Ultra-Thin strUT versus XiencE in a Diabetic pOpulation with Multi-Vessel Disease – 2 – India Study (TUXEDO-2-India)

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- BHMRC, New Delhi-110062

Study Co Chair: Dr. Sripal Bangalore
- Prof of Medicine and Director of Research, Cardiac Catheterization Laboratory,
- The Leon H Charney Division of Cardiology,
- New York university School of Medicine, NY, USA
• New Generation DES (Xience) have significantly improved safety and efficacy outcomes and represent the current standard of care in all patients and all lesion subsets.

• Newer-generation ultra-thin DES (<70 um) have shown to reduce the TLF by 16% driven by lower MI rates and lower rates of stent thrombosis
• In TALENT trial*, Supraflex; ultrathin strut biodegradable polymer-coated DES was found to be non-inferior to Xience; DOCE @ 4.9 % vs 5.3 % in Xience group (p for non-inferiority ≤0.001)

• The results of ultrathin strut biodegradable polymer-coated DES over second-generation durable polymer-coated DES in a higher risk population with diabetes and multi vessel disease has not studied.

• TUXEDO-India** trial had shown that Xience was superior to paclitaxel eluting durable polymer stent TAXUS in a diabetic population with predominantly single vessel disease.

@ cardiac death, TV MI, cl indicated TLR

Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes


Article Figures/Media Metrics

17 References 61 Citing Articles

October 29, 2015
DOI: 10.1056/NEJMoa150188
• The role of **PCI in diabetics with multivessel disease** has been undermined by the results of **FREEDOM** trial which showed superiority of CABG over PCI in MVD (after 2 years of follow up) in a 5 years (mean 3.8 in survivors) follow up.

• **FREEDOM** trial was done using **the first-generation stents** with high adverse events like myocardial infarction, restenosis and stent thrombosis.

• With the superiority in safety and efficacy shown by the new generation stents which include Xience and now ultra-thin strut stents the **results of FREEDOM in the current era need a reappraisal**.

• Optimal use of physiological studies like FFR/ iFR and use of intra **vascular imaging** have further improved the results of PCI.

• Agents **like SGLT2 inhibitors and GLP1 analogues** have improved event free survival of diabetic patients.

• In **SYNTAX Trial**, OMT use was associated with better outcomes with both PCI or CABG at 5 years FU.*

*Iqbal J et al: Circulation. 2015;131:1269- 1277*
TUXEDO-2-India

• Comparison of the clinical outcomes of an ultra-thin strut stent Supraflex Cruz versus Xience family of stents when combined with contemporary OMT in patients with diabetes mellitus and multi-vessel disease

• 85% patients will have 3 VD and 15% DVD

• Besides comparing the 2 stents for non-inferiority will also give an opportunity to compare the pooled data of the stent arms with the performance-based data of FREEDOM trial for all-cause mortality, MI rates and strokes at 5 years
## Xience Family of DES

<table>
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<tr>
<th></th>
<th>Catheter Technology</th>
<th>Balloon</th>
<th>Stent Design and Material</th>
<th>Strut Thickness</th>
<th>Drug/Dose</th>
<th>Coating</th>
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<tr>
<td>XIENCE V</td>
<td>MULTI-LINK VISION</td>
<td>Single-layer</td>
<td>MULTI-LINK VISION</td>
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<td>Biocompatible coating technology</td>
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Supraflex Cruz Sirolimus-eluting Stent System

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<th><strong>Supraflex Cruz, SMT</strong></th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Sirolimus (1.4 µg/mm²)</td>
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<td><strong>Polymer type</strong></td>
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<td><strong>Stent design</strong></td>
<td>Open-cell design</td>
</tr>
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<td><strong>Stent material</strong></td>
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</tr>
<tr>
<td><strong>Stent strut thickness</strong></td>
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<td><strong>No. of interconnectors</strong></td>
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<td></td>
<td>Length: 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 mm</td>
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<td><strong>Link type</strong></td>
<td>Long Dual Z (LDZ) link</td>
</tr>
<tr>
<td><strong>Stent drawing</strong></td>
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</table>
Importance of OMT after revascularization

Iqbal et al. Circulation 2015, published online February 24, 2015;
Supraflex Cruz: A very Deliverable Stent

- Best deliverability amongst available stents in the market in vitro testing.
- Lowest resistance recorded while maneuvering through complex anatomy.

Bench test results may not necessarily be indicative of clinical performance. Test performed by and data on file at SMT. Testing performed on Supraflex Cruz Sirolimus Eluting Coronary Stent System (2.50 x 40 mm) n=5, Ultimaster Stent System (2.5 x 38 mm) n=4, Orsiro Stent System (2.50x40 mm) n=5. Resolute Onyx Stent System (2.5 x 38 mm) n=4, Xience Sierra Stent System (2.5 x 38 mm) n=4, Synergy Stent System (2.5 x 38 mm) n=5, Catheter performance crossability test measures average force to cross a challenging lesion model

Ultimaster is a trademark of Terumo Corporation. Orsiro is a trademark or registered trademark of the Biotronik Group of Companies. Xience Sierra and Xience Xpedition are trademarks of the Abbott Group of Companies. Resolute Onyx is a trademark of Medtronic Inc. Synergy is a trademark of Boston Scientific Corporation or its affiliates.

*Data on File
A/B. Tortuous & heavily calcified pm-RCA followed by CTO in d-RCA

C/D. Easy delivery of long Supraflex Cruz 2.5x32 mm & 3.5x36 mm to md-RCA

E/F. Excellent result

AS, 66 yr old, male, SAP.
## TUXEDO-2-India: Study Devices

<table>
<thead>
<tr>
<th>Study Devices</th>
<th>Xience EES</th>
<th>Supraflex Cruz SES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abbott Vascular, USA</td>
<td>SMT, India</td>
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<tr>
<td>Stent Material</td>
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<td>Cobalt-chromium</td>
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<tr>
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<tr>
<td>Drug</td>
<td>Everolimus</td>
<td>Sirolimus</td>
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Study Objectives

Primary Objective
• To compare the clinical outcomes of PCI with the ultrathin Supraflex Cruz vs. Xience family when combined with contemporary optimal medical therapy (OMT) in patients with diabetes mellitus and multivessel disease with respect to target lesion failure* (TLF) at 12 months

Secondary Objective
• To evaluate whether the pooled cohort from both arms of the study (Supraflex Cruz + Xience) provides similar clinical outcomes (composite of all-cause mortality, nonfatal myocardial infarction (MI), or stroke- MACE) to CABG based on performance goal derived from the CABG arm of the FREEDOM trial at 5 years
  * cardiac death, TV MI and Ischemia driven TLR
Study Design

• A prospective, multicenter, open-label, randomized, controlled study in patients with diabetes mellitus and multivessel disease undergoing coronary revascularization
• 1800 participants will be randomized to Supraflex Cruz vs. Xience family in 1:1 fashion at 70 clinical sites in India
• Randomization will be stratified based on the number of vessel disease (2-vessel or 3-vessel) and antithrombotic regimen (Ticagrelor or Prasugrel).
• All patients will be on optimal guideline directed treatment for diabetes and associated problems like HT and dyslipidemias
• In each arm 85% patients with 3-vessel disease and 15% patients with 2-vessel disease will be randomized. Also, within vessel disease stratum equal allocation will be done for Ticagrelor and Prasugrel.
• The patients will be followed through 5 years to assess the clinical status and major clinical events
Study Design

Primary Objective of TUXEDO-2
Supraflex Cruz vs. Xience family
Compare TLF rate (cardiac death, TV-MI or ID-TLR) at 1-year

Secondary Objective of TUXEDO-2
Pooled PCI Cohort vs. CABG arm
Time to first occurrence of the composite of all cause death, nonfatal MI, or stroke (MACE) at 1-year and yearly up to 5 years

Diabetic Population with Multi-vessel Disease
Population of Diabetes mellitus with angiographically confirmed multivessel disease

Informed Consent and enrolment

Screening
Meet all the inclusion and none of the exclusion criteria and determine criteria for PCI

Eligible for PCI

Ineligible

Randomization (via IWRS)

Within 72 hrs. prior to index procedure

Supraflex Cruz Sirolimus eluting coronary stent system
Prasugrel/Ticagrelor

Xience family of Everolimus eluting coronary stent system
Prasugrel/Ticagrelor

PCI procedure + OMT

Follow up

1-Month±7 days (Clinic/Telephonic), 6-Month±30 days (Clinic), 12-Month±30 days (Clinic), 24-Month±30 days (Clinic), 36-Month±30 days (Telephonic), 48-Month±30 days (Telephonic), 60-Month±30 days (Telephonic)
Inclusion Criteria

• Age ≥18 years
• Defined Patient must have a diagnosis of diabetes mellitus (Type 1 or Type 2)
• Angiographically confirmed multivessel CAD [critical (≥ 70%) lesions in at least two major epicardial vessels and in at least two separate coronary artery territories (LAD, LCX, RCA)]. The population will consist of approximately 85% patients with triple vessel disease.
• Angiographic characteristics amenable to PCI as decided by the heart team.
• Indication for revascularization based upon symptoms of angina and/or objective evidence of myocardial ischemia (please refer MOO for angina classification)
• Willing to comply with all follow-up required study visits
• Signed informed consent
Exclusion Criteria

- Severe congestive heart failure (class III or IV according to NYHA, or pulmonary edema) at the time of enrollment. (please refer MOO for NYHA classification)
- Prior CABG surgery.
- Prior PCI with stent implantation within 6 months.
- Previous stroke within 6 months or patients with stroke at more than 6 months with significant residual neurologic involvement, as reflected in a Rankin Score > 1. (See MOO for Modified Rankin Score)
- Prior history of significant bleeding (within the previous 6 months) that might preclude use of dual antiplatelet therapy.
- In-stent restenosis of a target vessel.
Exclusion Criteria

- Two or more chronic total occlusions in major coronary territories that are targeted for revascularization.
- Acute ST-elevation MI (Q-wave) within 72 hours prior to enrollment requiring revascularization.
- Contraindication to PCI because of a coexisting clinical condition
- Intolerance or contraindication to aspirin or both clopidogrel and ticagrelor or prasugrel
- Extra-cardiac illness that is expected to limit survival to less than 5 years.
- Women who are pregnant, nursing or who plan to become pregnant while in the study
- Concurrent enrollment in another clinical trial
For Primary Objective: (Supraflex Cruz vs. Xience family)

- Comparison of composite endpoint of Target Lesion Failure of the Supraflex Cruz to the Xience group at 1-year [(cardiac death, target-vessel myocardial infarction (TV-MI) or ischemia-driven target-lesion revascularization (ID-TLR)]

For Secondary Objective: (PCI vs. CABG based on performance goal derived from the CABG arm from FREEDOM)

- Time to first occurrence of the composite of death, nonfatal MI, or stroke at 1-year and yearly up to 5 years.
Secondary Endpoints

For Primary Objective: (Supraflex Cruz vs. Xience family)

- ID-TLR
- ID-TVRO
- TVF
- Cardiac death
- Nonfatal MI
- All-cause mortality
- TV-MI
- MACE
- Bleeding on BARC scale
- Stent thrombosis
Secondary Endpoints

For Secondary Objective: (PCI vs. CABG based on performance goal from FREEDOM)

- Composite of death, myocardial infarction, stroke, or repeat revascularization (MACCE) at 1-year and yearly up to 5 years
- Individual components of the primary and secondary composite endpoints
Procedural End Points

- **Device Success:** An attainment of visually estimated, residual stenosis of < 30% of the target lesion
- **Lesion Success:** An attainment of < 30% residual stenosis using any device during the procedure
- **Procedural Success:** An attainment of lesion success without the occurrence of in-hospital MACE
- **Procedural Complication Rate:** This would include complete and individual angiographic occurrence of a dissection ≥ Type B, no re-flow, distal embolization, perforation or abrupt closure
Assessment Schedule

• Screening, Randomization, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months

Study Duration

• Enrollment will occur over approximately 18 months with an expected minimum of 12 months follow-up which shall be continued annually till 5 years via telephone.
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<thead>
<tr>
<th>Event schedule</th>
<th>≤ 14 days to ≤ 24 hours pre procedure</th>
<th>Index procedure</th>
<th>Post procedure</th>
<th>1 Month ± 7 days</th>
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<td>Type of visit</td>
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**Schedule of Assessment**
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• All stable coronary artery disease patients must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least 6 months after PCI followed by ASA monotherapy in definitely.

• There will be a randomization between Ticagrelor and Prasugrel(2x2) at the time of stent allocation

• All randomized participants must receive evidence-based guideline directed medical therapy as outlined in the MOO. The recommended goals of therapy will include:
  • Systolic blood pressure target of <130 mm Hg
  • Low density lipoprotein cholesterol (LDL-C) target of <70 mg/dl and ideally <50 mg/dl
  • Diabetes management including the use of SGLT-2 inhibitors
Primary Objective: (Supraflex Cruz vs. Xience family)

- With two sided 5 % (one sided 2.5 % level) of significance, assuming event rate of 11% with non-inferiority margin of 4.5%, considering 10% drop-out, 1800 participants with 1:1 randomization will provide at least 90% power to show the non-inferiority of Supraflex Cruz when compared with Xience.

- The primary endpoint of TLF will be evaluated using the difference in Kaplan-Meier event rates in the intent-to-treat population. The hypothesis test is designed to show non-inferiority of Supraflex Cruz to Xience for the primary endpoint with a one-sided alpha of 0.025. The null (H0) and alternative (HA) hypotheses are:
  - H0: $P_T - P_R \geq$ NI margin
  - HA: $P_T - P_R <$ NI margin

Where $P_T$ and $P_R$ are the proportion of participants with 12-month (Kaplan-Meier estimate) TLF rate for treatment and reference stent and NI is the non-inferiority margin.
Secondary Objective: (PCI vs. CABG based on performance goal derived from the CABG arm from FREEDOM)

• To compare the results of the combined Supraflex Cruz and Xience family arms of TUXEDO-2 with performance goal at 5-years derived from the CABG arm of FREEDOM (Composite of all-cause mortality, non-fatal myocardial infarction, or stroke). Assuming an estimated true rate of 21.6% (performance goal) for a 1-sided alpha level of 5%, 1800 subject will give approx. 90% power to meet the performance goal with true event rate of 18.7%.
Randomization Strategy

• A block stratified randomization approach will be followed to generate random allocations.

• Patients will be randomized into either of Supraflex Cruz arm or Xience family arm in the ratio of 1:1 respectively.

• Randomization will be stratified based on the number of vessel disease (2-vessel or 3-vessel) and antithrombotic regimen (Ticagrelor or Prasugrel).

• In each arm 85% patients with 3-vessel disease and 15% patients with 2-vessel disease will be randomized. Also, within vessel disease stratum equal allocation will be done for Ticagrelor and Prasugrel.

• All lesions for each patient treated at the index procedure, will receive the same assigned stent type.
Important Tips for Antiplatelets Randomization

• If the patient is on Ticagrelor and randomized to Ticagrelor, we can give a loading dose of Ticagrelor 180 mg and continue 90 mg BID.

• However, if the patient is on Ticagrelor and randomized to Prasugrel, then the loading dose should be 30 mg of Prasugrel on the table and from the next day of the procedure, the patient should continue to take Prasugrel 10 mg dose once daily.

• If the patient is on Clopidogrel before stenting, then the loading dose can be given either with Ticagrelor 180 mg or Prasugrel 60 mg based on the randomization and can continue with the Standard dose Ticagrelor 90 mg BID and Prasugrel 10 mg OD.
To,
Prof. (Dr.) Upenandra Kaul (DM)
M/s Bafna Hospital and Medical Research Center,
1, Tegkalabad Institutional area,
M.M. Road, New Delhi-110002

Date: 27 Oct. 2019

Sub: Notification regarding academic clinical trial entitled “Ultra-Thin strut versus Xience in a Diabetic population with Multi-Vessel Disease- 2- India Study (TUXEDO-2-india)” with licensed medical devices to be conducted in India - Reg.

Sr,
Please refer to your application no. DCGI/Notification/TUXEDO-2/2019/01 dated 28.08.2019 received by this office vide Diary no. 11547 and presentation before SEC (Cardiovascular & Renal) in its meeting held on 06.12.2019 and subsequent clarification DCGI/Notification/TUXEDO-2/2019/03 dated 12.12.2019 received by this office vide Diary no. 15,663 dated 13.12.2019.

The case has been deliberated in SEC (Cardiovascular & Renal) in its meeting held on 03.12.2019 wherein you presented the proposal as investigator initiated study. The study devices Supraflex and Xience family drug eluting stents are already approved and marketed in India.

The committee after detailed deliberation, recommended that there may not be any objection for the study as per the protocol presented based on clarification from the applicant whether it is academic clinical trial or otherwise.

The recommendations are considered and this office has no objection for conducting the subject mentioned academic clinical trial with the devices under the supervision of the following investigator and site mentioned and as per the protocol titled “Ultra-Thin strut versus Xience in a Diabetic population with Multi-Vessel Disease- 2- India Study (TUXEDO-2-india)” Protocol no. NII, Version 1.0 dated 22-07-2019 submitted to this Directorate subject to condition that the data generated during the study shall not be used and furnished to the Central Licensing Authority to manufacture or to import for marketing product in the country.

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<th>S. No</th>
<th>Name &amp; Address Of Principal Investigator</th>
<th>Clinical trial site</th>
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<tr>
<td>1</td>
<td>Dr. Upenandra Kaul,</td>
<td>Bafna Hospital,</td>
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<td>Chairman, Dean Head Genes and Dean</td>
<td>New Delhi</td>
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<td>Academics and Research, New Delhi</td>
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Yours faithfully,

V.G. Somasri
Controller General (I)

FDA Bhawan, Kotla Road,
New Delhi-110002.
File No.4-MD/CT-241/2019-DC
Directorate General of Health Services
Central Drugs Standard Control Organization
(Medical Devices Division)
FDA Bhawan, Kotla Road,
New Delhi-110002.

Dated: 14 Feb 2020

To,
Prof. (Dr.) Upendra Kaul (DM)
M/s Batra Hospital and Medical Research Center,
1, Tuglakabad Institutional area,
M.M. Road, New Delhi-110062


Sir,


The case has been examined in the light of documents submitted by you. In this regard, in the letter dated 27.12.2019 issued by this office. The protocol version and date is hereby amended as follows:

<table>
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<th>Read as</th>
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Yours faithfully,

(Dr. V. G. Somani)
Drugs Controller General (I)
As per Medical Device Rule 2017, Tuxedo study doesn’t fall under the preview of Clinical Trials as per the below clauses -

• **Page no. 143, Chapter 1, Clause 3a**
  “Academic clinical study” means a clinical study conducted for academic purpose on a medical device for the approved or a new intended use, new material of construction, new improved design or new population

• **Page no. 157, Chapter VII, Clause 51, sub-clause 3**
  No permission for conduct of academic clinical study on licensed medical device shall be required, where,-
  
  (a) the ethics committee approves such a study
  
  (b) the data generated during the study shall not be used to furnish to the central licensing authority to manufacture or to import for marketing any investigational medical device in the country.
As per New Drug Clinical Trial 2019, Tuxedo study doesn’t fall under the preview of Clinical Trials as per the below clauses -

**Page no. 158, Clause 28, sub-clause 1** -

No permission for conducting an academic clinical trial shall be required for any drug from the central licensing authority where,—

(I) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and

(Ii) the clinical trial referred to in clause (i) has been initiated after prior approval by the ethics committee for clinical trial; and

(iii) the observations generated from such clinical trial are not required to be submitted to the central licensing authority; and

(iv) the observations of such clinical trial are not used for promotional purposes.

Thank You