourinated Co-Polymer (PROMUS)	Flourinated Co-Polymer
Delivery System	• New catheter technology • Bi-Segment™ Inner for greater track and push • Balloon material designed for optimal performance	• Shorter balloon tapers • Higher RBP • Softer tip flexibility • "Significantly" lower deflation times 
Stent Design		
Sizes Available	TAXUS™ Element™ – 53 codes PROMUS™ Element™ – 47 codes	XIENCE Prime—46 codes

PtCr

Information to date. For internal use only. Do not copy, distribute or forward outside of Boston Scientific. Not for use in the US. Data on file. Please refer to glossary.

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 $\geq$ 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

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

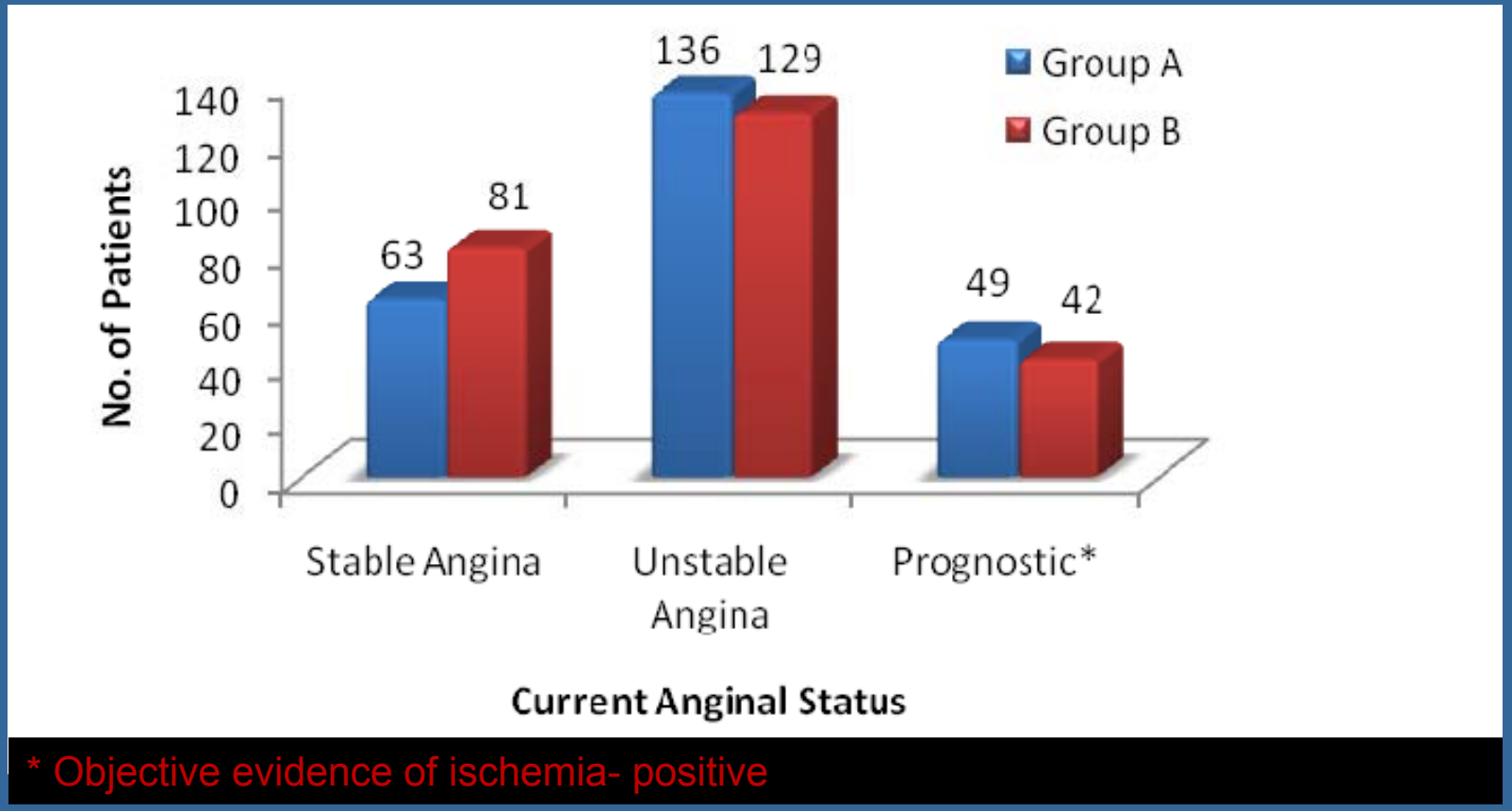
Total Patients Analysed
N= 500

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

[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

Total Patients Analysed
N= 500

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

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

Use of Stents n=500

Parameters	Group A n =248 n(%)	Group B (N=252) n (%)	*P Value*
Treated Lesions			
1	181 (73.0)	174 (69.0)	0.2938
2	57 (23.0)	61 (24.2)	0.8331
3	8 (3.2)	16 (6.3)	0.1421
Implanted Stents			
1	178 (71.8)	171 (67.9)	0.3272
2	55 (22.2)	63 (25.0)	0.5272
3	13 (5.2)	14 (5.6)	1.0000
4	0	3 (1.2)	0.2486

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

TUXEDO-INDIA - conclusion

- 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 $\pm$ 7.19, Av stent diameter 2.91 $\pm$ 0.35 . Average no of stents used= 1.4$\pm$0.64
- ACS in 51% patients.
- Primary end point TVF at 1 year.
- Recruitment of 1830 patients estimated to be completed by February 2013.

Study Organization

Principal Investigator	Dr Upendra Kaul
Steering Committee	Dr Ashok Seth, Dr Upendra Kaul, Dr Mathew Samuel, Dr Tejas Patel, Dr Hari Das, Dr Anil Dhall
Clinical Events Committee	Dr S C Manchanda, Dr Soma Raju, Dr R Tandon, Dr Sameer Shrivastava
Data Safety Monitoring Committee	Dr S C Manchanda, Dr Soma Raju, Dr. R Tandon, Dr Sameer Shrivastava Dr D K Shukla -Biostatistician