The latest clinical evidence in diabetics for the Amphilimus™ eluting polymer-free DES

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Barcelona
Spain
**Disclosure Statement of Financial Interest**

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abbott Vascular</td>
</tr>
<tr>
<td>(Institutional)</td>
<td></td>
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<tr>
<td>Consulting Fees/Honoraria</td>
<td>Astra Zeneca, Alvimedica</td>
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</table>
Clinical evidence

**SAFETY**
- Reduced DAPT duration
- Randomized trial *(Demonstr8 study)*

**EFFICACY**
- Diabetic patients
- NEXT randomized trial *(sub-group DM)*
- Real-world study *(Particip8)* *(sub-group DM)*
- RESERVOIR randomized trial *(Cre8 vs EES in DM)*
- Matched analysis Cre8™ vs EES
- ASTUTE registry - Diabetics
  - Matched analysis Cre8™ vs BES

**SPONSORED STUDIES**
- U-Short registry - DAPT
- Randomized trial Cre8 vs ZES *(ReCre8)*
- ASTUTE registry - DAPT

**INDEPENDENT STUDIES**
Clinical evidence

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The NEXT randomized study

**Primary Endpoint:** In-stent LLL at 6 months

Patients with ischemic myocardial symptoms related to de novo lesions (max 2 in 2 different vessels) in native coronary arteries

- **Cre8™ (n=162 pts)**
- **323 enrolled patients**
  - 11 European Sites
  - 100% angiographic f-up
  - 20% IVUS f-up
- **TAXUS™ Liberté® (n=161 pts)**

PI: Prof D. Carrié, Toulouse, France

Clinical FU

- 1M
- 6M
- 1 – 2 – 3 – 4 – 5Y

Angiographic/IVUS* FU

*Angiographic/IVUS Core Lab: BioClinica Leiden, The Netherlands

Carrié et al JACC, 2012, 59; 1371-76
The LLL in the DM subgroup is comparable to that obtained in the overall population.

Primary Endpoint: 6-month LLL

Overall population

- 60%
The NEXT randomized study

5 years cumulative TLF
(Cardiac death, TV MI, all TLR)

Overall population

Diabetic population

Comparable TLF and TLR in both overall population and diabetic subgroup for Cre8™. This is not the case for Taxus.
Clinical plan

**SAFETY**
- Reduced DAPT duration
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**EFFICACY**
- Diabetic patients
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  - Real-world study (Particip8) (sub-group DM)

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**Particip8 Study Design**

“Real world” patients with ischemic myocardial symptoms related to de novo coronary artery lesions, treated with Cre8

1186 patients
30 European Sites

Pre-specified diabetic subgroup

Diabetics patients submitted to angio FU

**Pl: A. Colombo - Italy**

**OBJECTIVE:** evaluate the safety and efficacy performances of Cre8, in patients comparable to the everyday’s clinical practice population, with a specific focus on diabetics subjects

**PRIMARY ENDPOINT:** 6-month incidence of clinical composite endpoint: Cardiac death/Target vessel MI/ Clinically indicated TLR

Clinical FU

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Angiographic FU (diabetic pre-spec. group)
Device-Oriented MACE at 1year

12month MACE* = CD + TV MI + CI TLR

Overall Population - 12month results -

Cardiac Death: 0.9% (CI: 0.41% ; 1.57%)
Target Vessel MI: 0.9% (CI: 0.47% ; 1.68%)
CI TLR: 1.0% (CI: 0.53% ; 1.79%)
MACE: 2.8% (CI: 1.93% ; 3.91%)

Diabetic Population - 12month results -

Cardiac Death: 1.7% (CI: 0.55% ; 3.90%)
Target Vessel MI: 1.7% (CI: 0.55% ; 3.90%)
CI TLR: 1.4% (CI: 0.37% ; 3.42%)
MACE: 4.7% (CI: 2.55% ; 7.63%)

*MACE as percent frequencies of the device–oriented clinical composite of CD, TV MI, CI TLR up to 12 months - ITT population - Diabetic population (N = 296) - Adjudicated events
Clinical plan

SAFETY

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  - Randomized trial (Demonstr8 study)

EFFICACY

- Diabetic patients
  - Real-world study with diabetic sub-group (Particip8)
  - Retrospective real-world study (Investig8)
  - Diabetic Randomized study (Reservoir)
  - Matched analysis Cre8™ vs EES
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U-Short registry - DAPT
Randomized trial Cre8 vs ZES (ReCre8)
ASTUTE registry - DAPT
RESERVOIR trial

Exclusion criteria
- Life-style changes only
- STEMI
- Bifurcation > 2.5mm
- Left Main/ostial LAD
- 3V with CABG indication
- GFR < 30 ml/min
- LVEF < 30%
- Contraindication DAPT

Primary endpoint: Neointimal volume obstruction by OCT
RESERVOIR trial

Primary endpoint: Neointimal Volume Obstruction

![Graph showing cumulative frequency of neointimal volume obstruction.

- **AES = Cre8**
- **EES = Xience family**

### NEOINTIMAL VOLUME OBSTRUCTION

<table>
<thead>
<tr>
<th>No. of lesions</th>
<th>Difference (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>-4.14 (-9.64 to 0.61)</td>
<td>0.376</td>
</tr>
<tr>
<td>&gt; 20 mm Stent length</td>
<td>-6.92 (-19.93 to 0.5)</td>
<td>0.952</td>
</tr>
<tr>
<td>&lt; 20 mm Stent length</td>
<td>-1.92 (-9.02 to 3.14)</td>
<td>0.193</td>
</tr>
<tr>
<td>&gt; 3.0 mm Stent diameter</td>
<td>-3.96 (-14.16 to 1.63)</td>
<td>0.119</td>
</tr>
<tr>
<td>&lt; 3.0 mm Stent diameter</td>
<td>-3.63 (-12.51 to 2.24)</td>
<td>0.467</td>
</tr>
<tr>
<td>LAD Target vessel</td>
<td>-0.33 (-3.24 to 2.93)</td>
<td></td>
</tr>
<tr>
<td>non-LAD Target vessel</td>
<td>-7.46 (-17.8 to 0.6)</td>
<td></td>
</tr>
<tr>
<td>Insulin DM treatment</td>
<td>-9.17 (-22.24 to 1.28)</td>
<td></td>
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<tr>
<td>Oral drugs DM treatment</td>
<td>-0.59 (-3.33 to 2.27)</td>
<td></td>
</tr>
<tr>
<td>≤ median HDL</td>
<td>-5.87 (-15.37 to -0.05)</td>
<td></td>
</tr>
<tr>
<td>&gt; median HDL</td>
<td>-1.75 (-10.61 to 4.66)</td>
<td></td>
</tr>
<tr>
<td>≤ median LDL</td>
<td>-9.11 (-19.96 to -0.09)</td>
<td></td>
</tr>
<tr>
<td>&gt; median LDL</td>
<td>1.52 (-1.24 to 4.66)</td>
<td></td>
</tr>
<tr>
<td>≤ median Hb1Ac</td>
<td>-10.62 (-22.58 to -1.69)</td>
<td>0.020</td>
</tr>
<tr>
<td>&gt; median Hb1Ac</td>
<td>2.20 (-1.0 to 5.52)</td>
<td></td>
</tr>
</tbody>
</table>

Late Lumen Loss (9 months)

AES = Cre8

EES = Xience family

<table>
<thead>
<tr>
<th>MLD (mm)</th>
<th>AES</th>
<th>EES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent</td>
<td>2.38 ± 0.44</td>
<td>2.19 ± 0.59</td>
<td>0.07</td>
</tr>
<tr>
<td>In-segment</td>
<td>2.09 ± 0.45</td>
<td>1.84 ± 0.61</td>
<td>0.02</td>
</tr>
</tbody>
</table>

In-stent LLL results in diabetics

- NEXT (diabetic subgroup): 0.12 ± 0.29
- PARTICIP8 (diabetic subgroup): 0.16 ± 0.13
- RESERVOIR: 0.14 ± 0.24

Randomized study

All-Comers study

Randomized study in DM

Company sponsored studies

Independent study
TLR at 3.5 years

Days from randomization

Log Rank p = 0.195

Polymers-based

12.1% (EES)

No polymer

5.2% (Cre8)
Clinical plan

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**SPONSORED STUDIES**
Matched analysis: Cre8 vs. BES

INSPIRE-1
(Italian Nobori Stent Prospective REgistry-1)

San Raffaele Scientific Institute
Humanitas Clinical Institute
Clinica Mediterranea
Istituto Clinico Città Studi
IRCCS Policlinico san Donato
EMO-GVM Centro Cuore Columbus
Policlinico Umberto I
Ospedale San Paolo

ASTUTE
(AmphilimuS iItalian mUlticenTre rEGistry)

San Raffaele Scientific Institute
Clinica Mediterranea
Istituto Clinico Città Studi
IRCCS Policlinico san Donato
EMO-GVM Centro Cuore Columbus
Ospedali Riuniti Marche Nord
Ospedale San Giovanni di Dio
Ospedale San Pietro, FBF
Ospedale Santa Corona
Cre8 is always statistically superior to BES:
- TLF = 5% vs. 13% (-62%; p<0.001)
- TLR = 4% vs. 9% (-57%; p=0.005)
Independent predictors of TLF in the propensity-score matched population

<table>
<thead>
<tr>
<th>Groups</th>
<th>Predictor variable</th>
<th>Predictor variable in TLF vs non-TLF</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>Chronic kidney disease</td>
<td>(29.5% vs. 8%)</td>
<td>&lt;0.001</td>
<td>4.24 (2.07-8.70)</td>
</tr>
<tr>
<td></td>
<td>LVEF</td>
<td>(49.04±10.52 % vs. 53.02±8.51 %)</td>
<td>0.023</td>
<td>0.965 (0.96-0.99)</td>
</tr>
<tr>
<td></td>
<td>Total stent length per pt</td>
<td>(37.3±19.05 mm vs. 29.9±17.8 mm)</td>
<td>0.006</td>
<td>1.02 (1.00-1.03)</td>
</tr>
<tr>
<td>DM</td>
<td>BD-BES vs PF-AES</td>
<td>(13% vs. 5%)</td>
<td>0.005</td>
<td>2.76 (1.36-5.56)</td>
</tr>
<tr>
<td></td>
<td>No of bifurcation per pt</td>
<td>(0.318±0.51 vs. 0.203±0.44)</td>
<td>0.068</td>
<td>1.73 (0.96-3.12)</td>
</tr>
<tr>
<td></td>
<td>Total stent length per pt</td>
<td>(48.0±29.6 mm vs. 34.25±22.9 mm)</td>
<td>0.008</td>
<td>1.02 (1.00-1.03)</td>
</tr>
</tbody>
</table>
Second-generation drug-eluting stents in diabetes: a Randomized trial (the SUGAR trial)

All-comers DM patients undergoing PCI

Amphilimus-Eluting Stents (AES)

1164 patients
26 Spanish Centers
Randomization 1:1

12 months **Primary Endpoint:** TLF (non-inferiority)

24 months **Co-Primary Endpoint:** TLF (Superiority)

PI: Rafael Romaguera
Hospital de Bellvitge

Co-PI: Pablo Salinas
Hosp. Clínico San Carlos

* Study funded by the Spanish Society of Cardiology
Diab8 randomized trial

All-comer patients with diabetes mellitus undergoing PCI

Cre8™ EVO

3040 patients
54 International Sites
Randomization 1:1

Everolimus Eluting Stent (EES)

PI: Antonio Colombo

Primary Endpoint
• EFFICACY = 12 months Target Lesion Revascularization (TLR)
  Sequential check for Non-inferiority (first step) and then for Superiority (second step)

Secondary main Endpoints
• EFFICACY = 24 months TLR for Superiority
• SAFETY = 12 months Cardiac Death + Target Vessel MI (CD + TVMI)

Clinical FU

  1 year
  2 years
  3 years
Conclusions

- The Cre8 stent represents a unique technology, different than classic polymer-based DES, because its abluminal reservoir design allows elution of the drug formulated with carriers.

- This technology has shown in several registries and RCT to be highly effective preventing target lesion failure in patients with DM, with a very low late loss (0.12-016) and a very low rate of events (specially after 6-9 months) in this population.

- The ongoing large-scale RCT SUGAR and Diab8 will further add evidences to the Cre8™ efficacy in the challenging patient population represented by diabetics.
Thank you for your attention