

# Percutaneous Coronary Intervention With a New Paclitaxel Eluting Balloon for the Treatment of in-Stent Restenosis and Small Vessel Disease: Mid-term Outcomes of the Spanish Multicenter Registry

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## Background

- In everyday practice, there is a small but significant population in whom the use of either BMS or DES may be considered inappropriate or even harmful

- In- stent restenosis
- *De novo* lesions in small vessels ( $\leq 2.5\text{mm}$ )
- Bifurcated lesions (111, 101, 011)
- Bifurcated lesions (001 of Medina classification)
- Contraindication to dual antiplatelet therapy



## Objectives

- In order to overcome the potential limitations of the stents....

The Spanish Dior Registry is a real world, prospective and multicenter registry of percutaneous coronary intervention set up to assess the efficacy and safety of a new paclitaxel--eluting balloon (Dior<sup>MT</sup>, Eurocor/Palex) in these settings



## Methods

- 191 patients and 199 lesions treated by using this new paclitaxel-eluting balloon ( $3\mu\text{g}/\text{m}^2$  balloon surface area) were included in this registry
- 
- ✓ Prospective real-world multicenter registry : 9 Spanish centers
  - ✓ Dual antiplatelet therapy (DAT) for at least 3 months
  - ✓ Clinical FU planned at 1, 6 and 12 months
  - ✓ Angiographic follow-up at 6-8 months in 40% of patients (3 centers)
- 
- ✓ **Inclusion criteria:**
    - ✓ Stent restenosis (BMS/DES); Small vessel disease (<2.5mm); bifurcated lesions (Dior to treat SB); ostial bifurcated lesions (OO1) and contraindication to DAT
  - ✓ **Exclusion criteria:**
    - ✓ Clinical: STEMI <24h and cardiogenic shock
    - ✓ Angiographic: lesion calcification, vessel tortuosity, lesion length greater than 30mm (using more than one balloon of 30mm for lesion)



## Study's Flowchart

Clinical/Angiographic eligible patient



**Target lesion** Pre-dilatation (Shorter balloon than the Dior)  
**Dior dilatation:** above nominal pressure + at least during 60sec



**Angiographic success:** a final residual lesion stenosis  $> 50\%$  in the TL and absence of  $>$  type B coronary dissection

→ **No angio success:**  
BMS

**Follow-up**

Clinical FU at 1 and 6 months and 1 year after the index procedure

Angiographic FU at  $7 \pm 2$  months in 3 centers (40% of population)

[www.registrodior.com](http://www.registrodior.com)



# 1st and 2<sup>nd</sup> Generation Paclitaxel- Eluting DIOR-Balloon (Eurocor-Palex. CE Marked. )

## 1. Paclitaxel

+

*Solubilizing agent to  
increase optimal drug  
delivery*

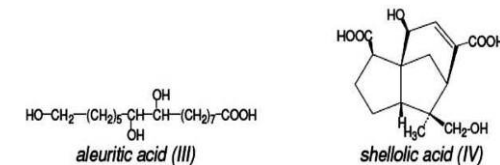
+

Micro-crystals (following  
dimethylsulfate treatment)

**Dior 1st G**

Posa et al. CAD 2008

The drug is dissolved in  
"Shellac" FDA approved  
substance graded as a food

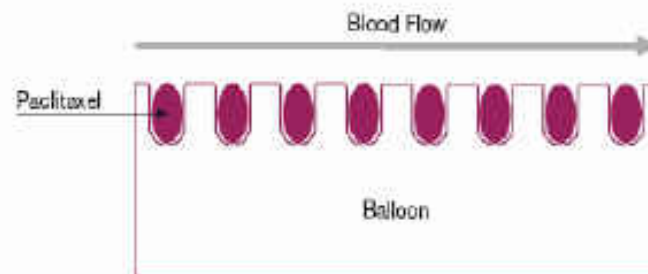


**Dior 2<sup>nd</sup> G**

Hemetsberger R, Posa A et al. J. Kardiol 2009

**3.-Coating method**

**3µg/mm<sup>2</sup> balloon-surface  
paclitaxel-coating**



**2. Balloon designed with 3  
folds of micro-porous surface.**  
The three-folded balloon protects  
the loaded drug from the early  
wash-off effect

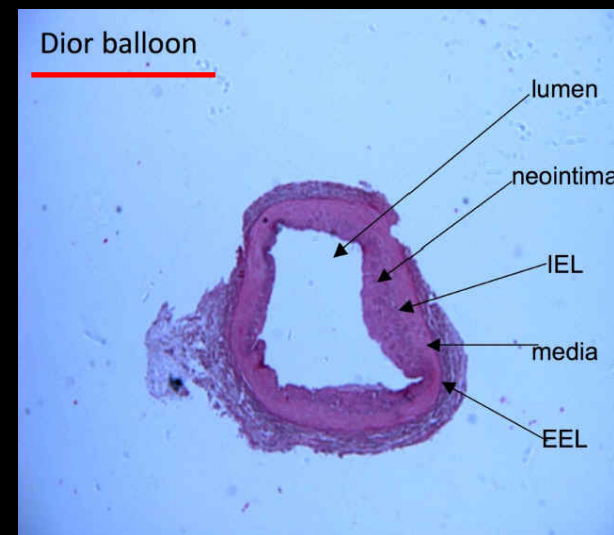
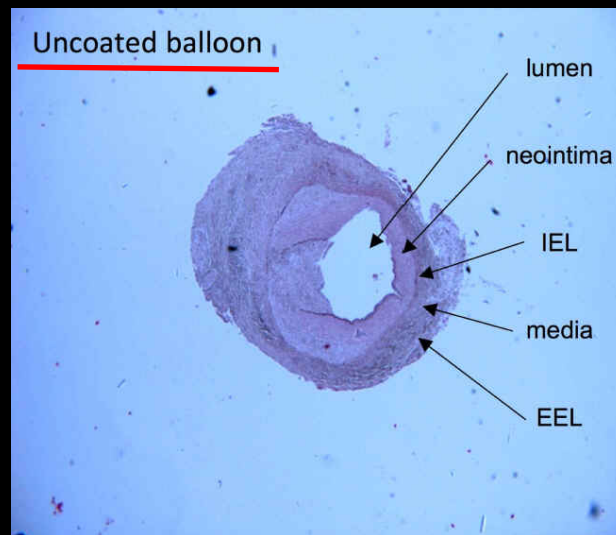


## DIOR-Balloon (Eurocor-Palex)

**Cell-culture experiments:** the brief contact between vascular and smooth-muscle cells and lipophilic taxane compounds (paclitaxel) inhibits the proliferation of such cells

→ **Pre-clinical animal model of PCI:**

**Randomized N=33**



**Porcine coronary artery overstretch injury model**

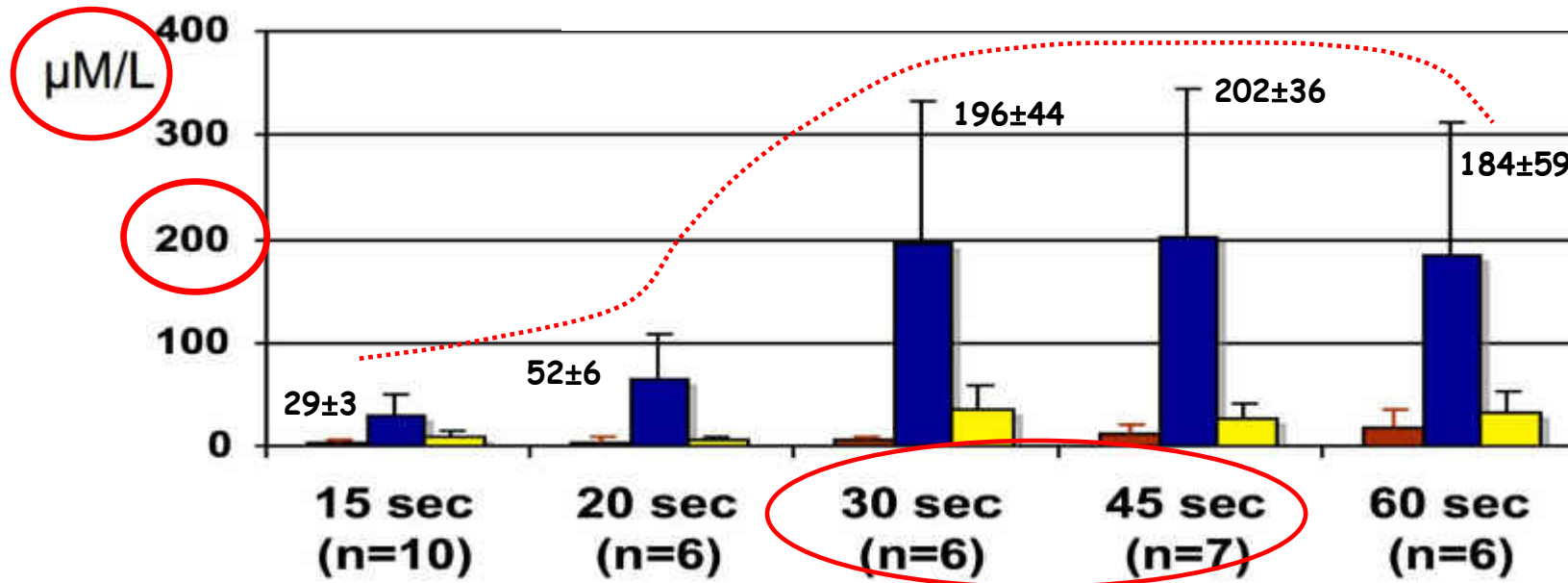
**Dior-DEB was significantly more effective in inhibition of neointimal hyperplasia as compared with non-coated balloon.**



## Inflation time-dependent tissue concentrations

Tissue concentration of paclitaxel dependig on balloon inflation time

Plateau concentration of the drug tissue



**Novel coating technology (Shellac) of DIOR 2G compared with 1st G:**

- Maximum tissue concentration of paclitaxel- inflation time of 30-45sec (60 sec Dior 1G) (better tolerated)

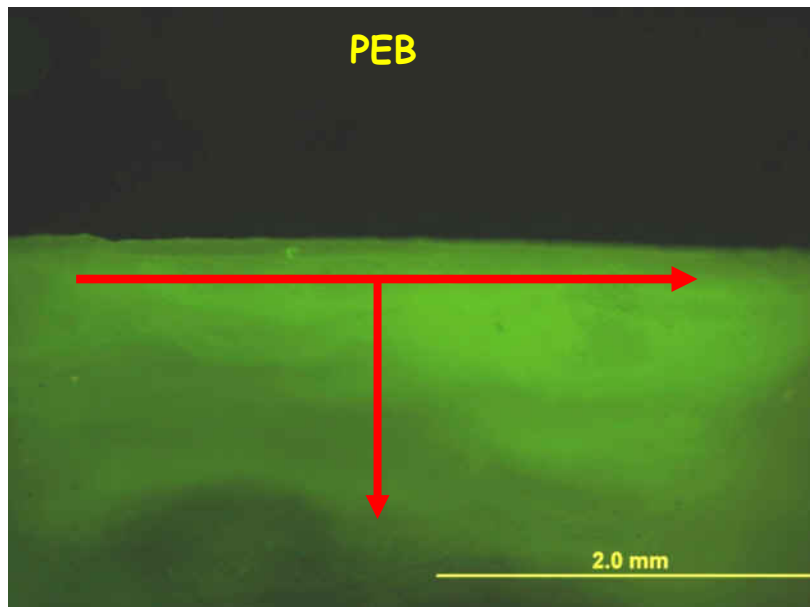




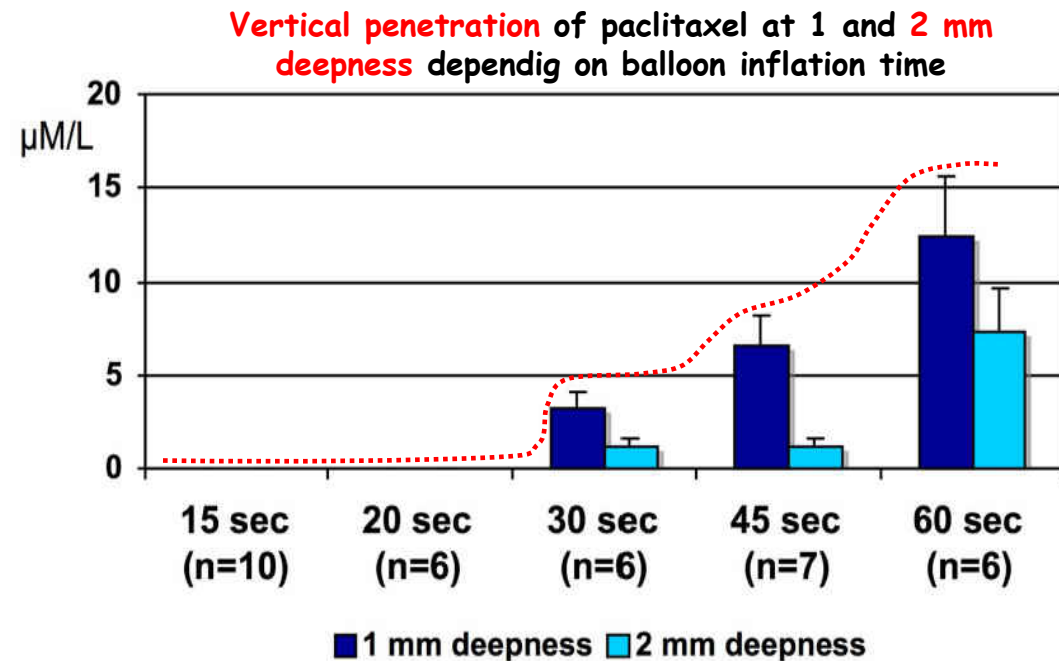
## Tissue distribution of the drug on the vessel

Fluorescence images of DIOR showed: (*"Oregon green 488 Fluorescent paclitaxel conjugate"*)

Homogeneous (vertical and longitudinal) distribution of paclitaxel\* on the vessel by simple diffusion, in contrast with DES



Fluorescence microscopy images





## New concept/modality of PCI: Drug-eluting balloon

- Promising initial clinical results in patients with:
  - In-stent restenosis:
    - Randomized trials: Paccocath ISR I<sup>10</sup> y ISR II<sup>11</sup> / 108 pts.) Plain balloon vs paclitaxel balloon (*matrix coating*)
    - Randomized trial : PEPCAD II trial (IRS of BMS) (66/65): Paclitaxel balloon (SeQuent Please) (*matrix coating*) vs Paclitaxel stent<sup>12</sup>
    - Registry (Dior): Dior (60) vs Cypher(80) vs Taxus(80) (Gyöngyösi et al. ESC-09)
  - Bifurcated lesions
    - DEBIUT registry (Dior; 20 pts, 1-4 mo FU)<sup>13</sup>
    - TCT 09: PEPCAD 5 registry: (28 pts, 9 mo, FU) (*matrix coating*)
- Exclusion criteria:
  - STEMI and non STEMI ( $\leq 48-72h.$ )<sup>11,12,13</sup>
  - DES in-stent restenosis<sup>12</sup>, renal failure<sup>11,12</sup>, FE  $\leq 30\%$ <sup>13</sup>
  - Small vessel  $\leq 2.5mm$ <sup>12,13</sup>

10. Scheller B et al . New Engl J Med 2006

11. Scheller B et al. Clin Res Cardiol 2008

11. Unverdorben M, Scheller B et al. Circulation 2009

13. Fanggoday JC et al. Cath Cardiovasc Interv 2008



## Demographic and Clinical Characteristics: N=191

• Age (years) (mean±SD)	65.6±10.4
• Male gender	80.0 (152)
<b>Risc Factors</b>	
✓ <b>Diabetes</b>	<b>31.6 (60)</b>
✓ Hypertension	71.1 (135)
✓ Dyslipidemia	63.2 (120)
✓ Current Smoker	31.1 (59)
✓ Renal impairment (creat >1.3mg/dl)	15.6 (25)
<b>Hystory of</b>	
✓ MI	38.9 (74)
✓ <b>PCI</b>	<b>66.8 (127)</b>
<b>Clinical presentation</b>	
✓ <b>ACS (%)</b>	<b>54.2 (103)</b>
✓ STEMI >24h	4.7 (9)
• <b>LVEF (≤ 50%)</b>	<b>31.5 (45)</b>
• 3 vessel disease	21.6 (41)

*Unless specified otherwise, values are % and (n) of patients*



## Baseline Lesion Characteristics

### Indication for use of DIOR

→ In-stent restenosis (ISR)	56.0 (107)
→ De novo lesion small vessel < 2.5mm*	38.2 (73)
✓ { Bifurcated lesion (111, 101, 011)*	12.0 (23)
✓ { Ostial lesion (001)*	6.8 (13)
✓ { Contraindication to DAT*	6.3 (12)

### Type of lesion

✓ In-stent restenosis (IRS)	56.0 (107)
• DES IRS	45.2 (47)
✓ De novo lesion	44.0 (84)
• Small vessel	38.2 (73)
• De novo lesion alone	49.3 (36)
• Bifurcated lesion	27.4 (20)
• Ostial lesion	13.7 (10)
• Contraindication to DAT	9.6 (7)
• No small vessel	5.8 (11)

### Bifurcation lesion

37.4 (71)

*Unless specified otherwise, values are % and (n) of patients*



## Baseline Procedural Characteristics

• Radial approach	54.2 (103)
• 6F- guide catheter	87.9 (167)
• Number of stent implanted outside the target lesion	32.6 (62)
✓ DES outside the target lesion	24.2 (46)
• <u>Pre-dilatation (plain balloon)</u>	100 (199)
✓ Diameter, mm (mean±SD)	2.4±0.5
✓ <u>Length, mm (mean±SD)</u>	14.6 ±3.9
• <b>Dior Balloon</b>	
✓ Diameter, mm (mean±SD)	2.7±0.5
✓ <u>Length, mm (mean±SD)</u>	19.2±5.1
✓ Main balloon pressure, mmHg, (mean±SD)	13.7±3.5
✓ <u>Inflation time (sec). (mean±SD)</u>	94.9 ±37.8
• Post-dilatation	27.5 (42)
• IIB-IIIa inhibitor	2.6 (5)

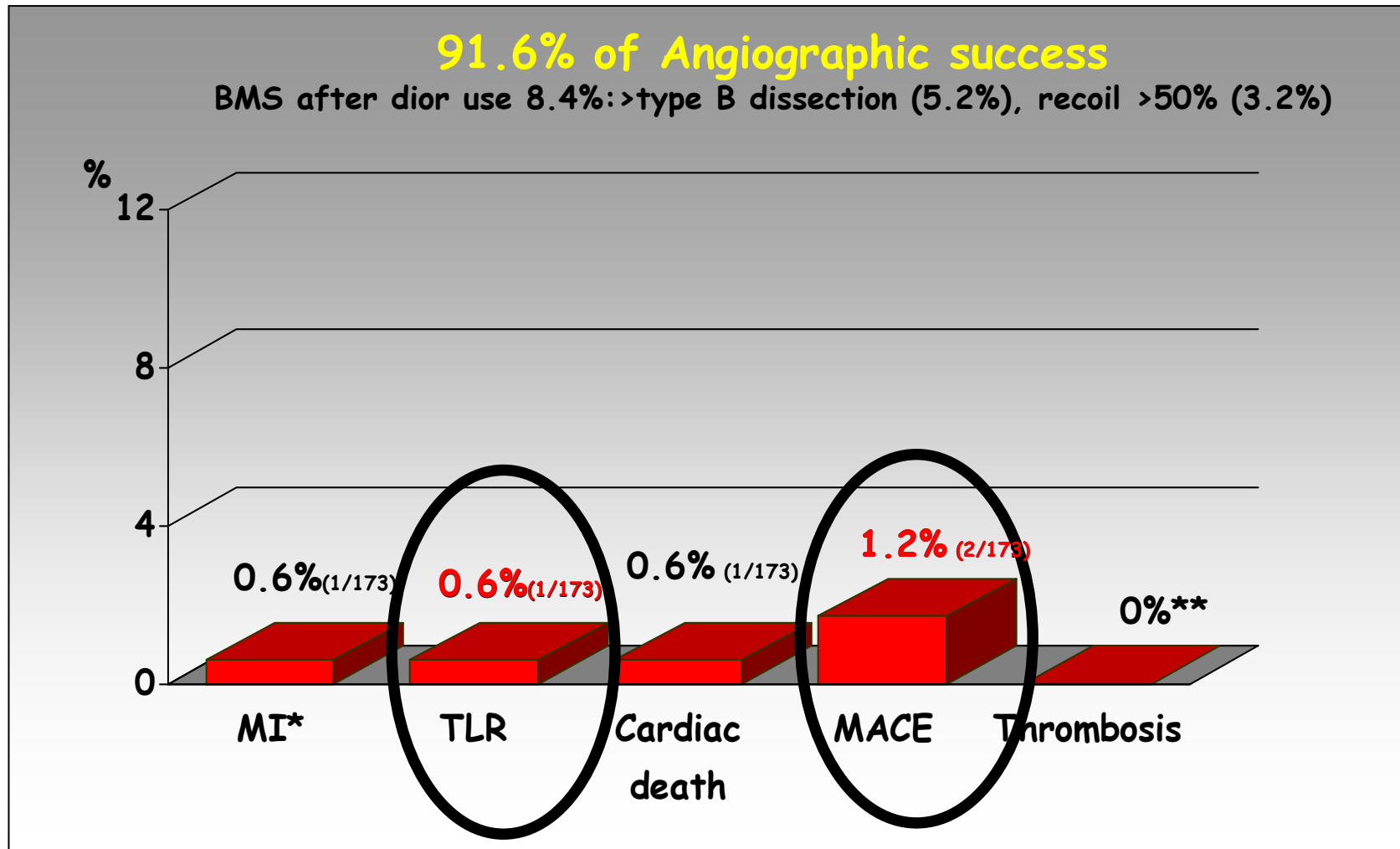
*Unless specified otherwise, values are % and (n) of patients*



# Cumulative Events at 1 month

(Completed in 173 patients)

*Non Hierarchical Ranking*



\* CPK and/or Troponin > 3 times ULN value + 1 criteria of: chest pain and/or typical changes on ECG

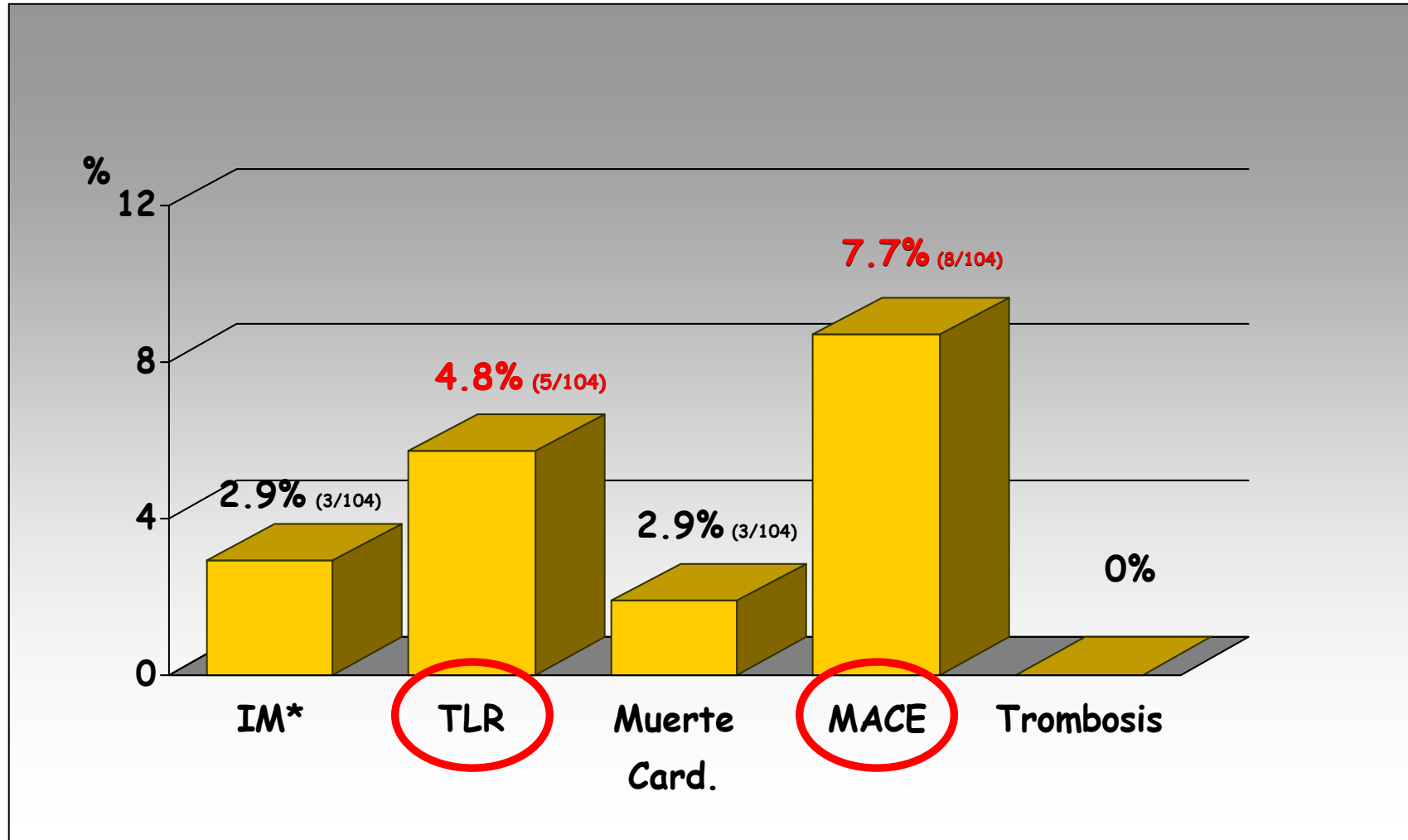
\*\*Definitive segment treated thrombosis (ARC). MACE: MI and/or TLR and/or Cardiac death



# Cumulative Events at 6 month

(Completed in 104 patients)

*Non Hierarchical Ranking*



*MACE: MI and/or TLR and/or cardiac death*



## Angiographic restenosis

- 3 center with systematic angio FU at 6-9 months
- For this analysis only centers with >60% angio FU were considered
- 1 center 93.8% (30/32pts) angio FU completed at 6.6±1.6mo.
  - Center with 72.5% of small vessel as indication of Dior use

Variable	Pre-PCI	Post-PCI	6mo FU
Reference diameter	2.2±0.4		
Lesion length	15.7±7.2		
MLD	0.5±0.3	1.7±0.4	1.3±0.6
Diameter stenosis %	78.4±14.5	23.4±9.6	39.3±24.1
Acute Gain		1.20 ±0.4	
In-segment late loss			0.4±0.6
Binary Restenosis, (n) %			3 (10%)

*Unless specified otherwise, values are mm (mean±SD)*





## In-stent restenosis subgroup (107 patients)

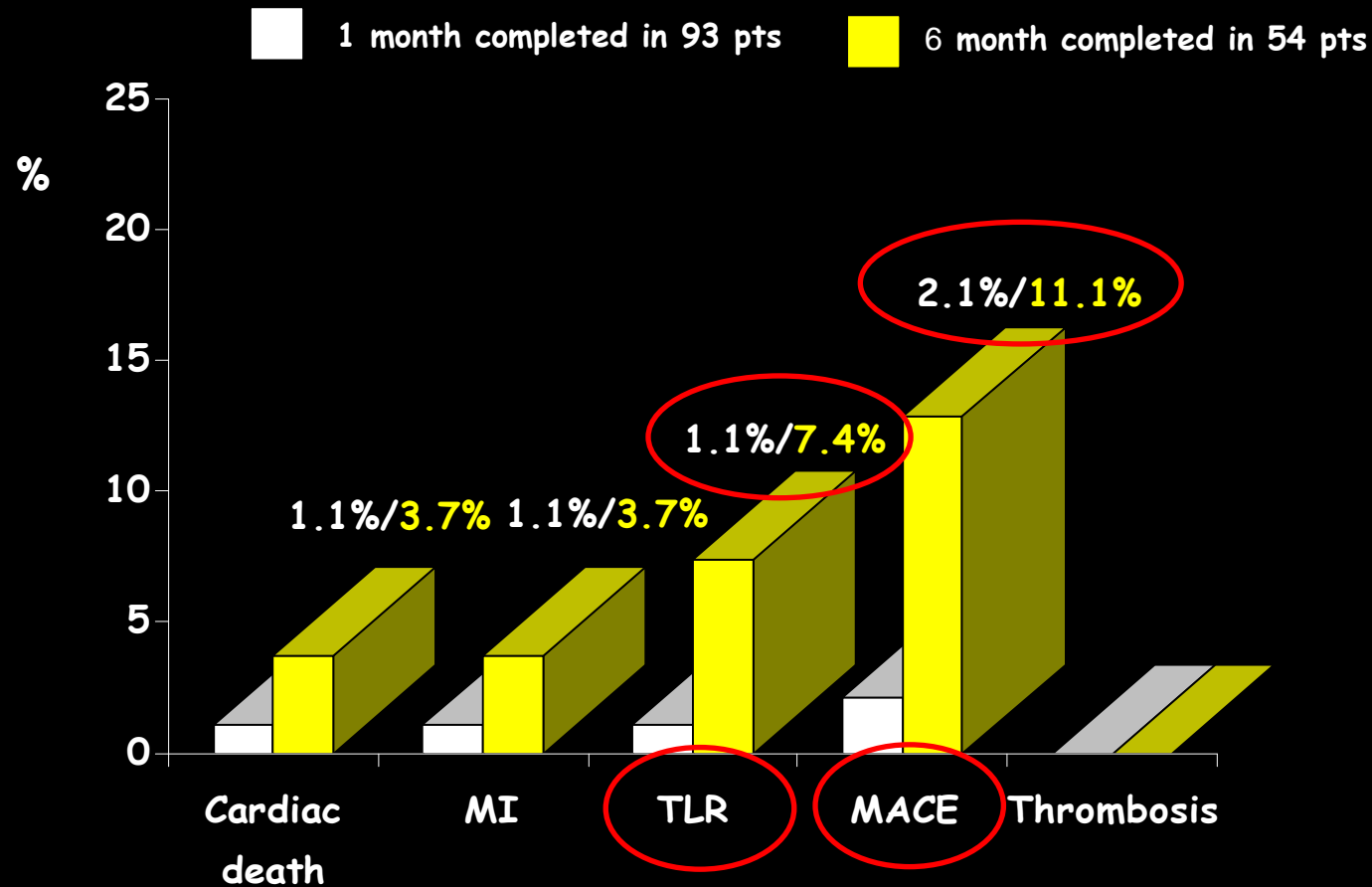
- **Clinical Charact.:**
  - Diabetes 33.6 (36)
  - LVEF <50% 36.8 (28)
  - Previous MI 47.7 (51)
  - ACS as clinical presentation 50.5 (54)
- **Lesion Charact.**
  - In-stent resrenosis of DES 44.8 (47)
  - Mid LAD 23.4 (25)
- **Procedural Charact.**
  - Number of stent outside TL 22.4 (24)
  - Dior balloon diameter, mm 2.9±0.4

*Values are % and (n) of patients*

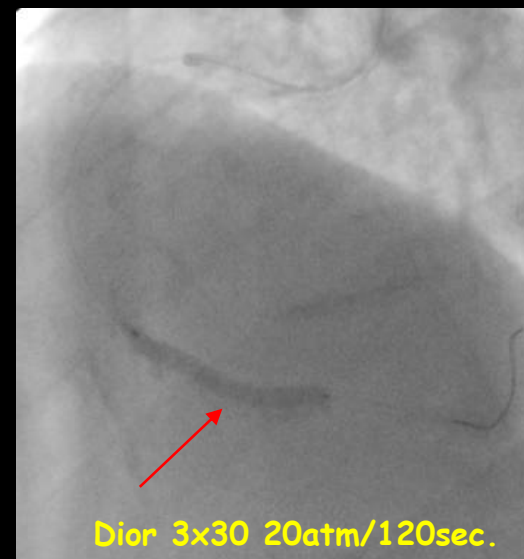
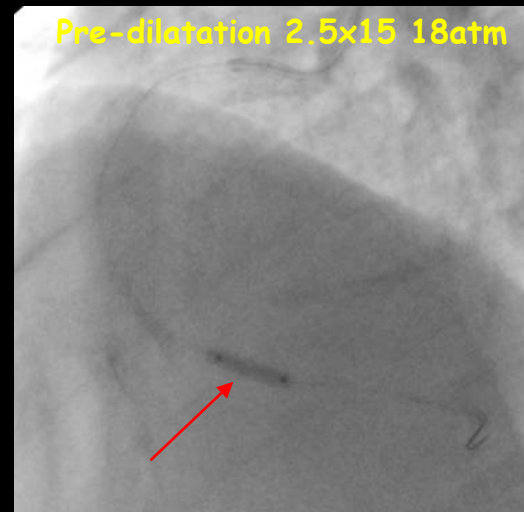
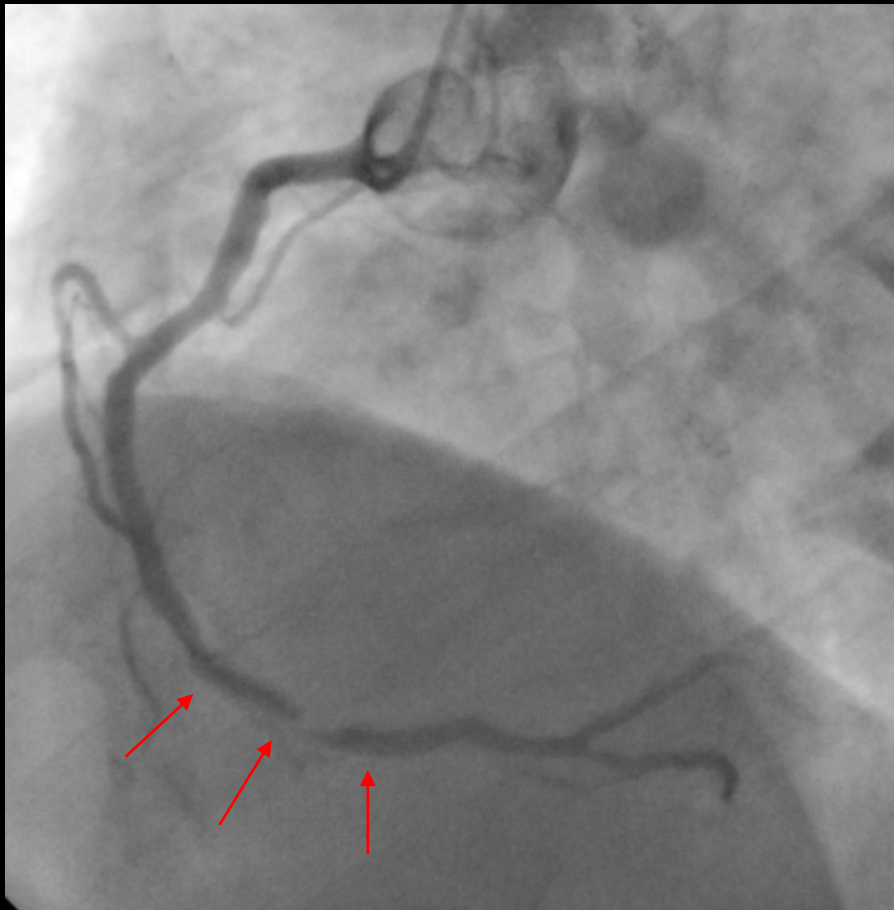


## In-stent restenosis subgroup (107 patients)

96.3% of Angiographic success



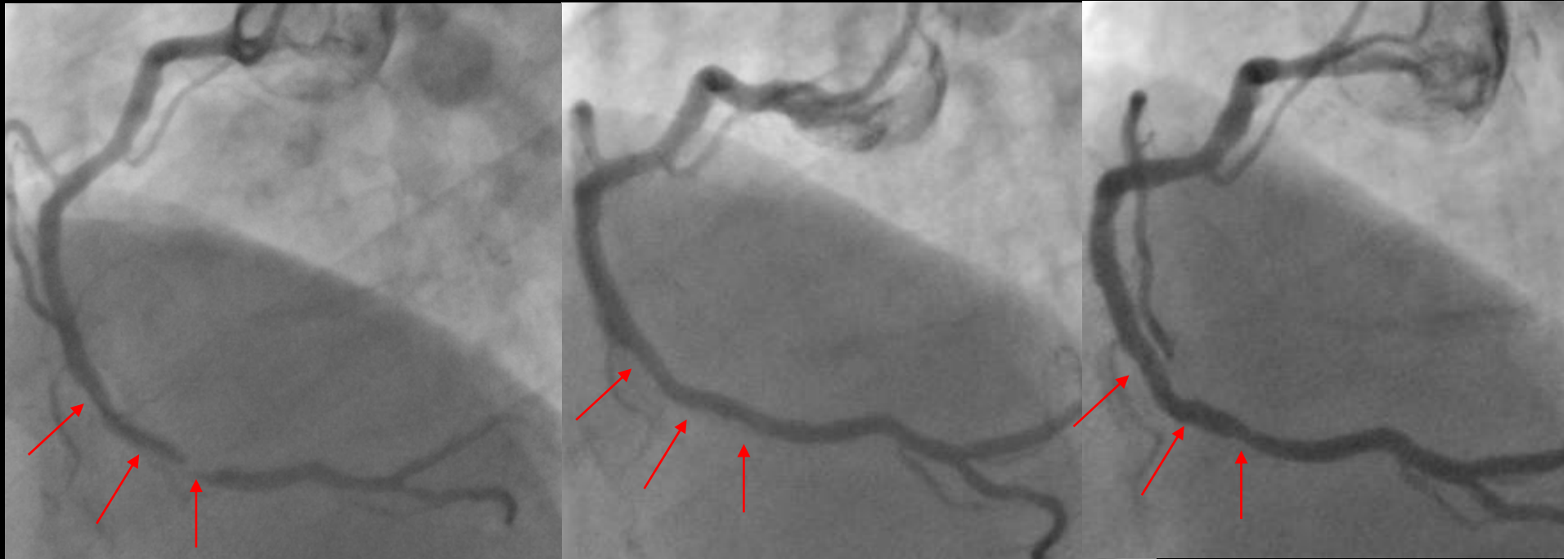
## Mid-Distal RCA DES in-stent restenosis



Baseline

Immediat result

6 mo angio FU





## Small vessel subgroup (73 patients)

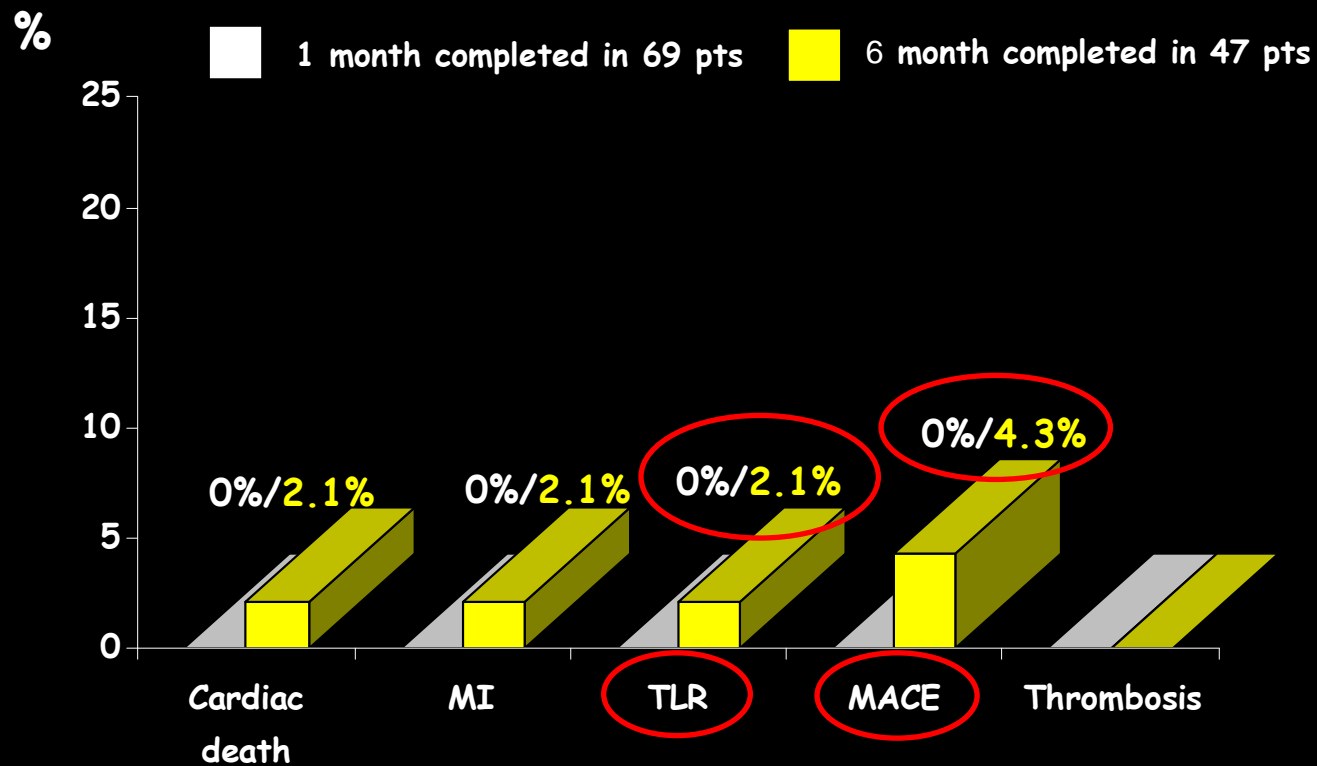
- **Clinical Charact. :**
  - Diabetes 32.9 (24)
  - **ACS as clinical presentation 67.1 (49)**
- **Lesion Charact.(small vessel)**
  - De novo lesion alone 49.3 (36)
  - Bifurcated lesion (111,011,101) 27.4 (20)
  - O01 ostial lesion 13.7 (10)
  - Contraindication to DAT 9.6 (7)
  - **Diagonal Branch 26 (19)**
  - **Bifurcation lesion 42.5 (31)**
- **Procedural Charact.**
  - Number of stents outside TL 52.1 (38)
  - Dior balloon diameter , mm **2.3±0.3**

*Values are % and (n) of patients*

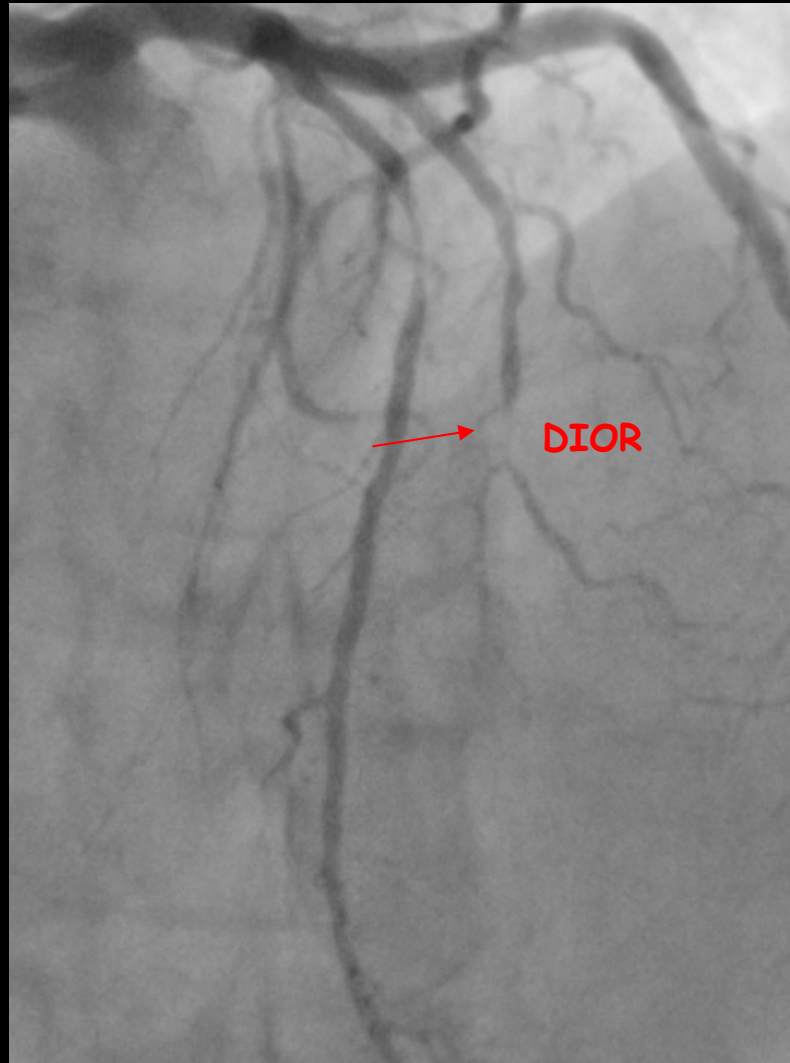


## Small vessel subgroup (73 patients)

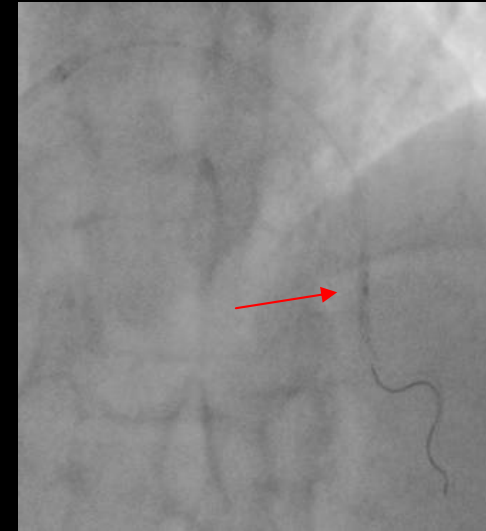
**90.4% of Angiographic success**  
(BMS after Dior 9.6% (7): coronary dissection)



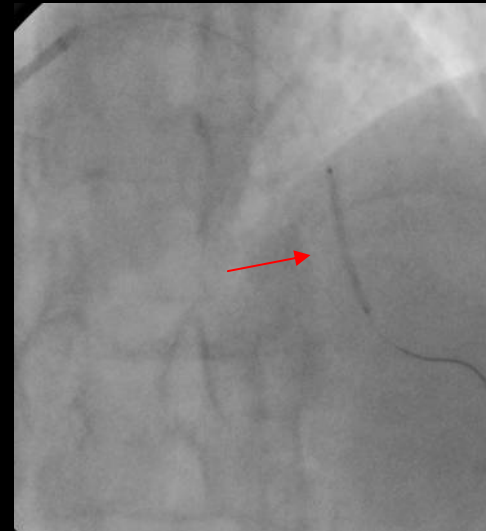
# Mid LAD lesion and first diagonal lesion (D1 small vessel)



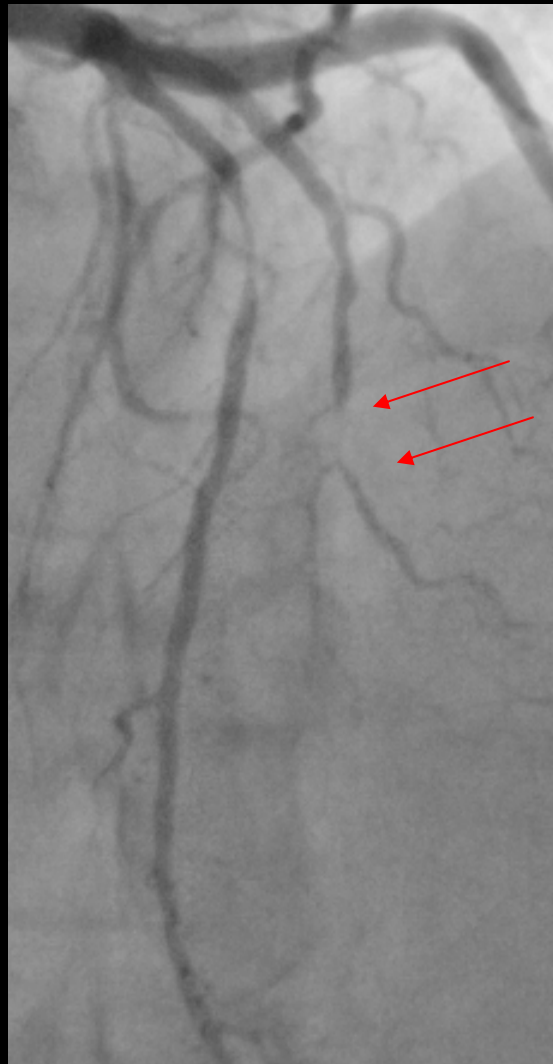
2x15 plain balloon 8atm/45sec.



2.0x25 Dior 14atm/80sec.



**Baseline**



**Immediat result**



**7 mo angio FU**







## Conclusions

In some situations in which previous interventions have been associated with a high risk of restenosis and/or stent thrombosis....

**The use of this new paclitaxel-eluting balloon (Dior<sup>MT</sup>, Eurocor/Palex), according to the strategy described, provides excellent acute angiographic results and mid-term outcome with 5% TLR at 6 months**



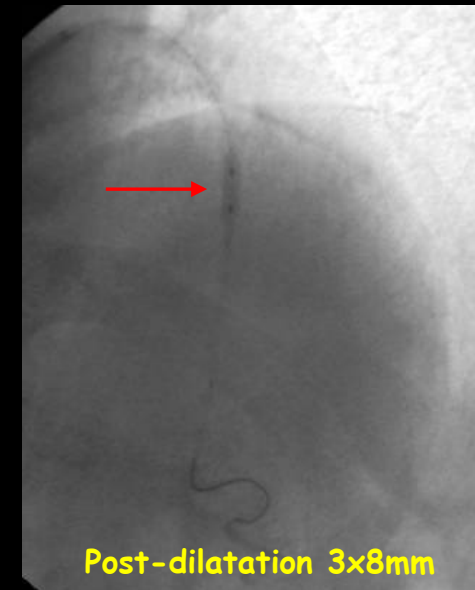
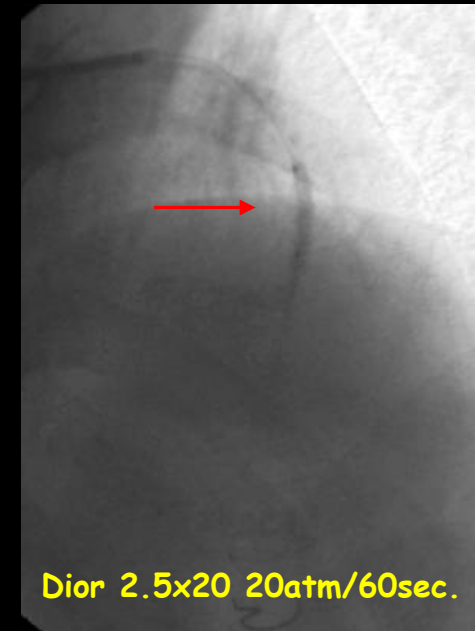
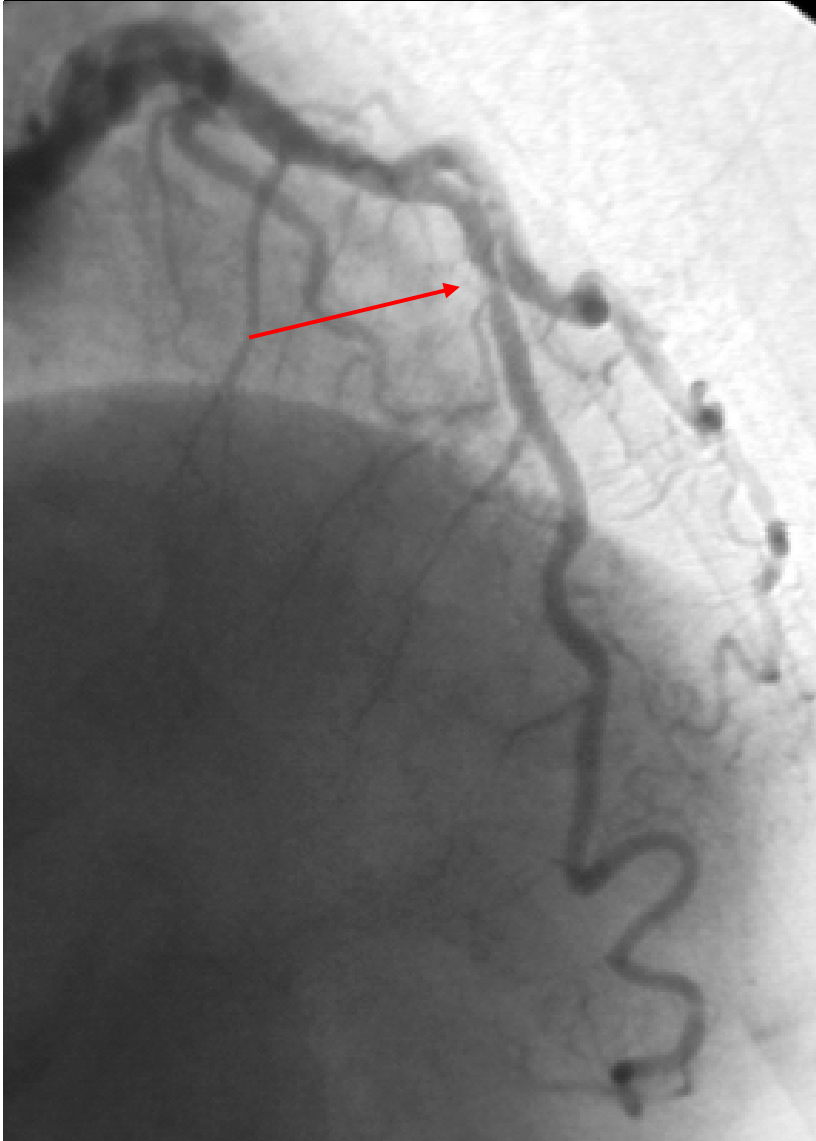
## Conclusions

Really promising preliminary results....

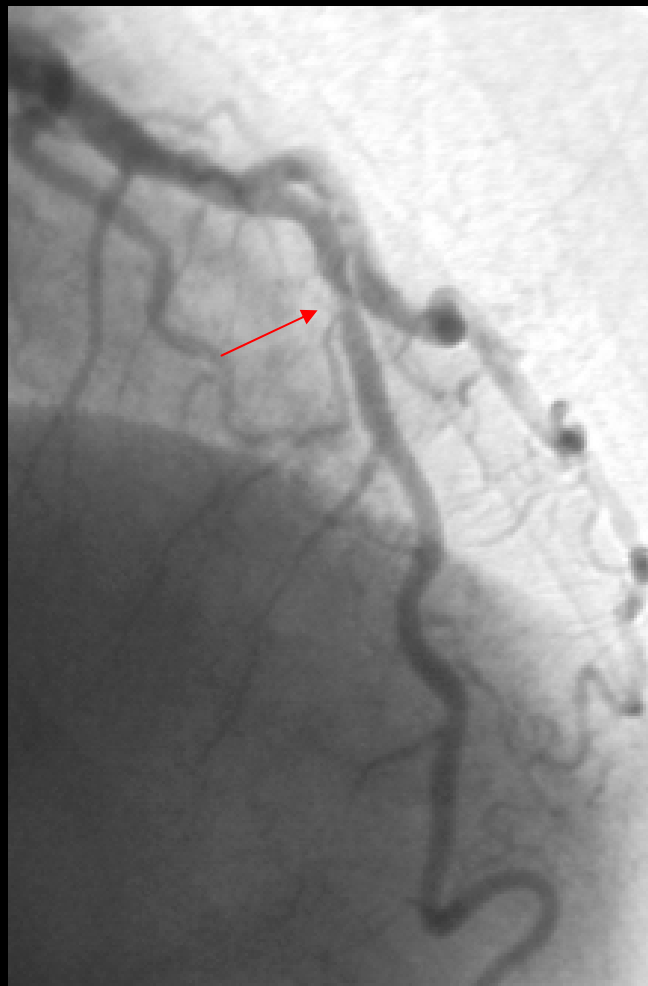
- **In-stent restenosis:** excellent outcomes consistent with previous results using DEB in randomized trials
  - Moreover, **this is real world registry**, providing additional information about ISR of small vessel, DES-ISR (48%), unstable presentation (50.5%)....
- **Small vessel:** remarkable results, not previously described
  - Really small vessel, including SB of true bifurcated lesions (111, 101, 011) and ostial lesions (001)

**Back up slides**

## Mid LAD BMS in-stent focal restenosis



**Baseline**



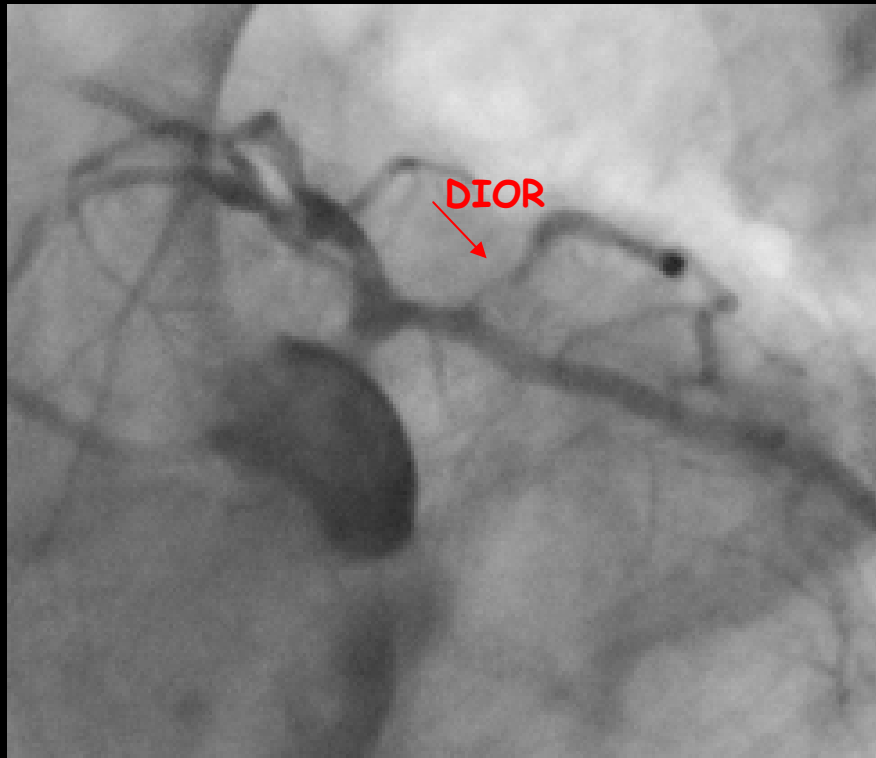
**Immediat result**



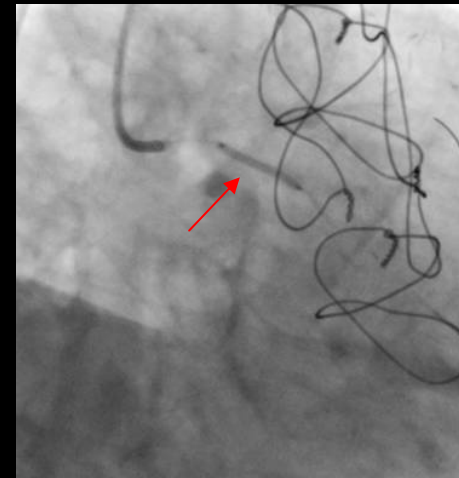
**8 mo angio FU**



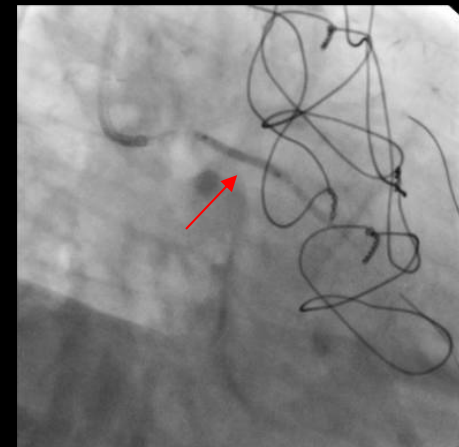
# Ostial LM stenosis + ostial first marginal lesion (OO1+ small vessel)



Pre-dilatation



Dior 2.25x25, 12atm/90sec.



**Baseline**

**Immediat result**

**6 mo angio FU**





## Novel Coating Technology of Dior 2G: Shellac

- **In-vitro:** Brief contact/paclitaxel inhibits the proliferation vascular and smooth-muscle cells
- **Animal Model:** Dior vs non-coated balloon: better in inhibition of neointimal hyperplasia
- **Novel coating method: "Shellac" 2on G of DIOR:**
  - 20-fold higher tissue concentration of paclitaxel
  - Max. tissue concentration/inflation time 30-45sec (tolerated+)
- **Homogeneous (Lg and vertical )distribution of paclitaxel on the vessel by simple diffusion, in contrast with DES**