CORONARY REVASCULARIZATION IN THE DIABETIC PATIENT

PCI in the Diabetic Patients: Current Challenges and Future Perspectives

Dr. Ramiro Trillo. Hospital Clínico de Santiago. Spain
Diabetes: A Global Emergency

* IDF Diabetic Atlas 7th Ed. vs 3rd Ed.
** IDF Diabetic Atlas 7th Ed. estimation
Diabetes: A Global Emergency

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

- **World**
  - **2015**: 415 million
  - **2040**: 642 million

- **North America and Caribbean**
  - **2015**: 44.3 million
  - **2040**: 60.5 million

- **Europe**
  - **2015**: 59.8 million
  - **2040**: 71.1 million

- **Middle East and North Africa**
  - **2015**: 35.4 million
  - **2040**: 72.1 million

- **South and Central America**
  - **2015**: 29.6 million
  - **2040**: 48.8 million

- **South East Asia**
  - **2015**: 78.3 million
  - **2040**: 140.2 million

- **Western Pacific**
  - **2015**: 153.2 million
  - **2040**: 214.8 million

- **Africa**
  - **2015**: 14.2 million
  - **2040**: 34.2 million
Randomized trials comparing 2\textsuperscript{nd} gen DES to 1\textsuperscript{st} gen DES in DM

The most effective 2nd gen. DES has failed to prove higher efficacy in diabetic patients vs. 1st gen. DES

![SPIRIT/COMPARE Pooled Patient Level Analysis](image)
DES efficacy in DM is worst vs. Non-DM

Today available DES, including the latest “-olimus” generations, have shown lower angiographic efficacy in diabetic patients compared to non-diabetics.

![Graph showing late lumen loss at 6/9 months](image)
Why -limus drugs are less effective in diabetics

1. Direct Resistance of diabetic cells to -limus drug

- 10 times higher “-limus” drug concentration is needed to achieve similar inhibition of non DM cells

2. Contribution of other hormones in limiting “-limus” action on cell proliferation

- 9 times higher “-limus” drug concentration is needed to stop Leptin-induced hyperplasia

To improve PCI efficacy in diabetic patients we need to increase the «-limus» drug concentration inside the diabetic cells!
The latest DES technology to improve efficacy in DM patients
Technology for very higher drug concentration into diabetic cells (higher efficacy):

**Amphilimus™ formulation**
Sirolimus and Fatty Acid are eluted together

Combined effect

- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency

Proprietary technology

- Sustained drug elution timing
- Modulated drug bioavailability
- Raised homogeneous drug distribution
- Enhanced drug stability

Amphilimus™ Formulation
Abluminal Reservoir Technology

proprietary polymer-free drug release system constituted by reservoirs on the stent's abluminal surface

**ARTERIAL WALL**
Drug elution is controlled and directed exclusively towards the vessel wall

**BLOOD FLOW**
No polymer
No drug
Abluminal Reservoir Technology

Abluminal Reservoir is the ONLY polymer-free technology able to provide the same elution kinetic obtained by the most effective polymeric DES.

- Peak drug tissue concentration during the first days
- 50% drug elution in approximately 18 days
- 65%-70% drug elution within 30 days
- Complete drug elution within 90 days

The Reservoir shape defines drug release kinetic (Fick law)
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

U-Short registry - DAPT

Randomized trial Cre8 vs ZES
(ReCre8)

ASTUTE registry - DAPT
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)

**INDEPENDENT STUDIES**
- ASTUTE registry - DAPT
The NEXT randomized study

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

Primary Endpoint: In-stent LLL at 6 months

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 NEXT randomized study
- Primary endpoint: 6 month LLL -

The LLL in the DM subgroup is comparable to that obtained in the overall population.
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 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
RESERVOIR trial

Primary endpoint: Neointimal volume obstruction by OCT
RESERVOIR trial

Primary endpoint: Neointimal Volume Obstruction

Primary endpoint: Neointimal Volume Obstruction

RESERVOIR trial

Primary endpoint: Neointimal Volume Obstruction

NEOINTIMAL VOLUME OBSTRUCTION

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of lesions</th>
<th>Difference (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>101</td>
<td>-4.14 (-9.64 to 0.61)</td>
<td></td>
</tr>
<tr>
<td>Stent length:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20 mm</td>
<td>49</td>
<td>-6.92 (-19.93 to 0.5)</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 mm</td>
<td>52</td>
<td>-1.92 (-9.02 to 3.14)</td>
<td></td>
</tr>
<tr>
<td>Stent diameter:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.0 mm</td>
<td>55</td>
<td>-3.96 (-14.16 to 1.63)</td>
<td></td>
</tr>
<tr>
<td>&lt; 3.0 mm</td>
<td>46</td>
<td>-3.63 (-12.51 to 2.24)</td>
<td></td>
</tr>
<tr>
<td>Target vessel:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>41</td>
<td>-0.33 (-3.24 to 2.93)</td>
<td></td>
</tr>
<tr>
<td>non-LAD</td>
<td>60</td>
<td>-7.46 (-17.8 to 0.6)</td>
<td></td>
</tr>
<tr>
<td>DM treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>39</td>
<td>-9.17 (-22.24 to 1.28)</td>
<td></td>
</tr>
<tr>
<td>Oral drugs</td>
<td>62</td>
<td>-0.59 (-3.33 to 2.27)</td>
<td></td>
</tr>
<tr>
<td>HDL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ median</td>
<td>49</td>
<td>-5.87 (-15.37 to -0.05)</td>
<td></td>
</tr>
<tr>
<td>&gt; median</td>
<td>48</td>
<td>-1.75 (-10.61 to 6.66)</td>
<td></td>
</tr>
<tr>
<td>LDL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; median</td>
<td>48</td>
<td>-9.11 (-19.96 to -0.09)</td>
<td></td>
</tr>
<tr>
<td>≤ median</td>
<td>49</td>
<td>1.52 (-1.24 to 4.66)</td>
<td></td>
</tr>
<tr>
<td>Hb1Ac:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; median</td>
<td>49</td>
<td>-10.62 (-22.58 to -1.69)</td>
<td>0.020</td>
</tr>
<tr>
<td>&lt; median</td>
<td>49</td>
<td>2.20 (-1.0 to 5.52)</td>
<td></td>
</tr>
</tbody>
</table>

Late Lumen Loss (9 months)

<table>
<thead>
<tr>
<th></th>
<th>AES</th>
<th>EES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 sub-group)**: 0.12 ± 0.29
- **PARTICIP8 (diabetic sub-group)**: 0.16 ± 0.13
- **RESERVOIR**: 0.14 ± 0.24

**Randomized study**

**All-Comers study**

**Randomized study in DM**

**Company sponsored studies**

**Independent study**
Clinical plan

**SAFETY**
- Reduced DAPT duration
- Randomized trial *(Demonstr8 study)*
- U-Short registry - DAPT
- Randomized trial Cre8 vs ZES *(ReCre8)*
- ASTUTE registry - DAPT

**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
- ASTUTE registry - Diabetics
- Matched analysis Cre8™ vs BES

**SPONSORED STUDIES**

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

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

San Raffaele Scientific Institute
Humanitas Clinical Institute
Clinica Mediterranea
Ospedali Riuniti Marche Nord
EMO-GVM Centro Cuore Columbus
Policlinico Umberto I
Ospedale San Paolo

ASTUTE
AmphilimuS iTalian 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)
CONTROL-8 registry

**Design**

- **DESIGN:** Prospective, non-randomized, single-arm, multi-center clinical evaluation of the CRE8 stent in diabetics and prediabetic patients
- **OBJECTIVE:** The aim of the study is to assess the clinical performance of Cre8-stent in a “real-world” cohort of diabetic and prediabetic patients:

- 443 diabetics and prediabetic patients
- 551 lesions enrolled
- January 2014-January 2017

- Clinical 1 month follow up
- Clinical 12 month follow up
- Clinical 24 month follow up

- 100 patients 1 year follow up QCA and OCT angiographic review
CONTROL-8 registry

PARTICIPANTS; 7 SPANISH HOSPITALS
(443 patients enrolled)

Primary endpoint: Cardiac death, Target vessel MI or TLR
CONTROL-8 registry

RESULTS
Medium follow up 234 days

0.8% stent thrombosis
Randomized Studies
ready to start
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

Zotarolimus-Eluting Stent (ZES)

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
Today DM represents a global emergency. DM patients are at higher risk of coronary events after PCI compared to those without DM.

All currently available DES have not provided better efficacy vs 1st generation DES (Taxus) in diabetic patients.

Reasons for lower DES efficacy in diabetics are: (1) VSMCs of diabetic patients are less responsive to –limus drugs; (2) High blood levels of the hormone leptin, which stimulates VSMCs proliferation, are often present in diabetic and overweight patients.

The Alvimedica Cre8™ DES (Amphilimus™ formulation → higher Sirolimus concentration in diabetic VSMCs/ Abluminal Reservoirs → prolonged polymer-free drug elution) has provided very solid data in DES efficacy in DM patients. The SUGAR and Diab8 randomized trials have been designed to prove Cre8 EVO superiority in all-comers DM patients.

Conclusions