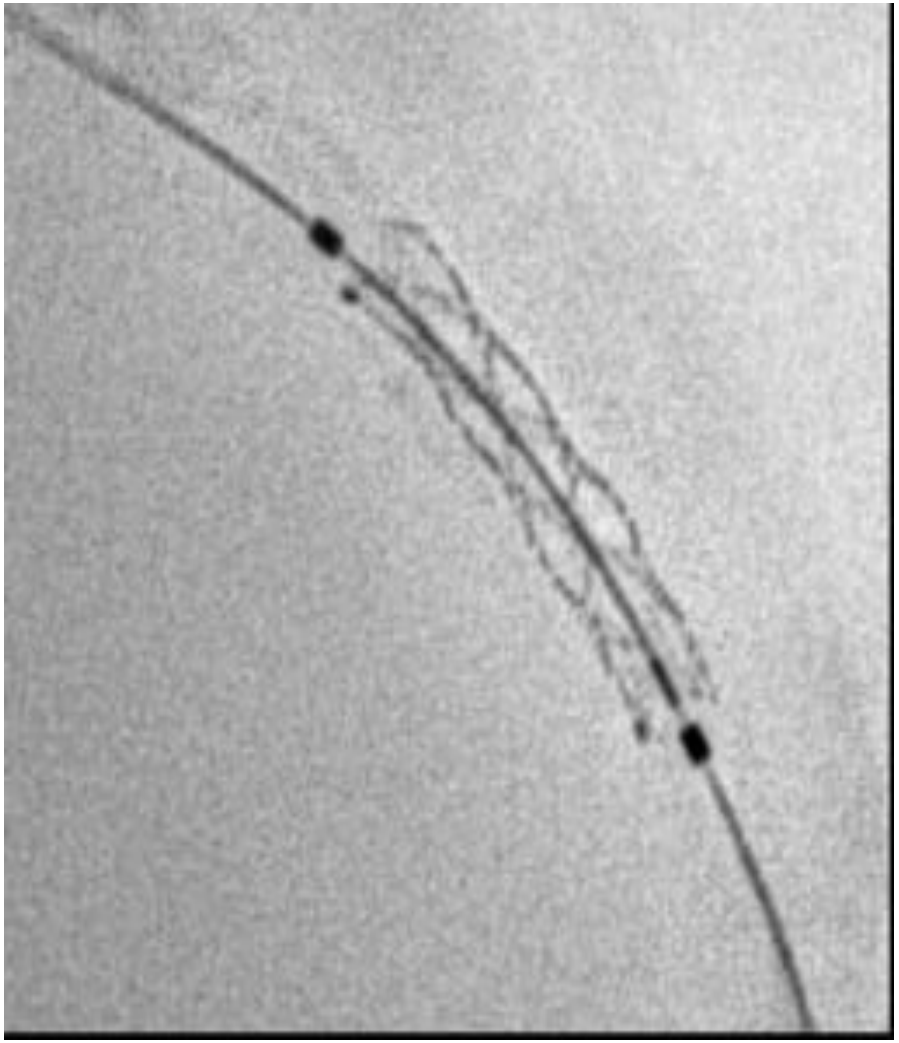
# “Cre8™ résultats cliniques”

**J BERLAND**
**Clinique Saint Hilaire**
**ROUEN**

Contrat de recherche Crea8 : Etude NEXT

# STENT à RESERVOIR Cre8™



# The NEXT randomized study

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

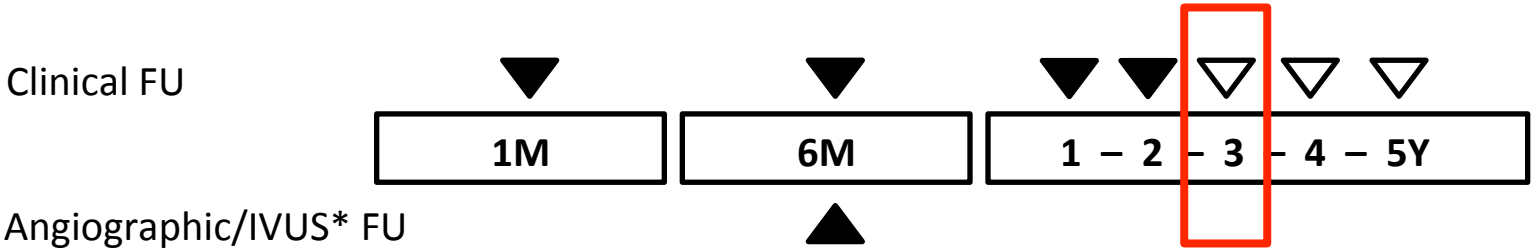
**Cre8™ (n=162 pts)**

**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




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

Carrié et al JACC, 2012, 59; 1371-76

# Patients' Risk Factors

| | Cre8™ (162 pts) | TAXUS Liberté (161 pts) | p value |
|---|---|---|---|
| Smoker | 55.6% (90/162) | 54.7% (88/161) | ns |
| Diabetes | 29.6% (48/162) | 24.2% (39/161) | ns |
| Hypertension | 64.2% (104/162) | 64.6% (104/161) | ns |
| Hyperlypidemia | 63.0% (102/162) | 60.9% (98/161) | ns |
| CAD Family History | 29.0% (47/162) | 25.5% (41/161) | ns |

# Pre-procedure angiographic data

| | | | |
|---|---|---|---|
| RVD (mm) | 2.76±0.42 | 2.79±0.43 | ns |
| Lesion length (mm) | 15.41±6.99 | 15.15±7.08 | ns |

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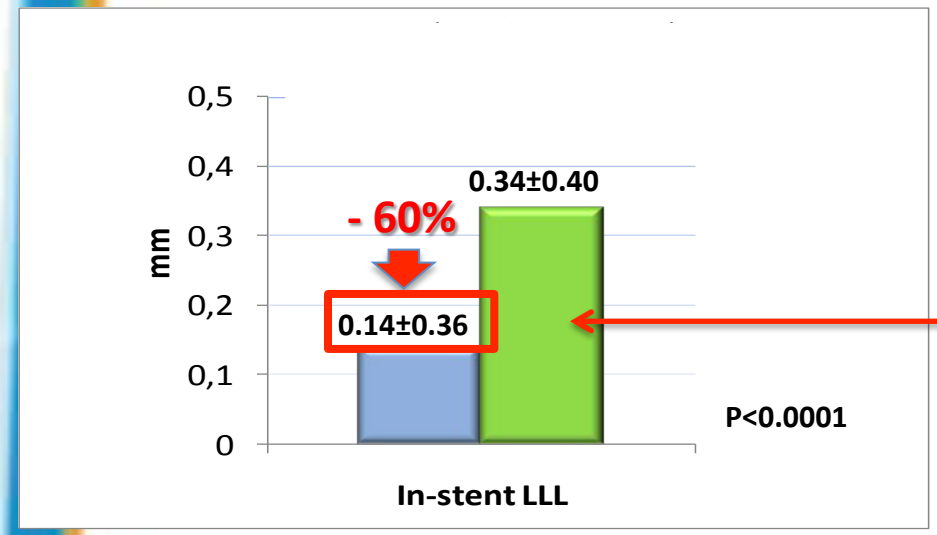
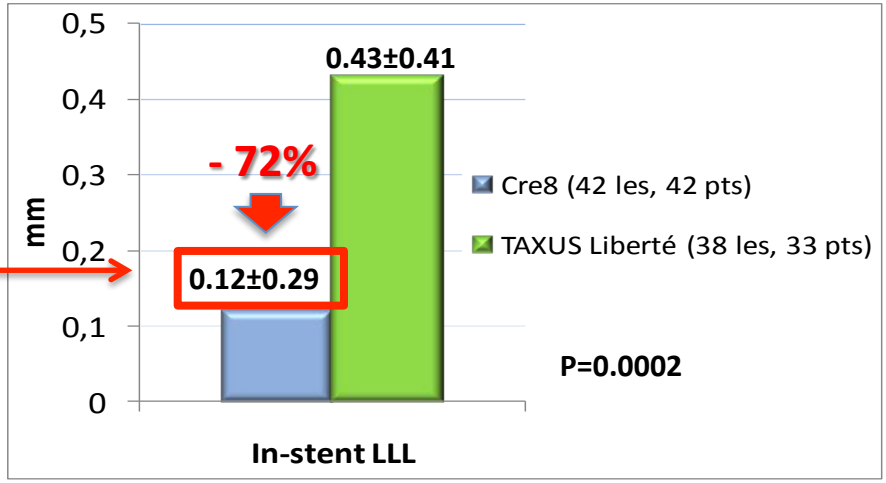
# Primary Endpoint:
## 6-month in-stent Late Lumen Loss

Overall Population

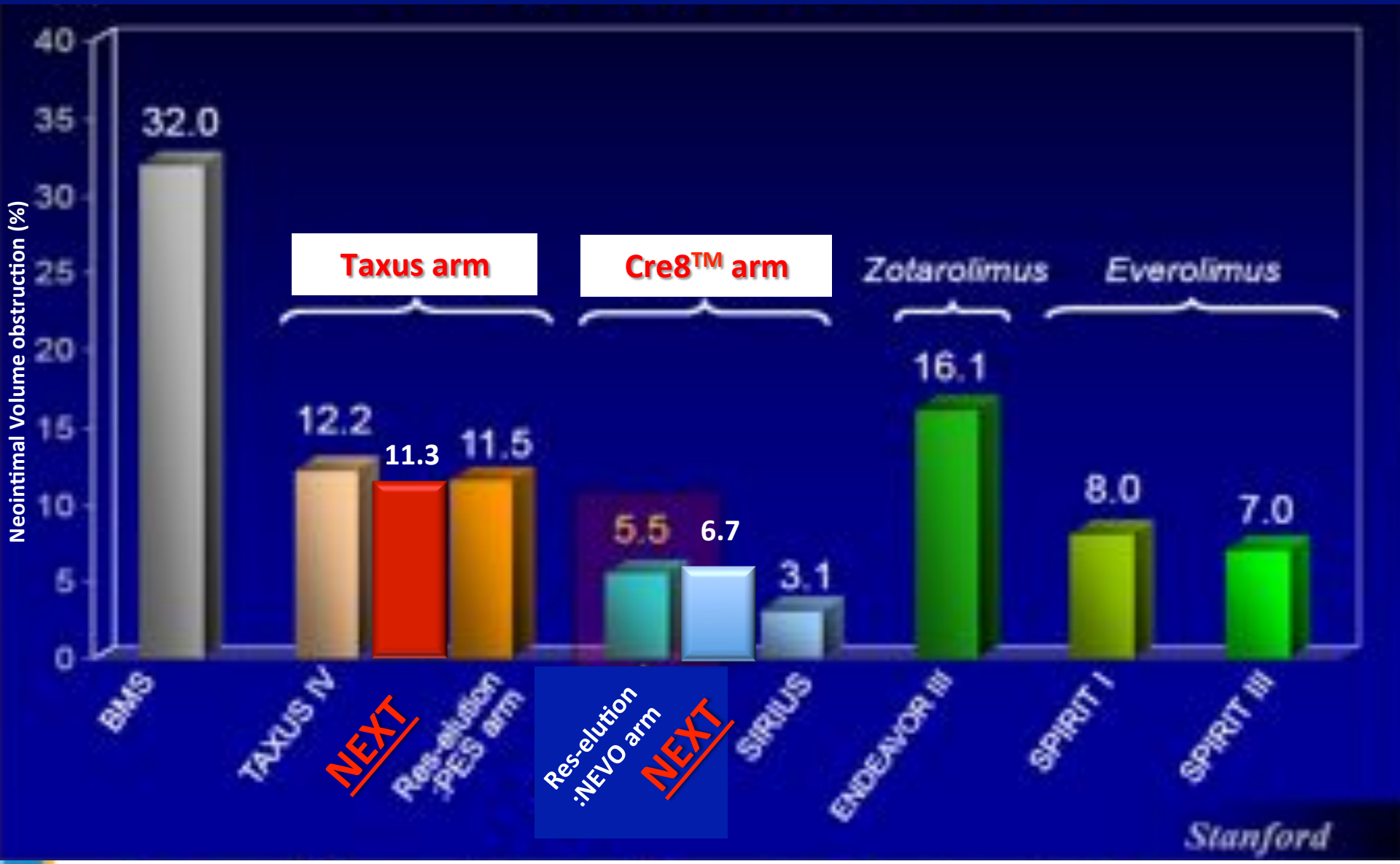



Diabetic subgroup




- The Late Lumen Loss in the diabetic subgroup is comparable to the Late Lumen Loss obtained in the overall population (never seen before)

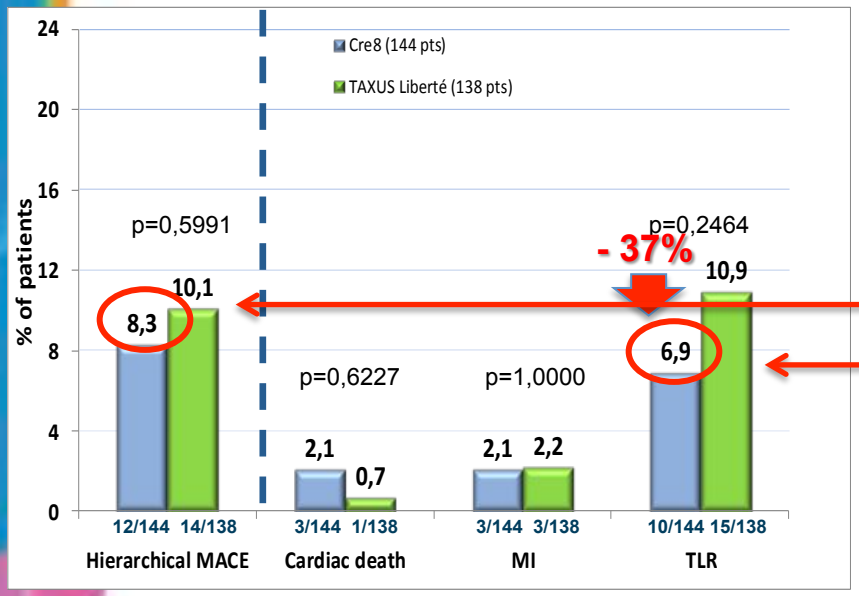
# Cre8™ 6-month IVUS results (NEXT study) compared to other DES in RCTs



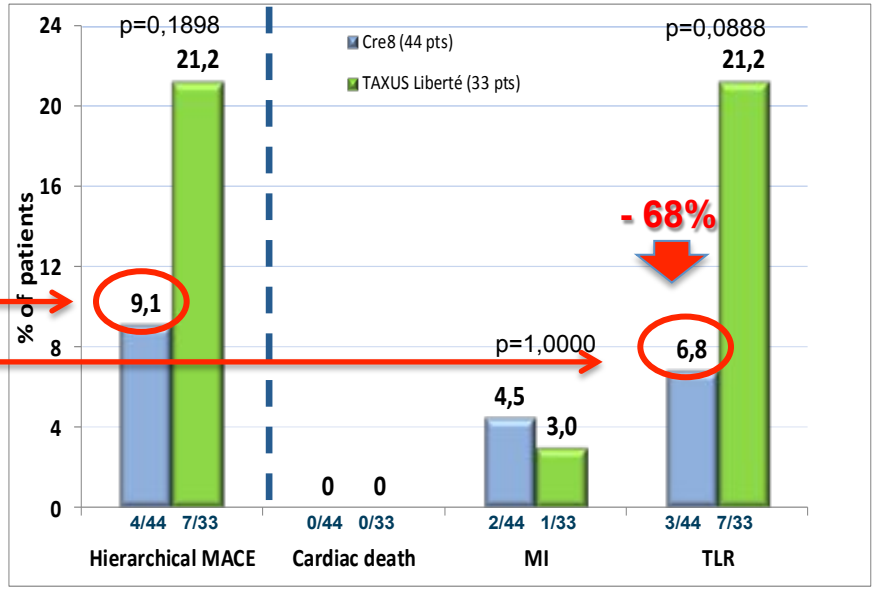
# 36-month cumulative MACE

## (Cardiac death, all MI, all TLR)

### Overall population




### Diabetic population




- Cre8 has shown that MACE and TLR in the diabetic subgroup are comparable to MACE and TLR obtained in the overall population!

# 36-month ARC Stent Thrombosis

| | Cre8 (158 pts) | TAXUS Liberté (157 pts) | p value |
|---|---|---|---|
| **Definite Stent Thrombosis** | | | |
| Acute Thrombosis (0-1 day) | 0% | 0% | - |
| Sub-acute Thrombosis (2-30 days) | 0% | 0.6% (1/157)* | 0.4984 |
| Late Thrombosis (31-365 days) | 0.6% (1/158)§ | 0% | 1.0000 |
| Very Late Thrombosis (365-730 days) | 0% | 0% | - |
| Very Late Thrombosis (730-1095 days) | 0% | 0% | - |
| **Probable Stent Thrombosis** | | | |
| All (0-1095 days) | 0% | 0% | - |
| **TOTAL (Definite + Probable)** | **0.6% (1/158)§** | **0.6% (1/157)*** | 1.0000 |

*Definite sub-acute thrombosis: 48 hours after the procedure the patient came back to hospital with MI. Angio control showed a stent thrombosis. Blood exams revealed clopidogrel not responsiveness. The patient was submitted to medical treatment.

§Definite late thrombosis: 11 months after the procedure the patient came back to hospital with MI. Angio control showed a stent thrombosis. The patient ,not responder to thienopyridine due to genetic mutation, had also stopped ASA treatment.

# Next study

## SAFETY

Reduced DAT duration

LBT EuroPCR2013

**Randomized trial (*Demonstr8*)**

Dedicated clinical trial on DAT

## EFFICACY

Diabetic patients

Real-world study with diabetic sub-group (***pARTicip8***)

Dedicated clinical trial on diabetics

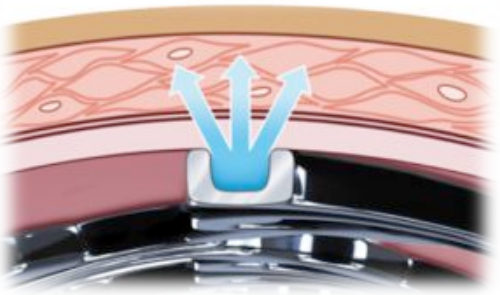
# Demonstr8 study: Rationale + background

- Millions of stable patients undergoing PCI with BMS implantation have taken 1month DAPT (ASA+Clop.) followed by ASA monotherapy to optimize safety and efficacy of PCI procedure - European Guidelines.
- Stent struts (un-)coverage & malapposition evaluated with OCT is considered a predictor of stent thrombosis *

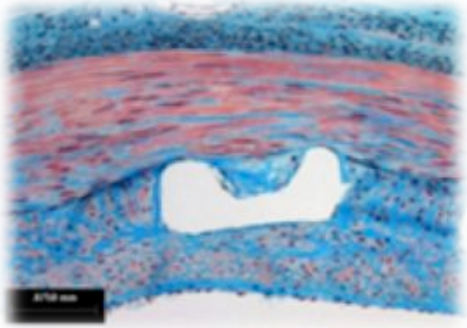
* Finn et al: Circulation,2007;115;2435-41

# Demonstr8 study: Rationale + background (2)

- Cre8™ is a polymer-free DES with Abluminal Reservoir Technology that completely elutes its formulation within 90d



- After complete drug elution, the Cre8™ becomes a BMS* and it interacts with blood and tissue as a standard BMS.



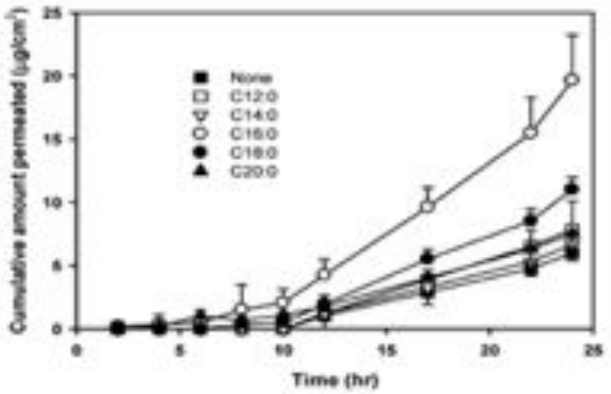
- The entire stent structure, including reservoirs, is homogeneously coated with BIS. This pure carbon coating enhances stent bio- and haemo-compatibility is proven in +10 years experience.

*Moretti et al, Eurointervention 2012;7:1087-1094

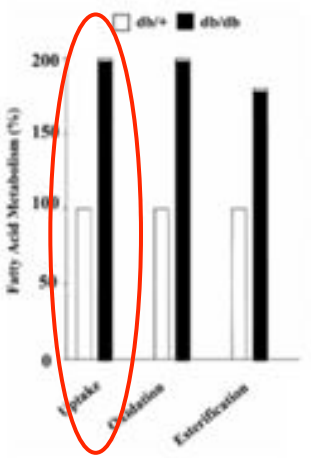
# Amphilimus Formulation
# Sirolimus + Organic Acid

- **Cre8™ employs a permeation enhancer (organic acid = fatty acid) in its formulation.**

1) Fatty acids are used to improve trans-dermal and skin delivery of many different drugs.*




2) Cardiac fatty acid uptake is double in diabetic mice model.**




**Drug + Permeation enhancer** = **Increased drug concentration (diabetes)**

* Drug Delivery, 15:373-379, 2008

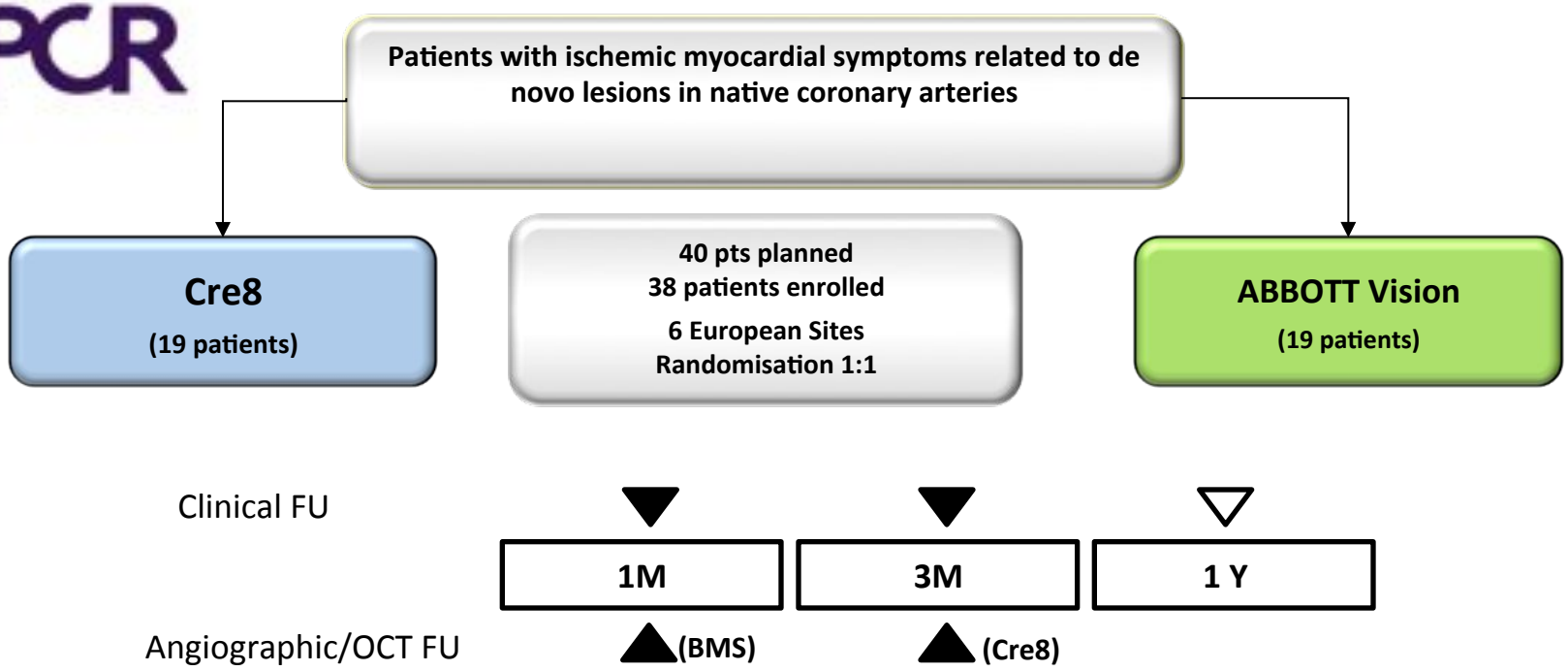
** Cardiac fatty acid uptake and metabolism in db/+ and db/db mice. Curr Cardiol Rev. 2008 February; 4(1): 12-21

# Study Aim

- The purpose of the Demonstr8 study is to prove Cre8™ non inferiority in terms of stent strut coverage evaluated with OCT at three months after stent implantation compared to a well known BMS at one month.

- Hypothesis: if coverage is comparable, at 3 month the Cre8™ (that has become a BMS) could be treated as BMS at 1 month; *just Aspirin*.

# Demonstr8: Study design



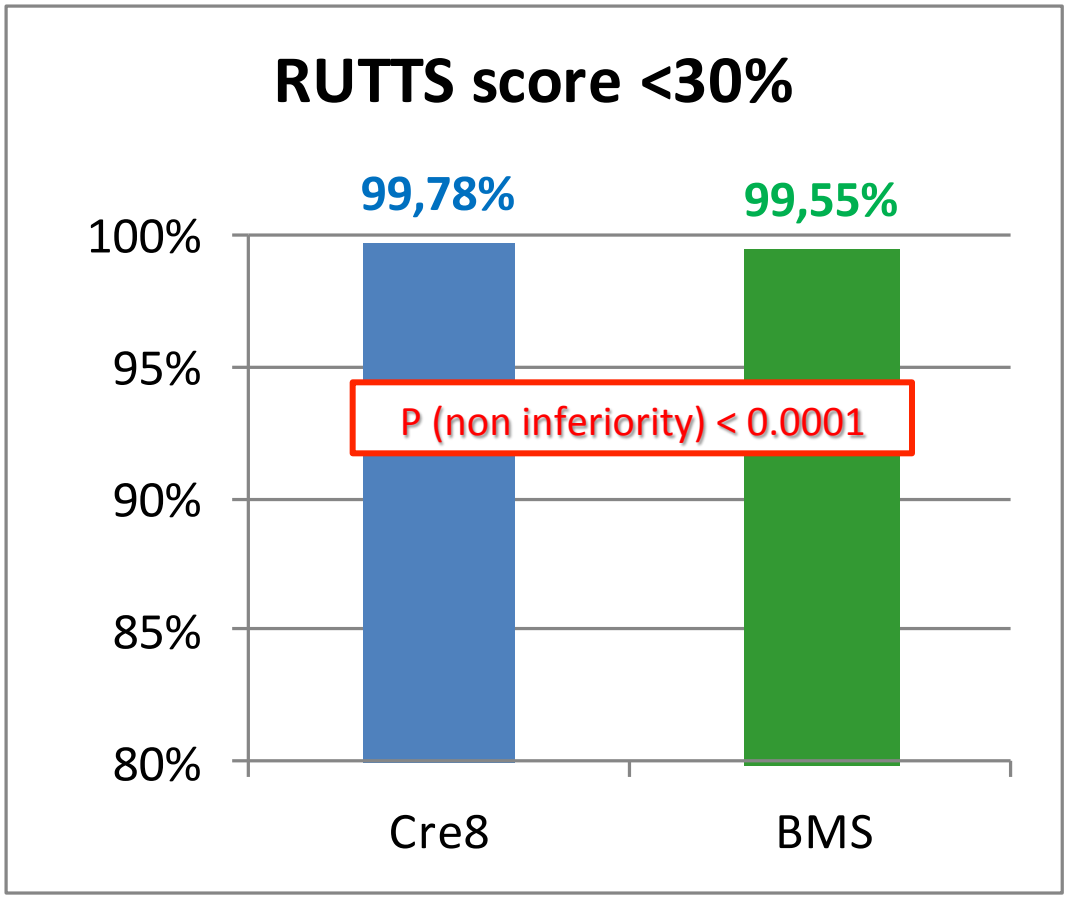

## Centers:

- **PI: Prof. F. Prati, Rome, Italy (8)**
- Dr. M. Valgimigli, Ferrara, Italy (10)
- Prof. P. R. Stella, Utrecht, Netherland (10)
- Dr. F. Burzotta. Rome, Italy, (4)
- Dr. M. De Benedictis, Turin, Italy, (3)
- Dr. A. Ramondo, Bassano del Grappa, Italy, (3)

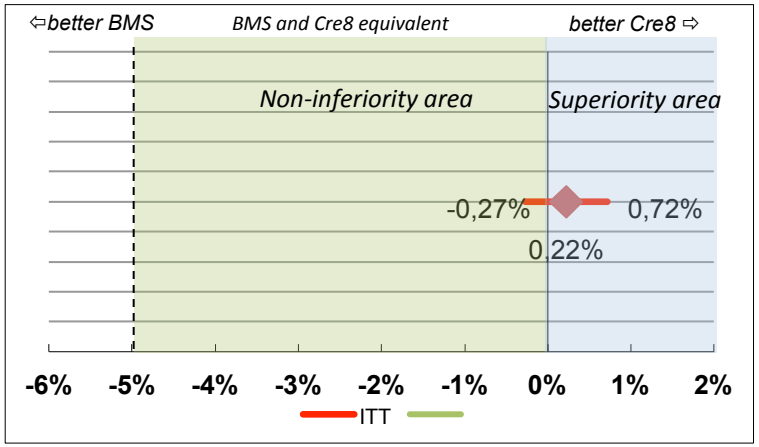
**Corelab**

# Primary endpoint: Results - I

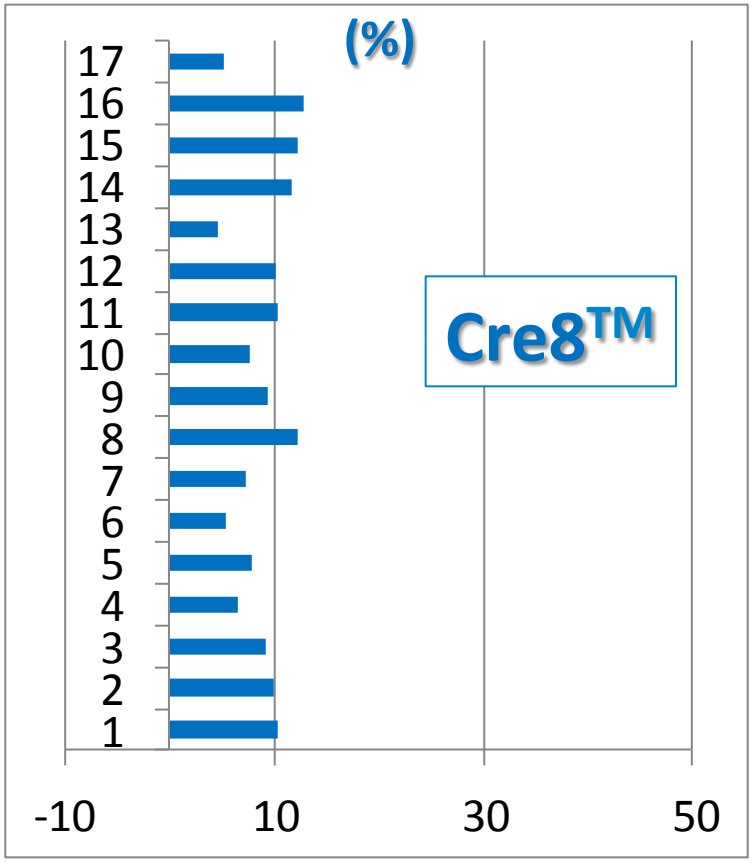
- Analyzed patients: 35 (Cre8:17pts; BMS:18pts)
- Total analyzed struts = +17000
- Total analyzed sections = +2000

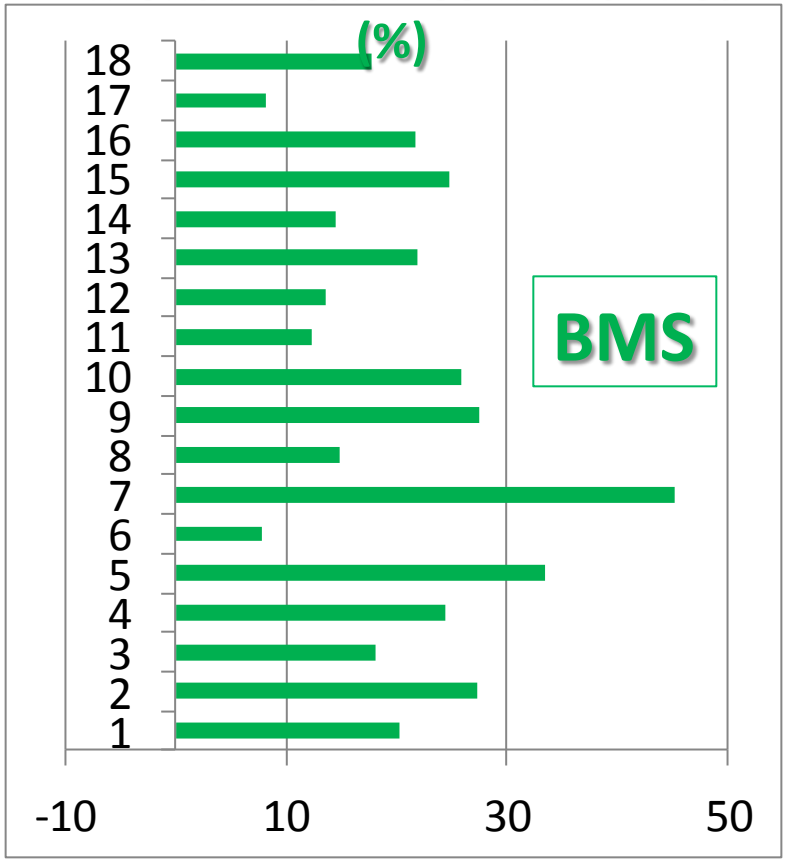



Pre-specified margin for non-inferiority = 5%



# Secondary endpoints: Results - OCT




**8.90 ± 4.26** | **21.34 ± 12.16**

P (Superiority) < 0.0001

# Next study

## SAFETY

Reduced DAT duration

Randomized trial
(***Demonstr8 study***)

Dedicated clinical trial on DAT

## EFFICACY

Diabetic patients

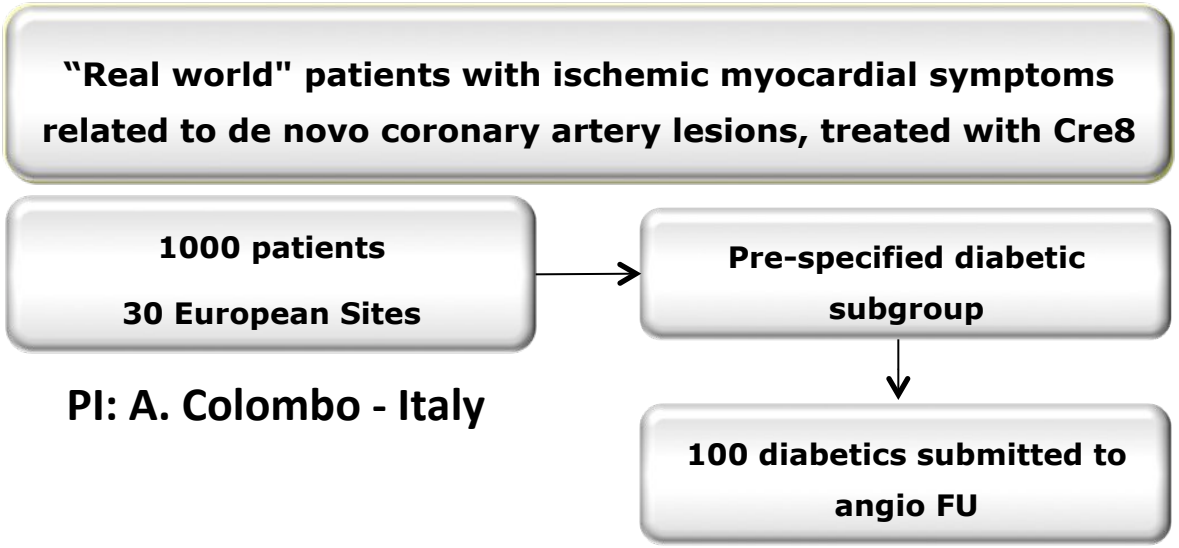
Enrollment completed

**Real-world study with diabetic sub-group (pARTicip8)**

Dedicated clinical trial on diabetics

# pARTicip8 clinical trial

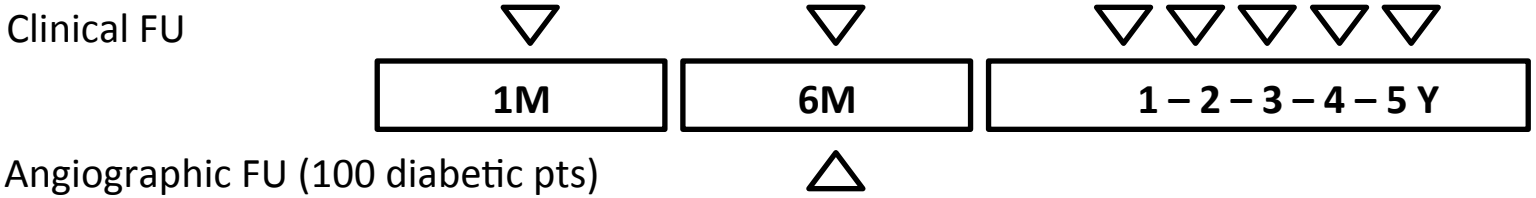
Prove ART (Abluminal Reservoir Technology) clinICal benefIt in "all comers" PATiEnts



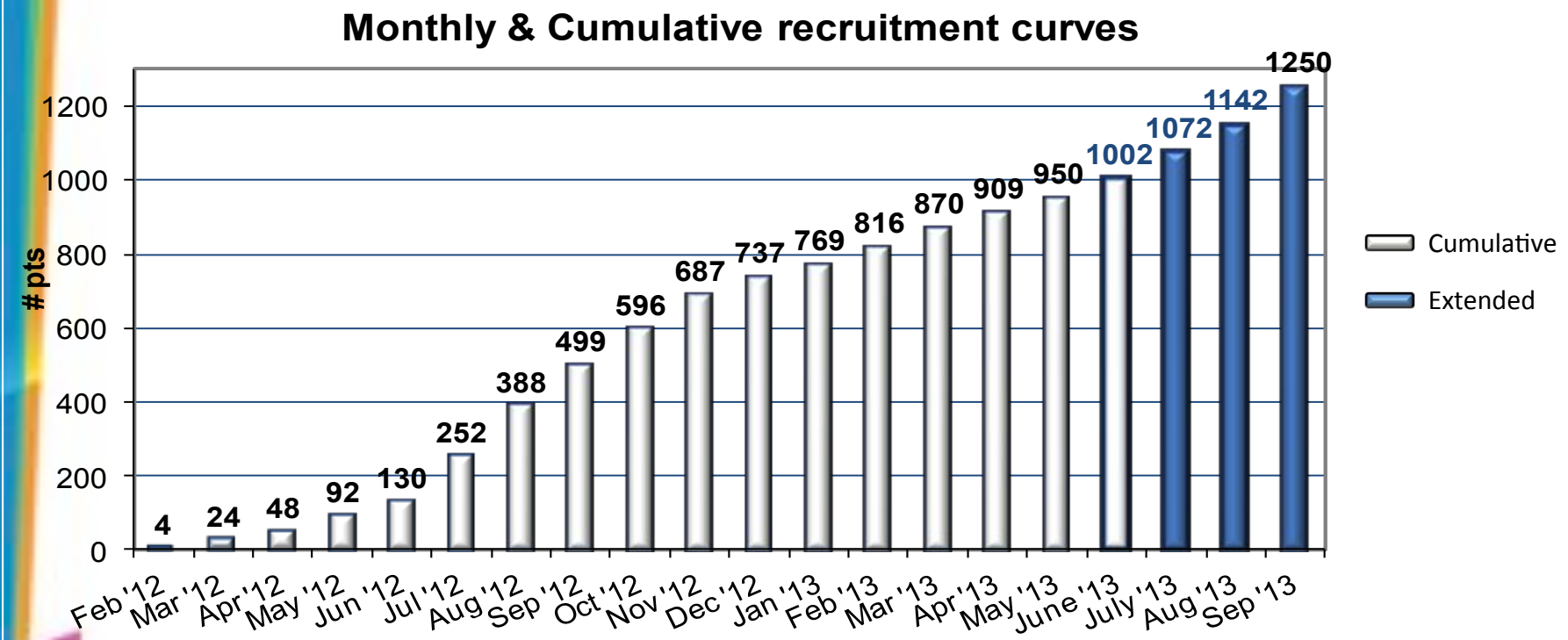

**OBJECTIVE:** evaluate the safety and efficacy performances of Cre8, in patients comparable to the everyday's clinical practice population, with a specific focus on diabetics subjects

**PRIMARY ENDPOINT:** 6-month incidence of clinical composite endpoint:

Cardiac death/Target vessel MI/Clinically indicated TLR



# pARTicip8 clinical trial

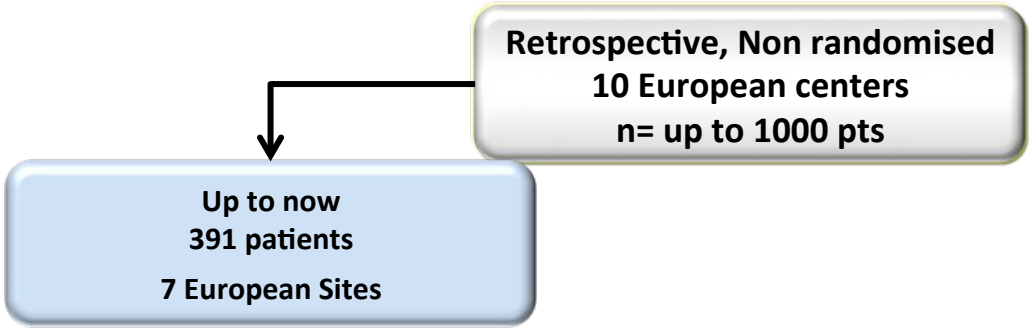



- Sites: 30 (Austria, Belgium, France, Germany, Italy, Norway, Spain, The Netherlands)

# Investig8

MultIceNtric and RetrospectiVe REgiStry in 'real world' paTients with polymer-free drug elutInG stent CRE8.

# Investig8: Study design




## Study objective:

- To collect clinical evidences of the CRE8™ stent performances implanted in everyday clinical practice from a maximum of 15 centers

## Primary Endpoint:

- Incidence of clinical composite endpoint from index procedure to 12 months: Cardiac death / Target vessel MI / Clinically driven TLR

## Secondary Endpoints:

- Incidence of clinical composite endpoint from index procedure to 12 months: All deaths / all MI / any revascularization
- Incidence of stent thrombosis from index procedure to 12 months, classified according to ARC definition

Analysis ongoing

Clinical (phone call)

1Y

# Investig8: Study design

- **Inclusion Criteria**
  - Patient has received at least one CRE8 stent for the treatment of coronary artery disease;
  - Patient has at least one year follow-up;
  - Patient has been implanted not later than the end of July 2012.

- **Exclusion Criteria**
  - Patient has been included in a previous clinical study on CRE8 stent;
  - Patient didn't consent to provide personal clinical data during telephone follow-up.

# Investig8: Patient disposition

- **Interim analysis (First seven centers)**

| **Patients** | **391** | |
|---|---|---|
| Available for analysis | 88.5% | 346 |
| Refusing participation | 1.5% | 6 |
| Lost | 10.0% | 39 |

# Baseline Clinical Characteristics

| | | |
|---|---|---|
| **Male** | **80.3%** | (278/346) |
| **Mean Age (yrs)** | **67 ± 10** | |
| **Silent ischemia** | **44.8 %** | (155/346) |
| **Symptomatic ischemia** | **55.2 %** | (191/346) |
| **- Stable angina** | **22.0 %** | (42/191) |
| **- Unstable angina** | **10.5 %** | (20/191) |
| **- Myocardial infarction** | **67.5 %** | (129/191) |
| **- STEMI** | **30.2%** | (39/129) |
| **- NSTEMI** | **62.8%** | (81/129) |
| **- NA/Unknown** | **7.0%** | (9/129) |

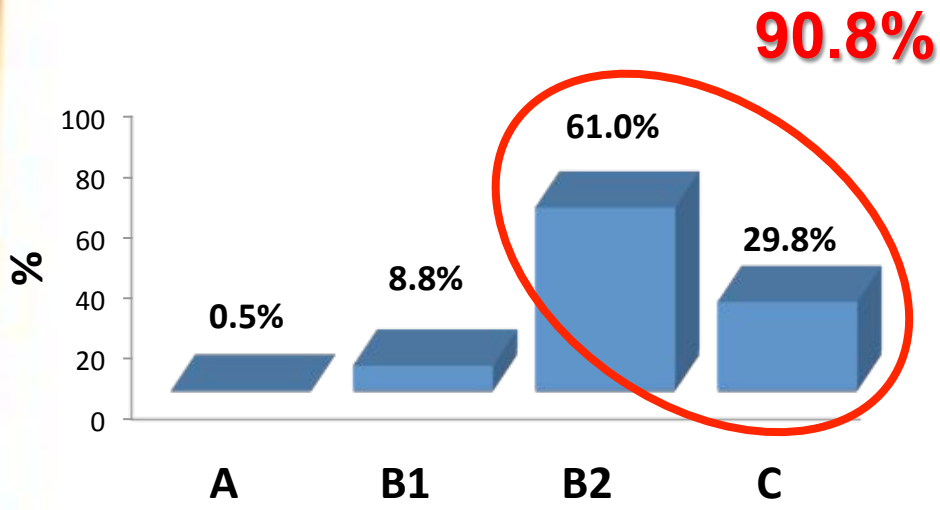
# Cardio-vascular risk factors

| | | |
|---|---|---|
| **Smoke** | **42.77%** | (148/346) |
| **- Current smoker** | **53.4%** | (79/148) |
| **- Ex smoker** | **46.6%** | (69/148) |
| **Diabetes mellitus** | **34.68%** | (120/346) |
| **- ID diabetes** | **24.2%** | (29/120) |
| **- NID diabetes** | **75.8%** | (91/120) |
| **Hypertension** | **57.80%** | (200/346) |
| **Hypercholesterolemia** | **37.86%** | (131/346) |
| **Family history of CAD** | **9.25%** | (32/346) |
| **Other disease*** | **27.46%** | (95/346) |

*PVD, SKD, stroke,…

# Target Lesion Characteristics

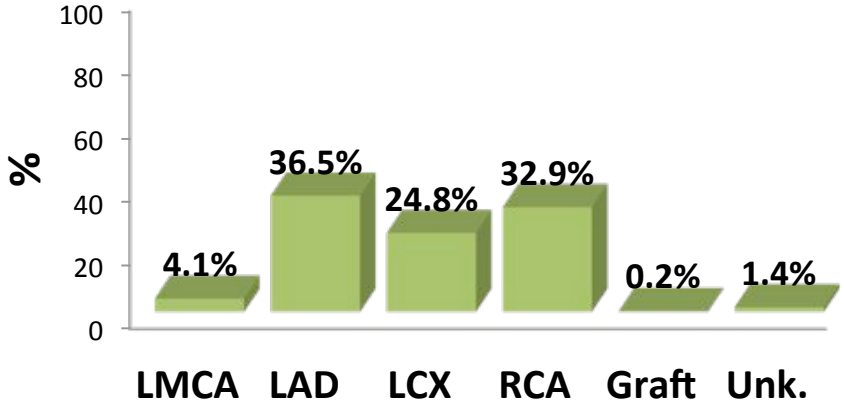
## Lesion classification ACC/AHA




**Ostial** 16.02% (66/412)

**Bifurcation** 19.76% (81/410)

## Vessel location



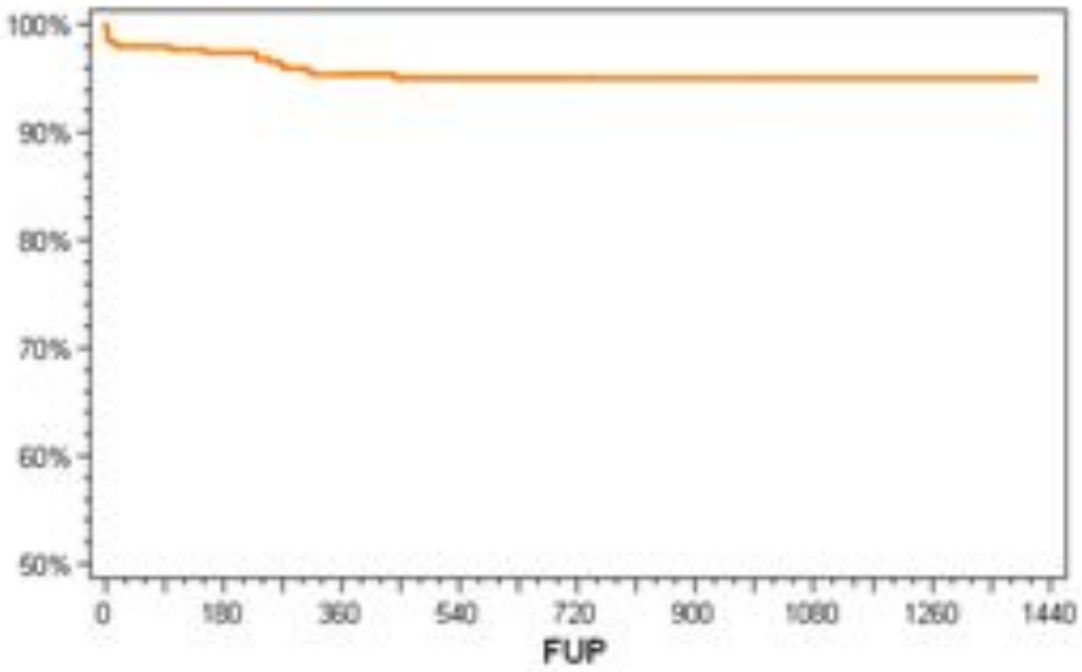
# Primary endpoint

**Primary Endpoint**: Composite of Cardiac Death / Target Vessel MI / Clinically indicated TLR at 12 months

| **Composite** | **4.6%** | (16/346) |
|---|---|---|
| **Cardiac/sudden/unknown death** | 1.4% | (5/346) |
| Cardiac | 1.2% | (4/346) |
| Sudden/unknown | 0.3% | (1/346) |
| **TV Myocardial Infarction** | 1.2% | (4/346) |
| STEMI | 0.6% | (2/346) |
| MI unk. type | 0.6% | (2/346) |
| **Clinically indicated TLR** | 2.0% | (7/346) |
| CABG | 0.3% | (1/346) |
| Re-PCI + stent | 0.9% | (3/346) |
| Re-PCI | 0.9% | (3/346) |

# Freedom from events
## (Actuarial curve – Kaplan Meyer)

Freedom from events (composite of Cardiac Death / Target Vessel MI / Clinically indicated TLR)




| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pts at risk | 345 | 338 | 336 | 332 | 329 | 261 | 206 | 55 | 8 | 4 | 3 | 3 | 1 | 1 | 1 | 1 | 0 |

- **Freedom from events at 12 month: 95.7% (C.I. 94.6%-96.8%)**

# Secondary endpoints

**Secondary endpoint**: Stent thrombosis at 12 months (ARC)

| **Probable/Definite Thrombosis** | **1.2%** | (4/346) |
|---|---|---|
| **Definite thrombosis** | **0.6%** | **(2/346)** |
| Acute | 0.3% | (1/346) |
| Subacute | 0.3% | (1/346) |
| Late | - | |
| **Probable thrombosis** | **0.6%** | **(2/346)** |
| Acute | - | |
| Subacute | 0.6% | (2/346) |
| Late | - | |

euro PCR 2014

# The Tel Aviv Medical Center Cre-8 study

Shmuel Banai, MD
Tel Aviv Medical Center
Israel

EuroPCR 2014

# Methods

- **Study:** A prospective, single arm, open labeled, non-randomized, single center study
- **Patients:** All comer population (STEMI, ACS, stable/elective)
- **Exclusion criteria:** None, except ISR
- **Follow up:** Clinical follow up at 30 day, 6 and 12 months
- **End points:** Death, MI, stroke, unplanned PCI and clinically driven target lesion revascularization (TLR)

Informed consent was obtained from each patient prior to the procedure

# Results- study population

| Clinical characteristics (n=215) | n (%) |
|---|---|
| Gender, male (%) | 188 (87) |
| Age , years median (range) | 64 (38-92) |
| Hypertension (%) | 54 (25) |
| Dyslipidemia (%) | 182 (84) |
| DM type II (%) | 83 (38) |
| Current Smoking | 57 (26) |
| PVD | 18 (8) |
| s/p MI | 63 (29) |
| s/p PCI | 114 (53) |
| s/p CABG | 25 (12) |
| s/p TIA/CVA | 24 (11) |

# Results –procedural data

| Setting | n (%) |
|---|---|
| STEMI | 10 (5) |
| ACS ( NSTEMI, unstable angina) | 102 (47) |
| Stable/Elective | 103 (48) |
| **Stents** | **Mean (range)** |
| Number of stents per patient | 1.3 (1-4) |
| Mean stent length in mm | 19.6 (12-31) |
| Mean stent diameter in mm | 2.9 (2.5-4) |
| **Lesions treated** | **n (%)** |
| Bifurcations | 32 (12)<br>provisional stenting-30<br>T-stenting -2 |
| Unprotected LM | 3 (1) |

EuroPCR 2014

# Results
# 1-year outcomes

| | Patients n (%) | Remarks following coronary angiography |
|---|---|---|
| STEMI | 0 (0) | |
| Non STEMI | 5 (2) | 1 related to the Cre8<br>4 unrelated |
| Death | 2 (1) | 1- out of hospital sudden death: ST can not be ruled out<br>1- non-cardiac death |
| Stroke | 1 (0.5) | |
| Unplanned PCI | 9 (4) | 1 TLR (non STEMI, ISR)<br>8 non TLR or TVR, patent Cre8 stents |
| Clinically driven TLR | 1 (0.5) | |
| Clinically driven TVR | 1 (0.5) | |

# CONCLUSIONS

L'étude randomisée NEXT a montré la supériorité du stent Cre8 sur le TAXUS en terme de « late loss » avec une efficacité comparable chez les diabétiques et les non diabétiques.

L'étude randomisée Demonst8 a confirmé une couverture équivalente des mailles du Cre8 et d'un stent nu à 1 mois faisant envisager une durée courte (<3 mois) de double AAP.

Les registres en cours et les études cliniques futures devraient confirmer l'excellent profil de sécurité et d'efficience de ce nouveau stent.

# Cre8™: EFFICACY Distinctive Features

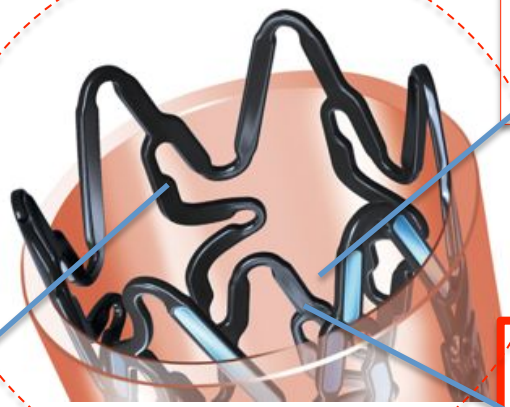
**Polymer-Free platform**

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall

EFFICACY

**Abluminal Reservoir Technology (ART)**

Controlled and directed elution to the vessel wall



**Bio Inducer Surface (BIS)** = 2nd generation pure carbon coating

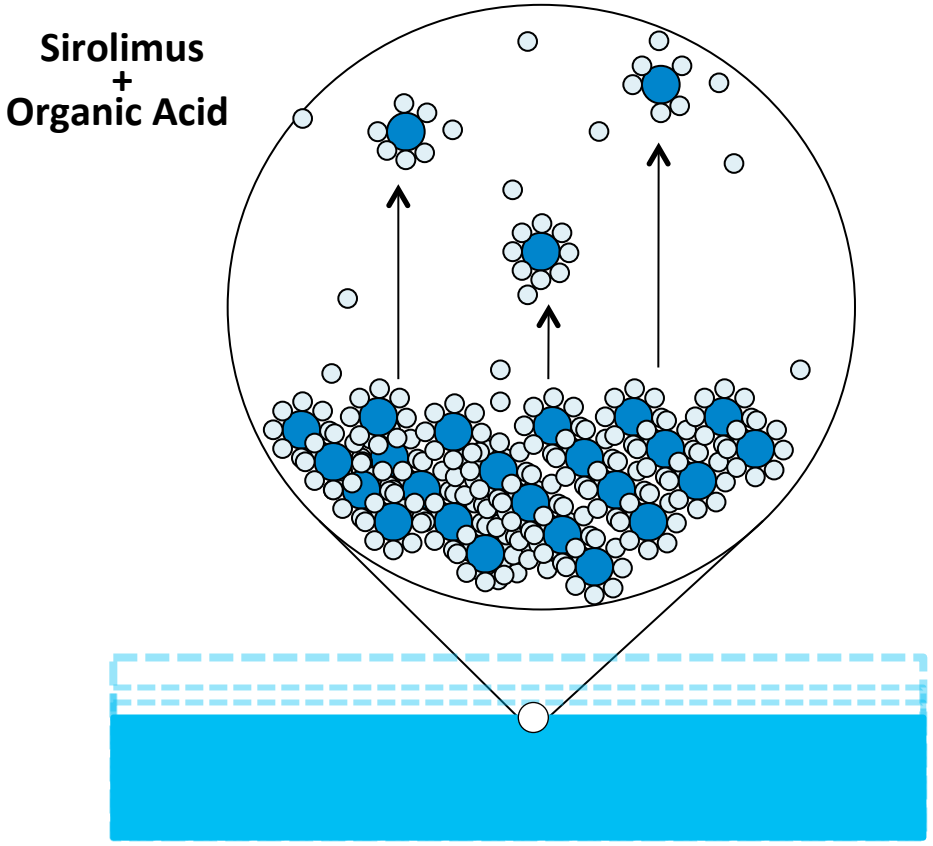
Optimal haemo-compatibility vs. lumen blood flow

**Amphilimus Formulation = Formulated Sirolimus with an organic acid**

EFFICACY

Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy

# 2) Cre8 employs a permeation enhancer (organic acid) in its formulation




CID Amphilimus™ Formulation