PALAIS DES CONGRES BIARRITZ 8/9/10 JUIN 2016
www.appac.fr

APPAC
ACTUALISATIONS ET PERSPECTIVES EN PATHOLOGIE CARDIOVASCULAIRE

« Le patient Diabétique, un Challenge »

P. Motreff, N. Combaret, G. Souteyrand

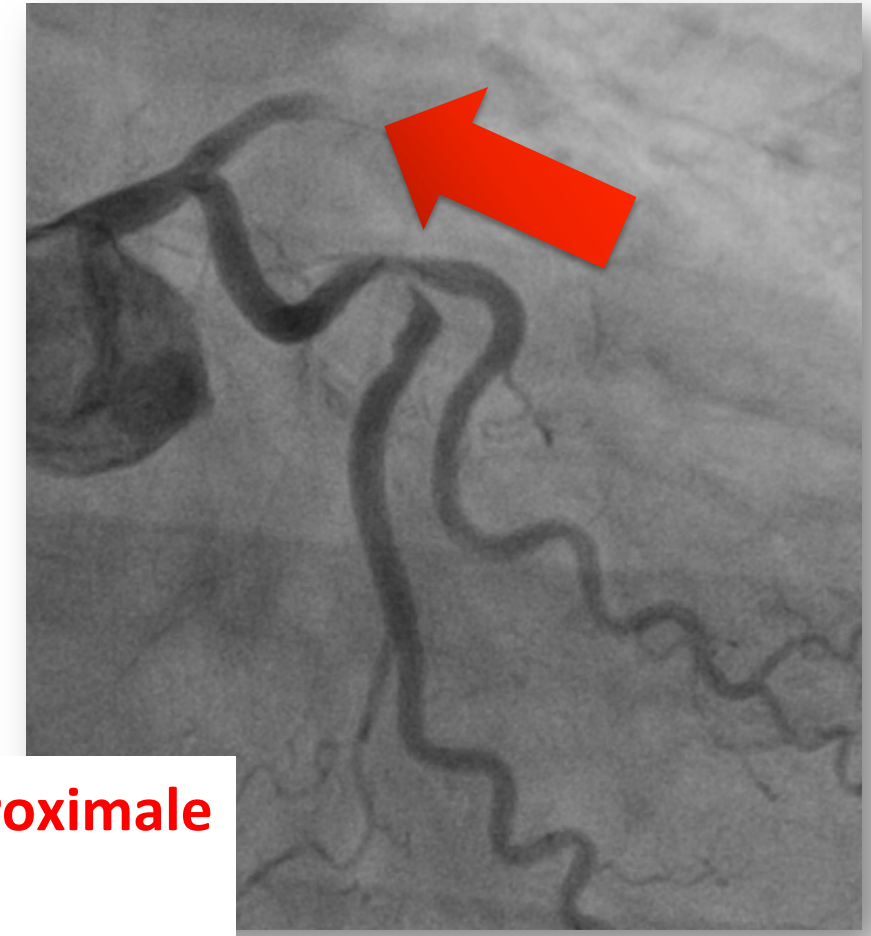
Conflits d'intérêts :

Pascal Motreff

Consutlting : Saint-Jude Medical, Terumo, Abbott, Biotronik

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

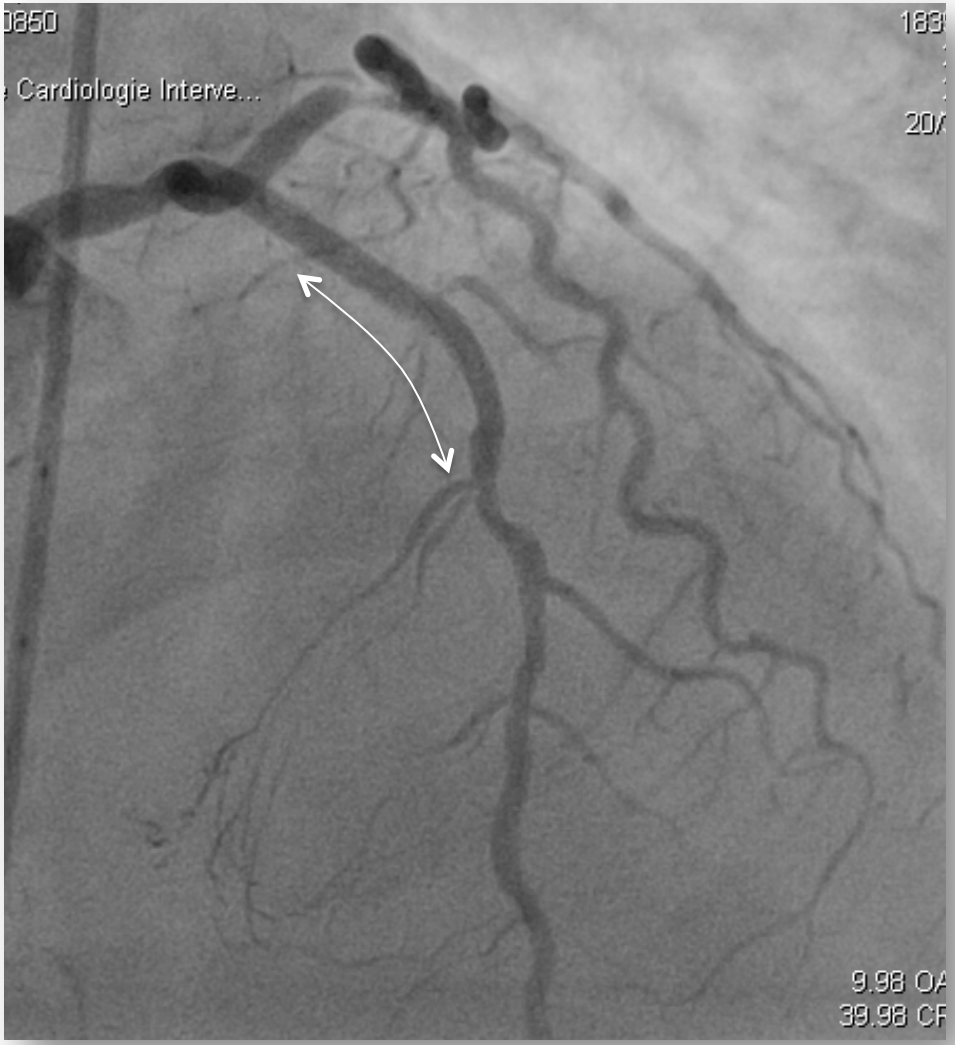
Coro à H2



- Occlusion thrombotique **IVA proximale**
- Sténose Cx Medina 1.1.1
- CTO sur CD

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

Coro à H2



Angioplastie primaire IVA

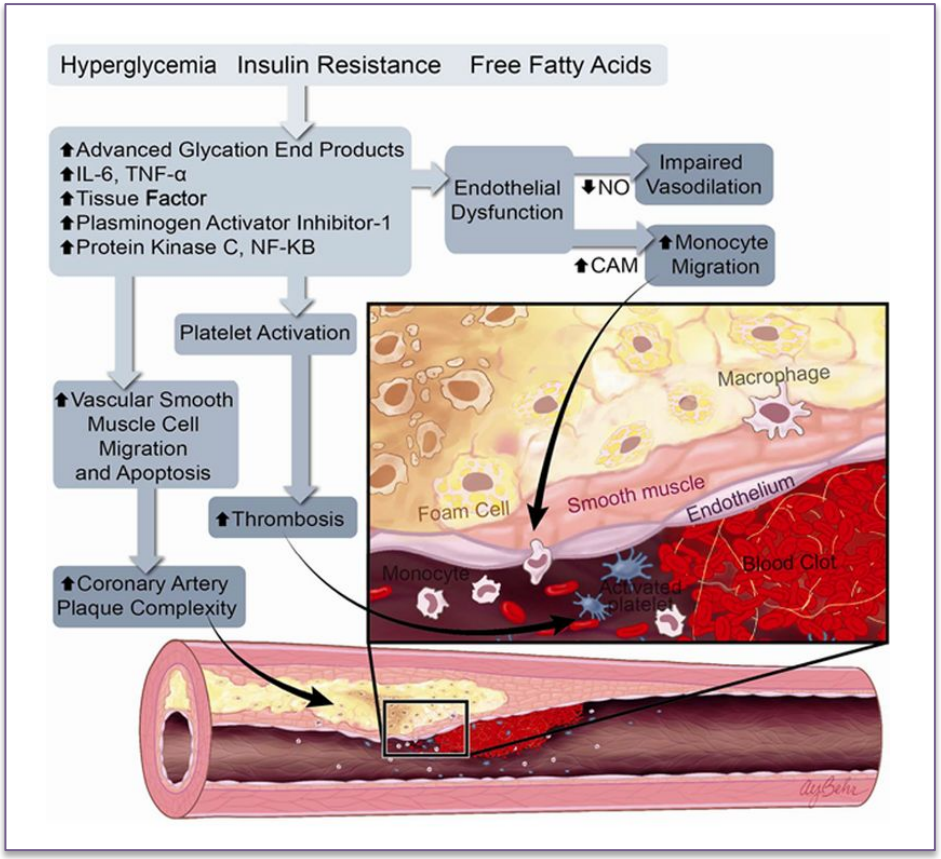
Synergy® 3.0 x 20mm

?

Le patient Diabétique

Particularités du diabétique

- **Athérosclérose précoce : multiples facteurs**
- **Coronaropathie fréquente**, sévère, diffuse et évolutive
- **Activation plaquettaire**
- **Resténose**



Armstrong EJ, Circulation 2013

Le patient Diabétique

Particularités du diabétique

- **Plus de multitronculaires**
- Moins bons résultats de l'angioplastie mais aussi des pontages
- Comorbidités (insuffisance rénale)
- **Moins bon pronostic**

Risque de maladie coronaire = **x 2** à **x 4**
Mortalité du diabétique = **75% CV**
25-30% des PCI = diabétiques

Revascularisation ?

Le patient Diabétique

Recommandations

2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

Table 4. Recommendations for CAD Revascularization to Improve Survival

2012 Recommendation	2014 Focused Update Recommendations	Comments
Class IIa 1. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery.[58–65] *(Level of Evidence: B)*	Class I 1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD.[66] *(Level of Evidence: C)*	New recommendation

CABG indicates coronary arter… coronary intervention; and RCT, r…

Class IIa

1. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery.[58–65] *(Level of Evidence: B)*

Le patient Diabétique

Recommandations

2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update

Class I

1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD.[66] *(Level of Evidence: C)*

2. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery.[58–69] *(Level of Evidence: B)*

Le patient Diabétique

Recommandations

Specific recommendations for revascularization in patients with diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
In patients presenting with STEMI, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits.	I	A	363
In patients with NSTE-ACS, an early invasive strategy is recommended over non-invasive management.	I	A	180,338, 364–366
In stable patients with multivessel CAD and/or evidence of ischaemia, revascularization is indicated in order to reduce cardiac adverse events.	I	B	93,367
In patients with stable multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	106,175,349
In patients with stable multivessel CAD and SYNTAX score ≤ 22, PCI should be considered as alternative to CABG.	IIa	B	346,350
New-generation DES are recommended over BMS.	I	A	351,352
Bilateral mammary artery grafting should be considered.	IIa	B	368
In patients on metformin, renal function should be carefully monitored for 2 to 3 days after coronary angiography/PCI.	I	C	

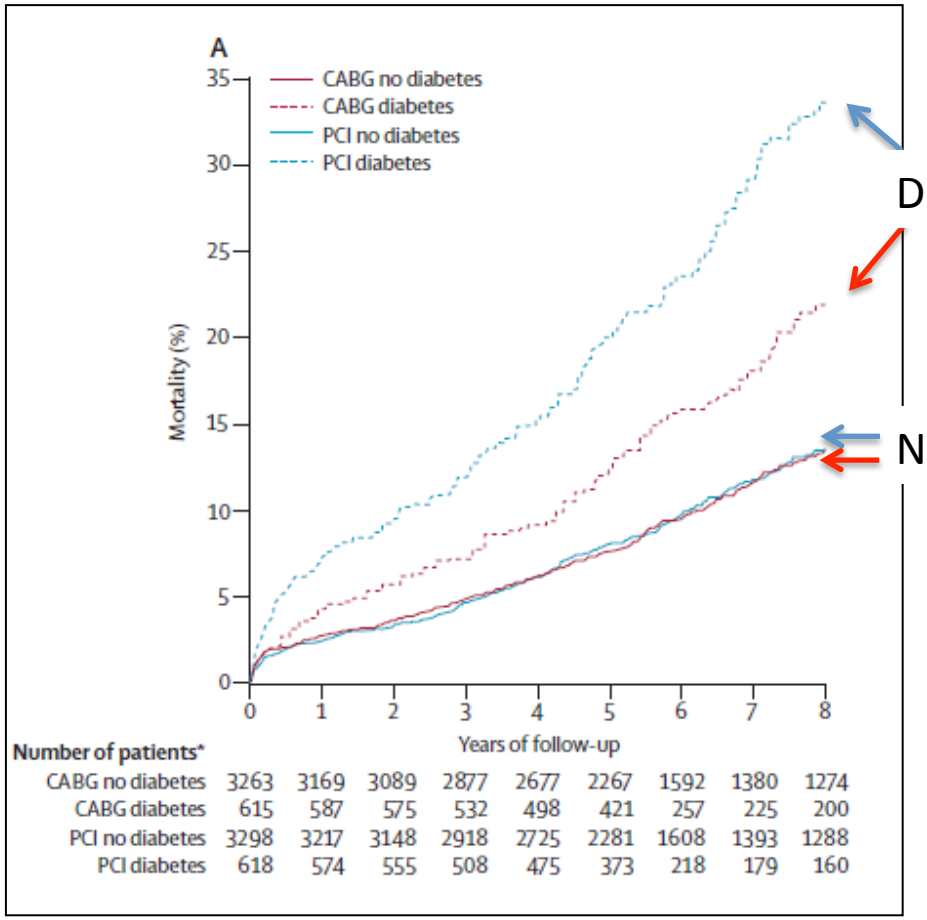
2014 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Windecker S, Eur Heart J 2014

Le patient Diabétique

Meta-analyses



Mortalité à 8 ans = 34% PCI

Diabétiques

Mortalité à 8 ans = 22% CABG

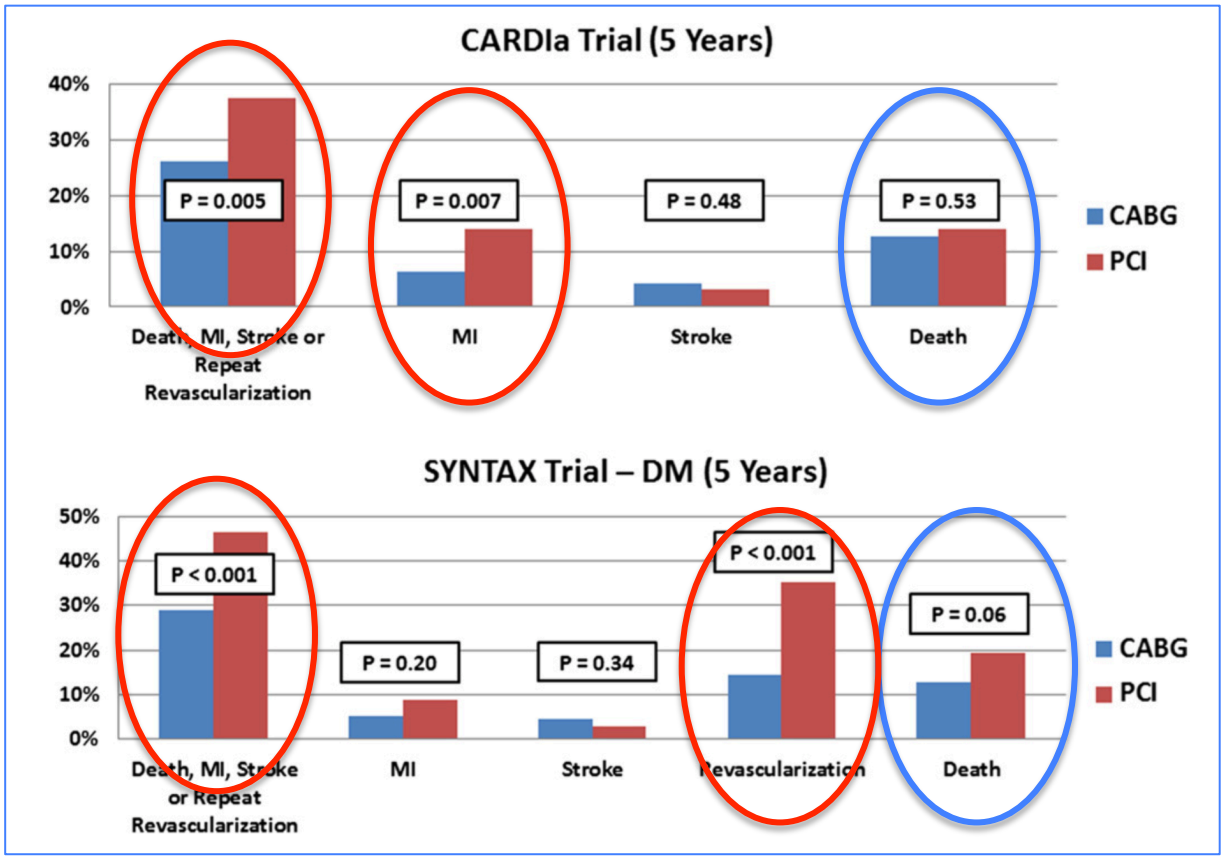
Non Diabétiques

10 études, 7812 pts
dont 1233 Diabétiques
(POBA ou BMS)

Hlatky M, Lancet 2009

Le patient Diabétique

Etudes plus récentes…

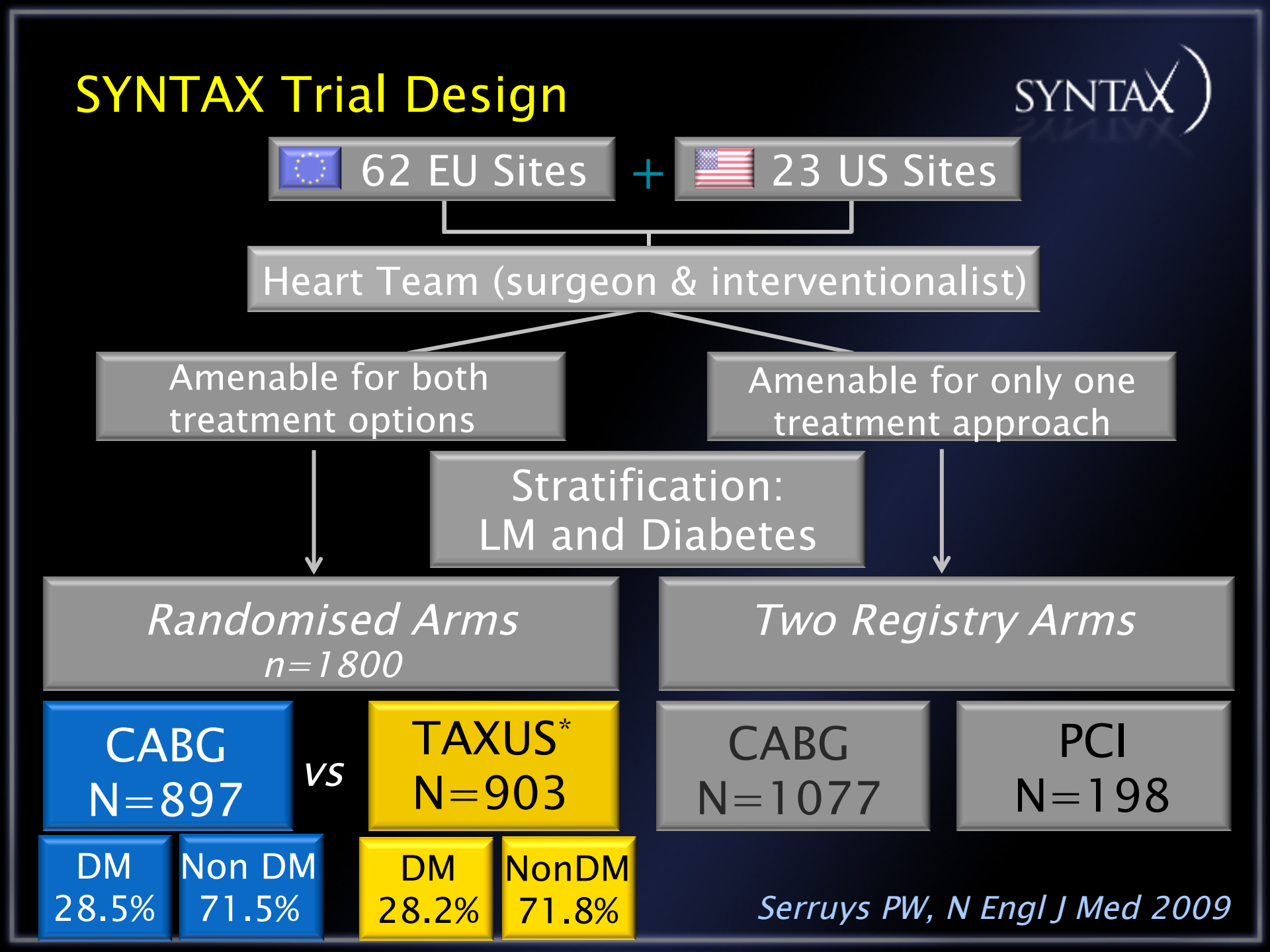


CARDIa
SES (71%) et BMS

SYNTAX
PES

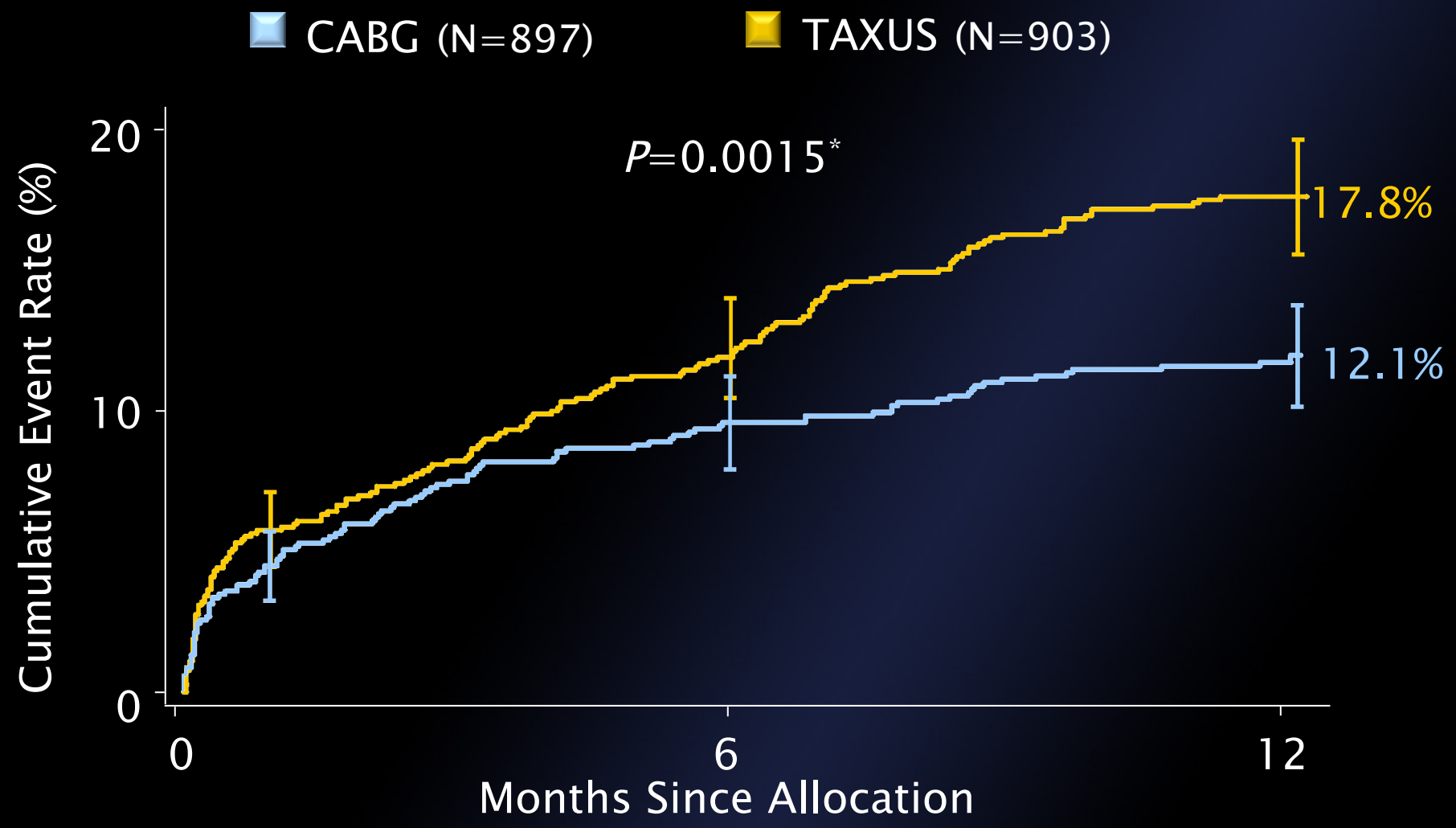
Kapur A, J Am Coll Cardiol 2010
Serruys PW, N Engl J Med 2009

SYNTAX Trial Design



Serruys PW, N Engl J Med 2009

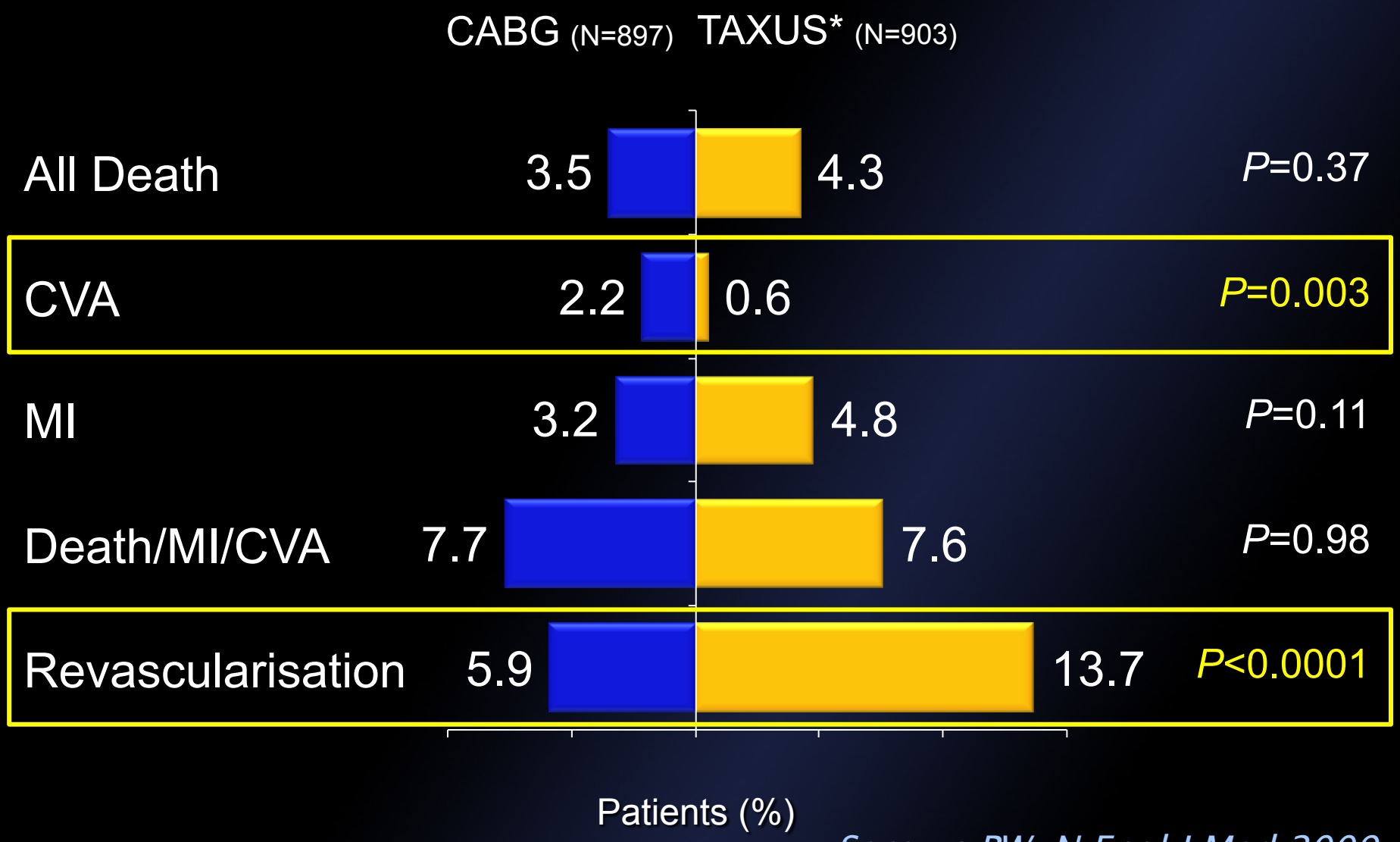
MACCE to 12 Months



Event Rate ± 1.5 SE. *Fisher's Exact Test

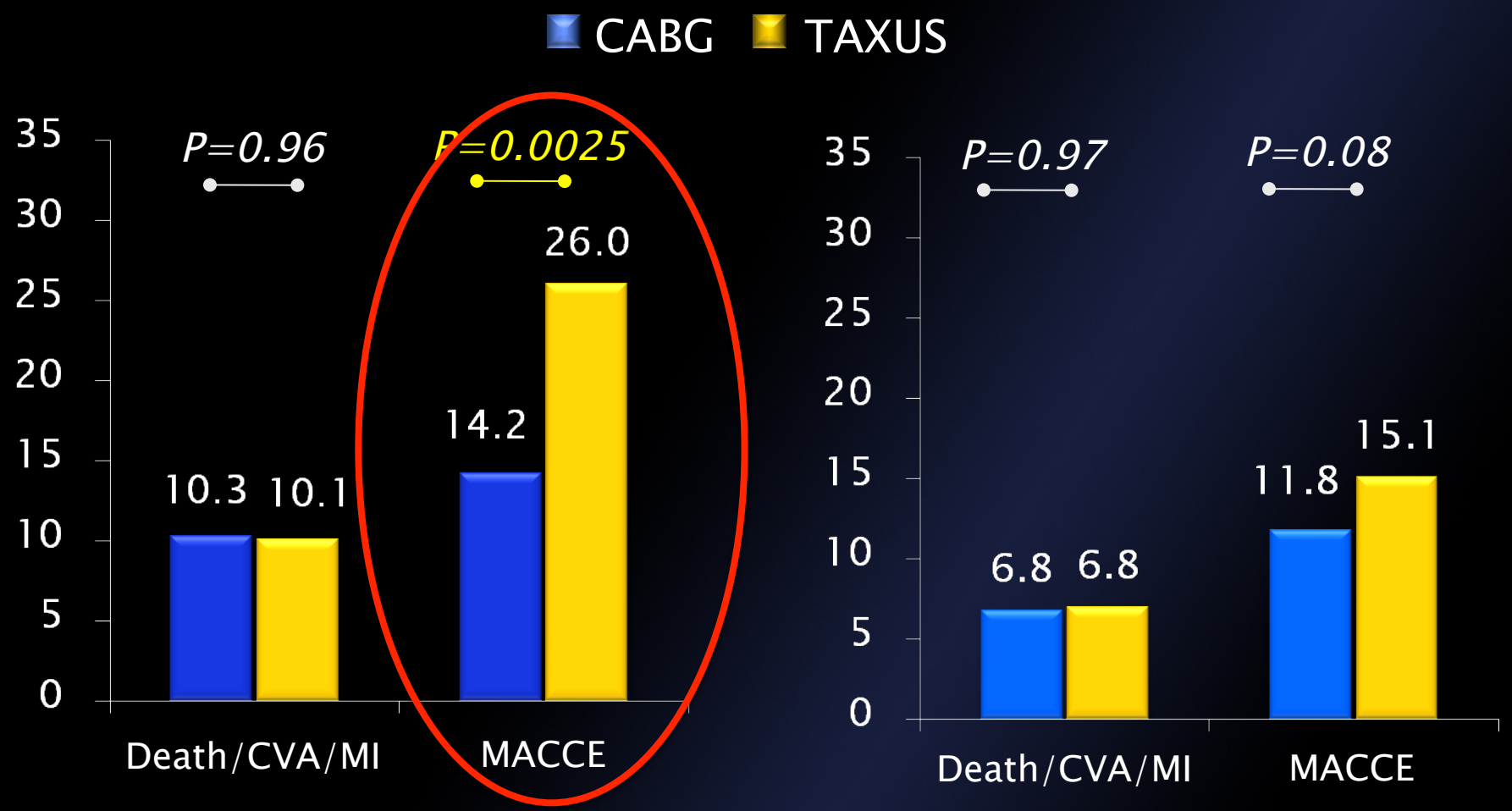
Serruys PW, N Engl J Med 2009

12 Months Clinical Event Rates



Serruys PW, N Engl J Med 2009

Outcome according to Diabetic Status



Diabetic (Medical Treatment)
N=452

Non-Diabetic
N=1348

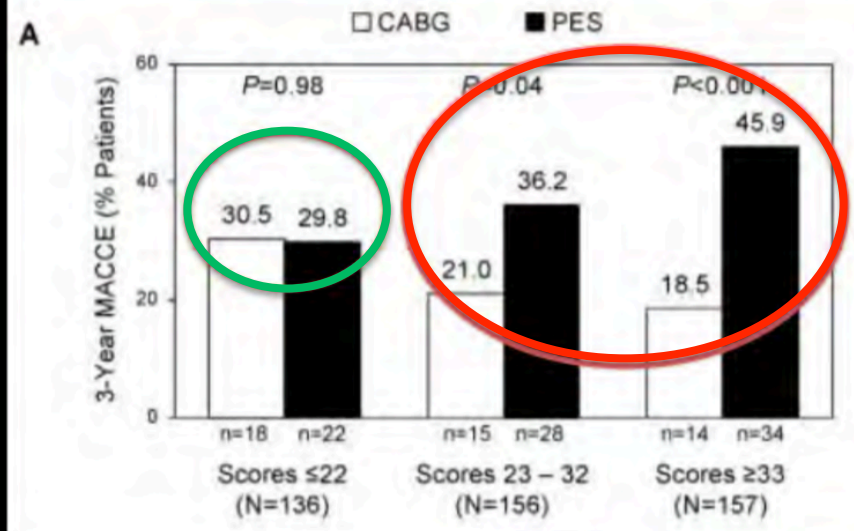
Diabetic and Nondiabetic Patients With Left Main and/or 3-Vessel Coronary Artery Disease

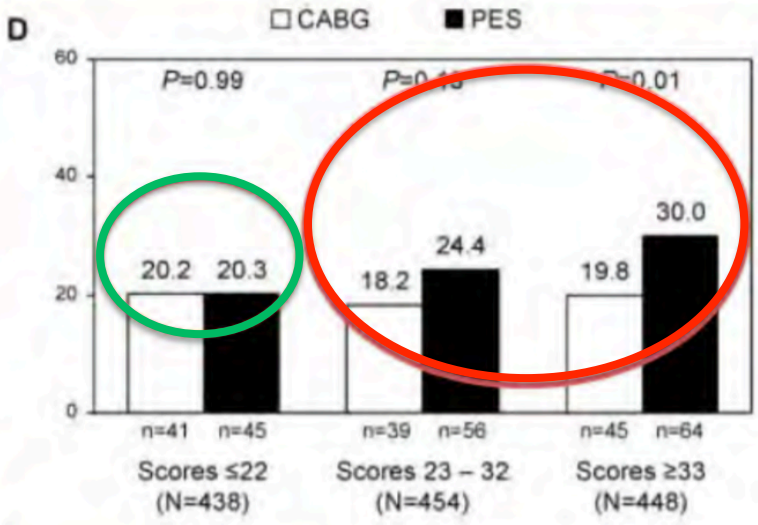
Comparison of Outcomes With Cardiac Surgery and Paclitaxel-Eluting Stents

SYNTAX

3 Year Outcomes according to SYNTAX score and Diabetic Status

Diabetes	No Diabetes

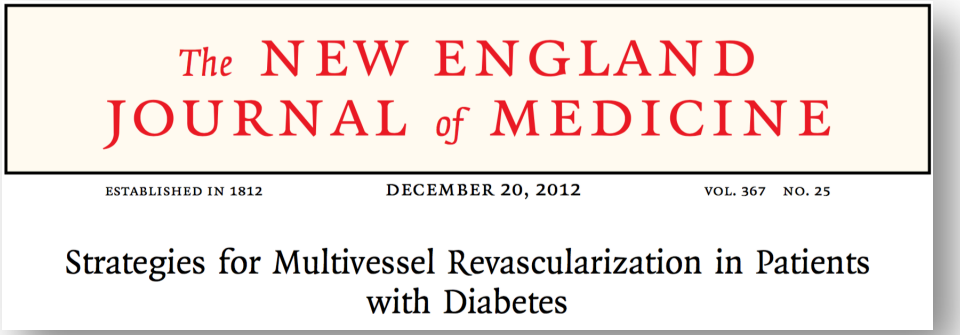




Banning AP, J Am Coll Cardiol 2010

Le patient Diabétique

FREEDOM



<u>2005-2010</u>, 1900 diabétiques inclus et suivi > 2ans
140 centres

- Age moyen 63 ans, SYNTAX moyen = 26 (un tiers ≤ 22)
- **83% tritronculaires**
- **Randomisés : CABG vs PCI**

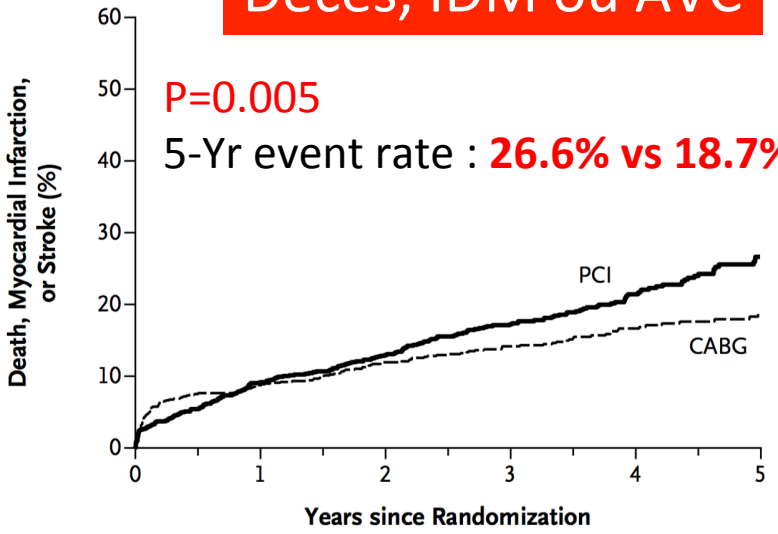
Farkouh ME, N Engl J Med 2012

Le patient Diabétique

FREEDOM

A Primary Outcome

Décès, IDM ou AVC



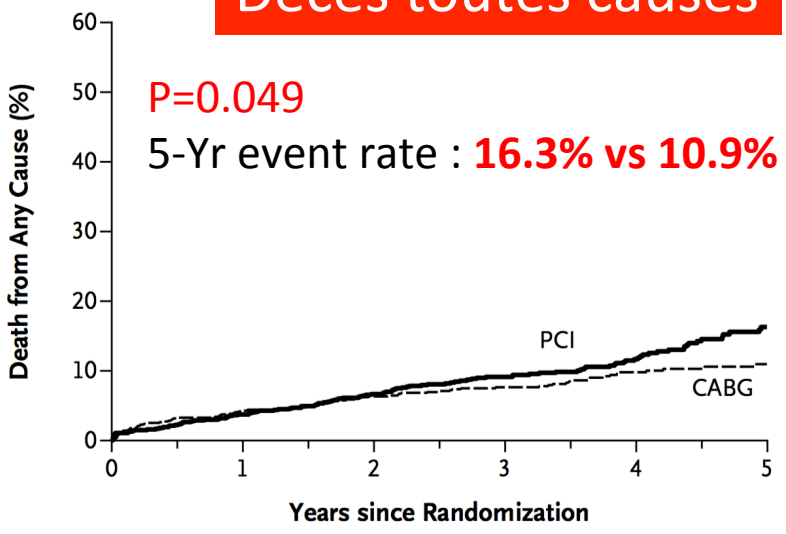
P=0.005

5-Yr event rate : **26.6% vs 18.7%**

No. at Risk						
PCI	953	848	788	625	416	219
CABG	947	814	758	613	422	221

B Death

Décès toutes causes



P=0.049

5-Yr event rate : **16.3% vs 10.9%**

No. at Risk						
PCI	953	897	845	685	466	243
CABG	947	855	806	655	449	238

Farkouh ME, N Engl J Med 2012

FREEDOM

Estimates of Key Outcomes at 2 Years and 5 Years after Randomization.

Outcome	2 Years after Randomization		5 Years after Randomization		Patients with Event		P Value*
	PCI	CABG	PCI	CABG	PCI	CABG	
	number (percent)				*number*		
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	205	147	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	118	86	0.049
Myocardial infarction	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	99	48	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	22	37	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	75	55	0.12

Table 3. Kaplan–Meier Estimates of Major Adverse Cardiovascular and Cerebrovascular Events at 30 Days and 12 Months after the Procedure.

Event	30 Days after Procedure			12 Months after Procedure		
	PCI	CABG	P Value	PCI	CABG	P Value
	number (percent)			*number (percent)*		
Major adverse cardiovascular and cerebrovascular events	45 (4.8)	47 (5.2)	0.68	157 (16.8)	106 (11.8)	0.004
Death	8 (0.8)	15 (1.7)	0.12	32 (3.4)	38 (4.2)	0.35
Myocardial infarction	17 (1.8)	15 (1.7)	0.82	54 (5.8)	30 (3.4)	0.02
Stroke	3 (0.3)	16 (1.8)	0.002	8 (0.9)	17 (1.9)	0.06
Repeat revascularization	31 (3.3)	10 (1.1)	0.002	117 (12.6)	42 (4.8)	<0.001

Farkouh ME, N Engl J Med 2012

EDITORIAL COMMENT

Coronary Revascularization for Patients With Diabetes

Updated Data Favor Coronary Artery Bypass Grafting*

Coronary Revascularization Strategies in Patients With Diabetes and Multivessel Coronary Artery Disease

Has the Final Chapter Been Written?*

Percutaneous coronary invervention versus coronary artery bypass grafting: A meta-analysis

Surgical Revascularization versus Percutaneous Coronary Intervention and Optimal Medical Therapy in Diabetic Patients with Multi-Vessel Coronary Artery Disease

*Gennaro Giustino, George D. Dangas**

Ellis SG, J Am Coll Cardiol 2013
Armstrong JE, Circulation 2013
Marso SP, J Am Coll Cardiol 2014
Tu B, Ann Intern Med. 2014
Giustino G, Prog Cardiovasc Dis 2015
Smit Y, J Thorac Cardiovasc Surg 2015
Bundhun PK, Cardiovasc Diabetol 2016

ORIGINAL INVESTIGATION Open Access

Coronary artery bypass surgery compared with percutaneous coronary interventions in patients with insulin-treated type 2 diabetes mellitus: a systematic review and meta-analysis of 6 randomized controlled trials

Pravesh Kumar Bundhun, Zi Jia Wu and Meng-Hua Chen*

Coronary Revascularization in Diabetic Patients

A Systematic Review and Bayesian Network Meta-analysis

Coronary Artery Revascularization in Patients With Diabetes Mellitus

Le patient Diabétique

Meta-analyses

- **CABG =** tendance (ancienne) à moins de mortalité
  moins de réintervention +++
  plus d'AVC
- **Décision individuelle**

REVIEW | Annals of Internal Medicine

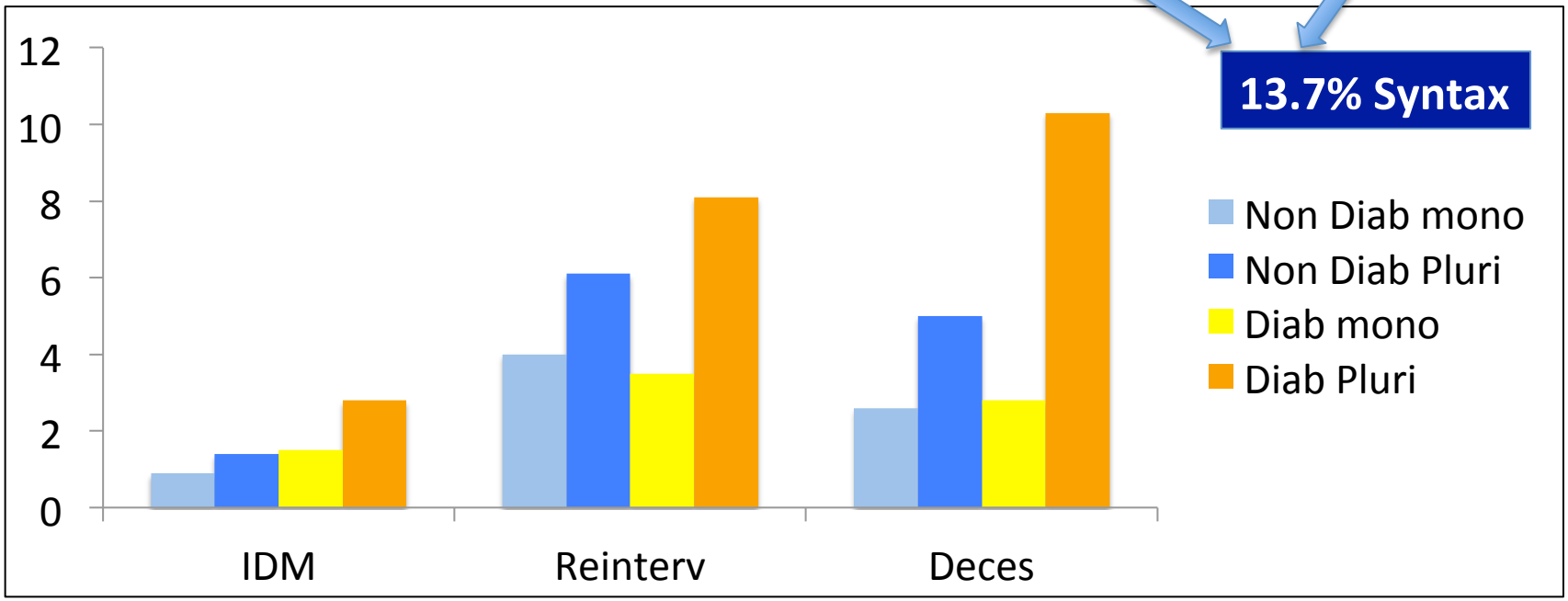
Coronary Revascularization in Diabetic Patients

A Systematic Review and Bayesian Network Meta-analysis

Tu B, Ann Intern Med. 2014

Conclusion: Coronary artery bypass grafting seems to be the preferred revascularization technique in diabetics, especially if long-term survival is anticipated. However, because of residual uncertainties and increased risk for stroke with CABG, clinical judgment is required when choosing a revascularization technique in patients with diabetes.

2014-2015	Non diabétiques = 73%			Diabétiques = 27%		
n= 27880	ø lésion	Mono T	Pluri T	ø lésion	Mono T	Pluri T
	30%	28%	**41%**	23%	24%	**52%**
% sur total	22	20	30	6	6	14
PCI	2%	62%	**66%**	2%	53%	**60%**
@ 1 an IDM		0.9%	1.4%		1.5%	2.8%
@ 1 an Réinterventions		4.0%	6.1%		3.5%	**8.1%**
@ 1 an Décès		2.6%	**5.0%**		2.8%	**10.3%**



Le patient Diabétique

Décision en Heart Team : PCI ou CABG?

Contexte Clinique	• Angor stable, ischémie silencieuse • SCA ST+ ou non ST+ • Choc cardiogénique
Lésions Coronaires	• Nombres de Troncs touchés • Score SYNTAX • Accesibilité aux pontages ou PCI
Patient	• Etat général, Fraction d'éjection VG • Préférence • Compliance DAPT, traitement anticoagulant • Chirurgie programmée (cardiaque ou non)
Age et Comorbidités	• Espérance de vie • EUROSCORE ou STS Score • ATCD de Chirurgie Cardiaque • Insuffisance respiratoire, rénale…

Type de chirurgie proposée … Type de stent utilisé

Diabétique multitronculaire

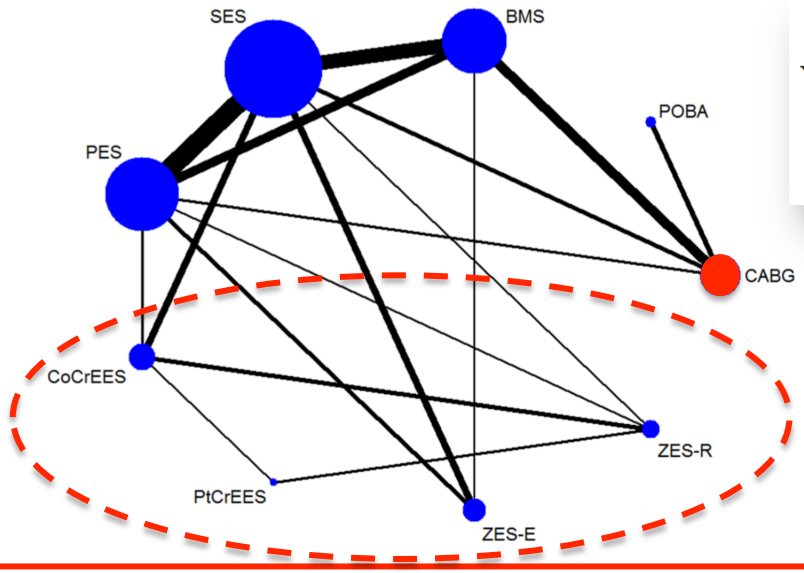
Table 1. Major Recent Studies Comparing PCI With CABG Among Patients With DM

Trial Name	Study Period	Type of PCI	Patients per Arm, n	Patients With DM, n (%)	Follow-Up, y	Primary End Point in DM	Outcome in DM
BMS or DES							
ARTS-I	1997–1998	BMS	600 BMS 605 CABG	208 (17.3)	5	Composite MACCEs	CABG<BMS
ARTS-II	2003–2003	Cypher SES	607 SES 605 CABG (from ARTS-I)	255 (21.0)	5	Composite MACCEs	CABG<SES<BMS
BARI 2D	2000–2008	PTCA/BMS/DES	1605 PCI 763 CABG	2368 (100)	5	All-cause mortality	Similar outcomes for medical therapy and revascularization
CARDia	2002–2007	BMS or Cypher SES	256 PCI 254 CABG	510 (100)	5	Composite all-cause death, nonfatal MI, and nonfatal stroke	No difference between CABG and PCI
DES							
SYNTAX	2005–2007	TAXUS PES	903 PES 897 CABG	452 (25.1)	3	Composite MACCEs	Increased MACCEs in PCI
FREEDOM	2005–2010	TAXUS PES or Cypher SES	953 PCI 947 CABG	1900 (100)	5	Composite all-cause mortality, MI, and stroke	CABG better for DM in all outcomes
PRECOMBAT	2004–2009	Cypher SES	300 SES 300 CABG	192 (32)	1	Composite MACCEs	No difference between PCI and
EXCEL	2010–current	Xience V EES					

DES

SYNTAX	2005–2007	TAXUS PES	903 PES 897 CABG
FREEDOM	2005–2010	TAXUS PES or Cypher SES	953 PCI 947 CABG

Armstrong EJ, Circulation 2013

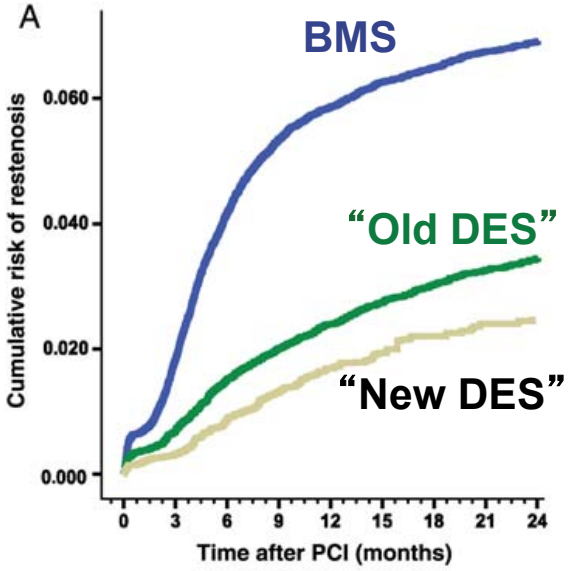


Outcomes With Coronary Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention for Patients With Diabetes Mellitus

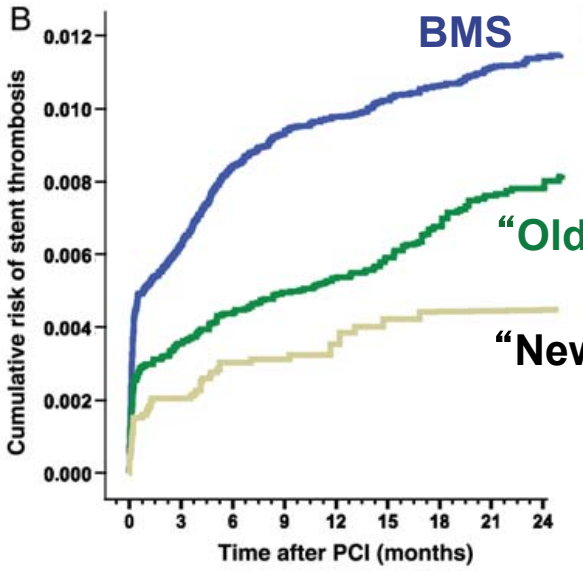
Can Newer Generation Drug-Eluting Stents Bridge the Gap?

Bangalore S, Circ Cardiovasc Interv 2014

Restenosis @ 2 years



Definite ST @ 2 years



SCAAR Registry (94384 pts)

Sarno G, Eur Heart J 2012

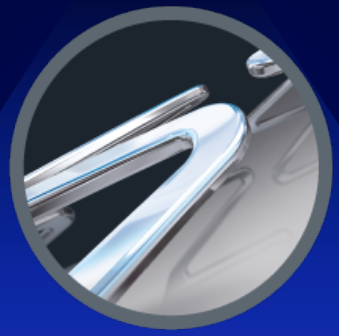
SYNERGY Stent Technology Design

Platinum Chromium Platform

- 74µm (0.0029in) strut thickness
- ↑ Visibility
- ↑ Strength
- ↑ Flexibility
- ↑ Conformability
- ↓ Recoil

Everolimus-Eluting

- 100µg/cm^2
- 3 month release time



Ultrathin Abluminal Coating

Bioabsorbable Polymer Coating (PLGA)

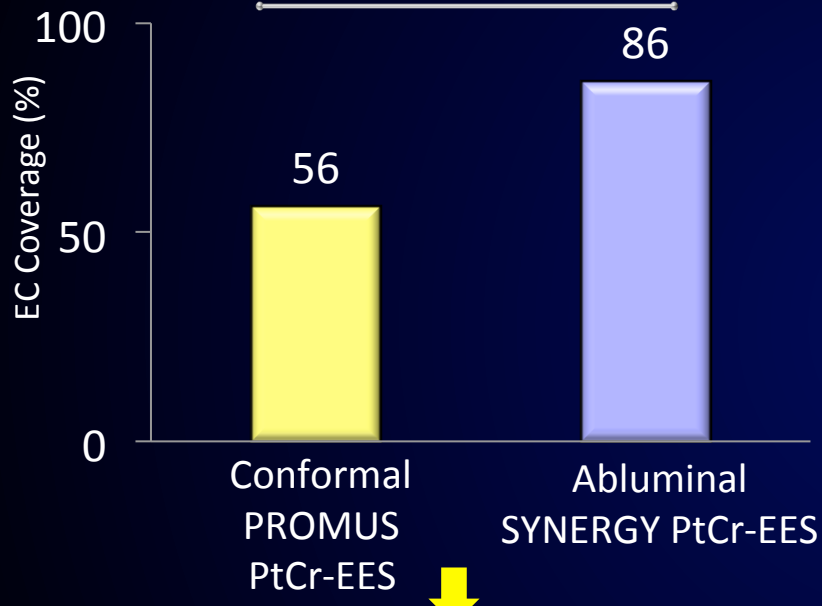
- Abluminal
- 4µm thick
- 85:15 ratio
- <4 month absorption time

Abluminal vs. Conformal Polymer

Abluminal coating significantly improves endothelialization COVERAGE and FUNCTION

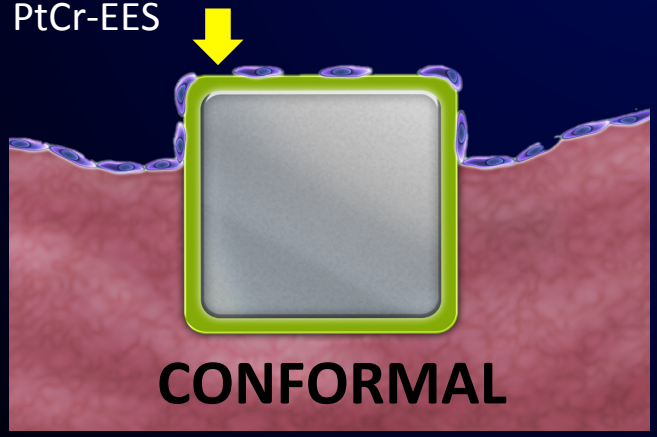
% Endothelial Cell (EC) COVERAGE
21 day cell assay

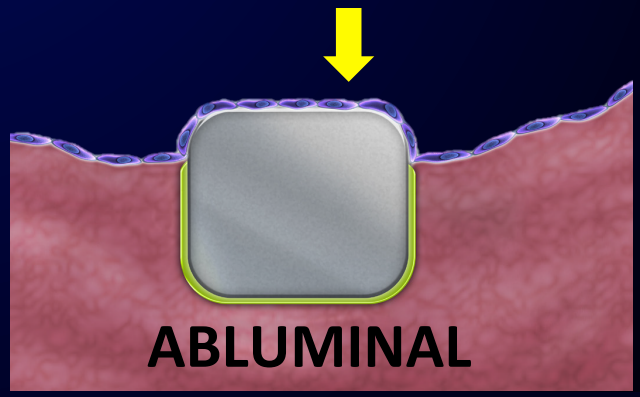
P<0.001



Endothelial Cell (EC) FUNCTION

Greater localization of VE-Cadherin at cell junctions →Improved EC function



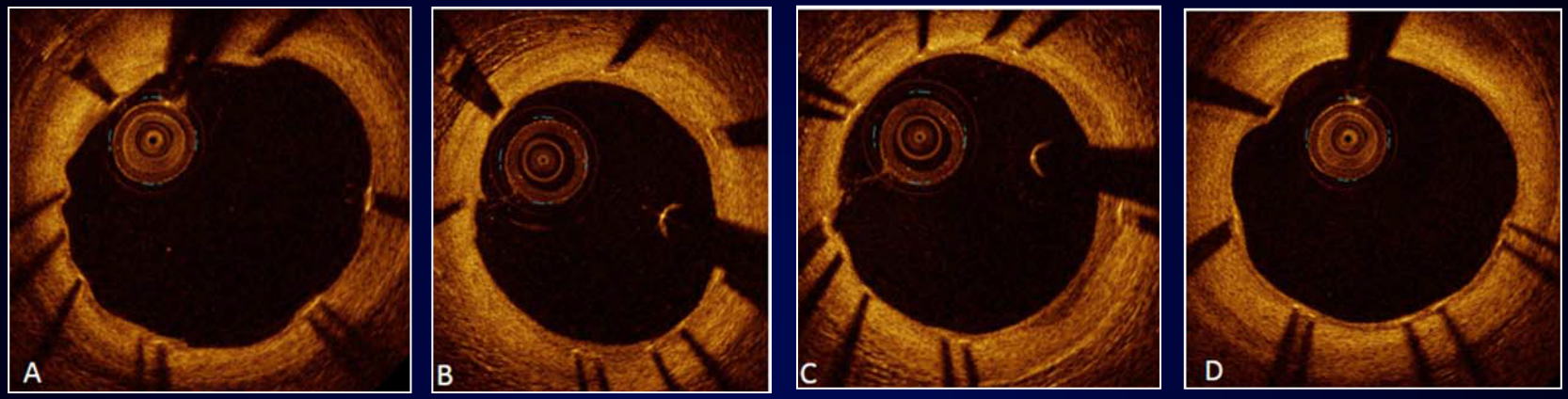


Mike Eppihimer, PhD at EuroPCR 2013/2014.

Early healing assessment with OCT of SYNERGY at 3 and 6 months after implant

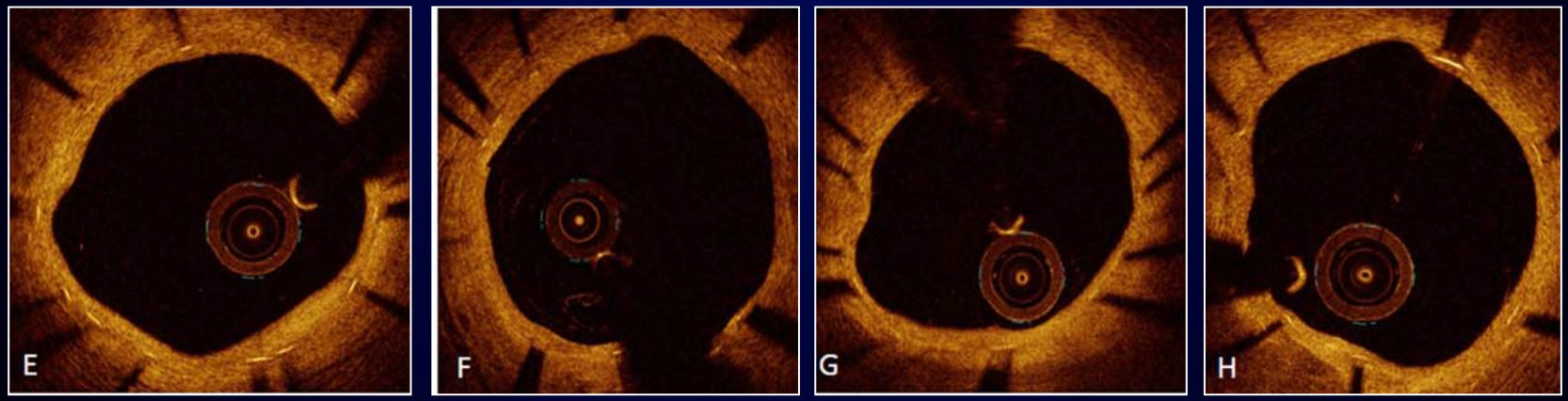
A-D: Different Case Examples of SYNERGY at 3 months

3 MONTH



E-H: Different Case Examples of SYNERGY at 6 months

6 MONTH

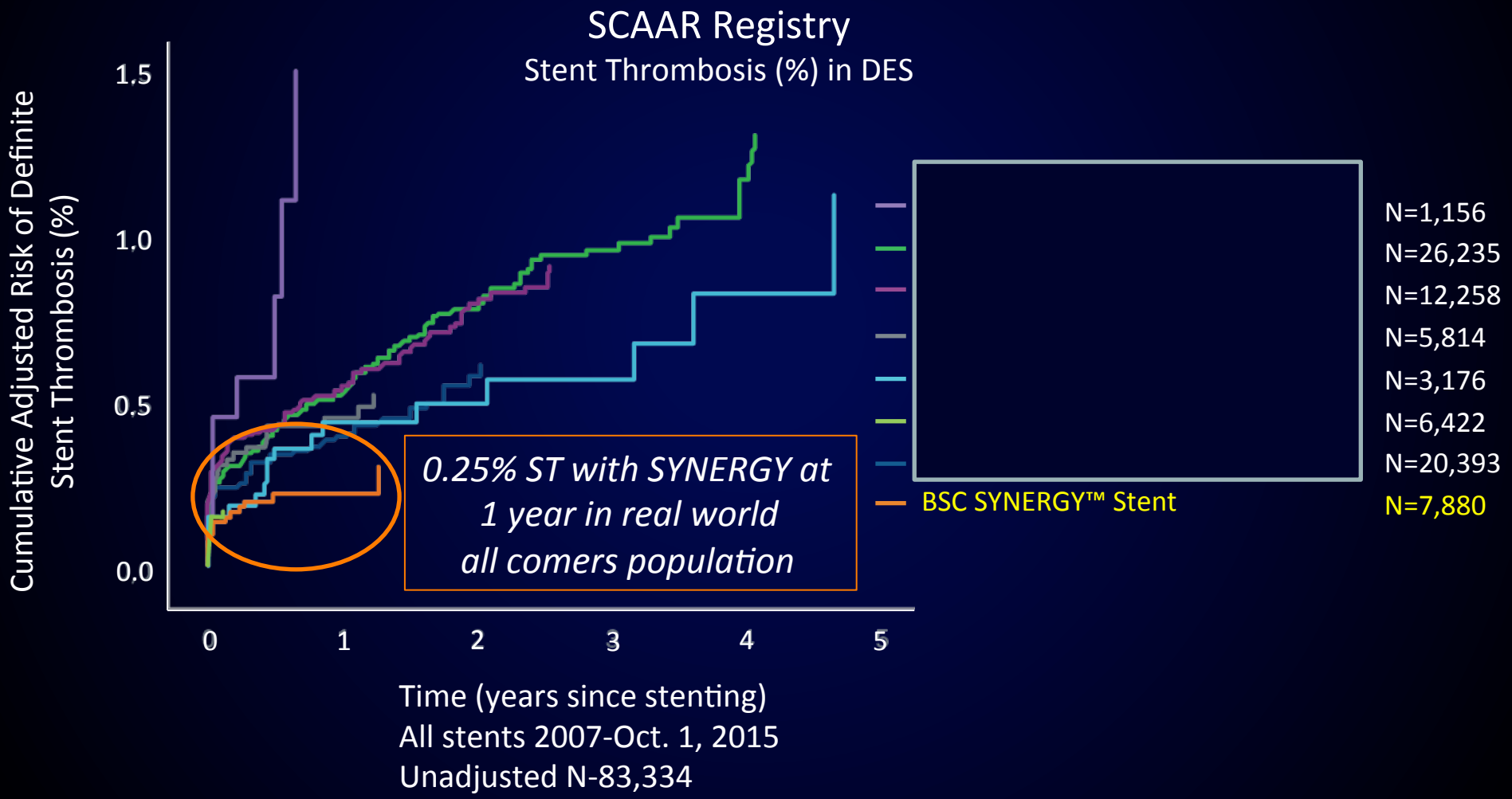


SYNERGY is associated with a high degree of intimal coverage and apposition at 3 months post implant with additional increase at 6 months

De la Torre Hernandez, et al. Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.

Case study not necessarily representative of all cases. Results in other cases may vary.

SYNERGY Stent reported lowest rates of ST in real-world SCAAR Registry

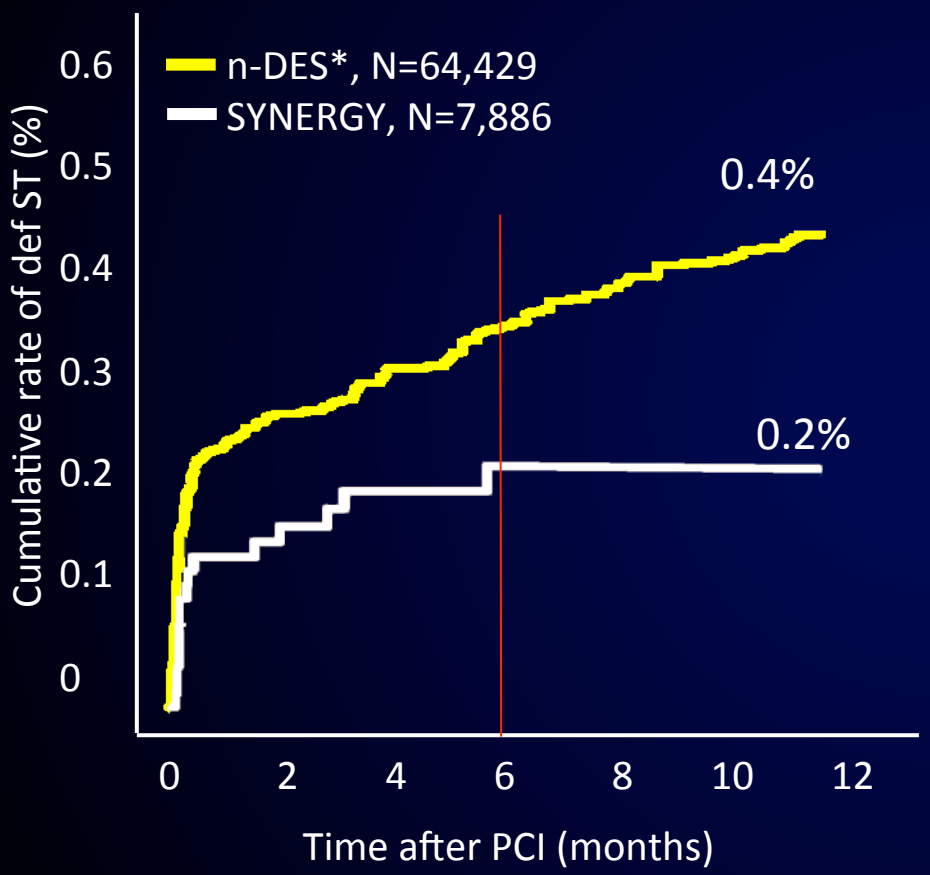


*The risk of Stent thrombosis is based on the Kaplan Meier Estimate. For the Ultimaster stent only 9 stent thromboses was reported in 1156 stents. Eight of these in one hospital. Adapted from presentation by Stefan James, MD at TCT 2015.

SCAAR Registry Definite ST Rates

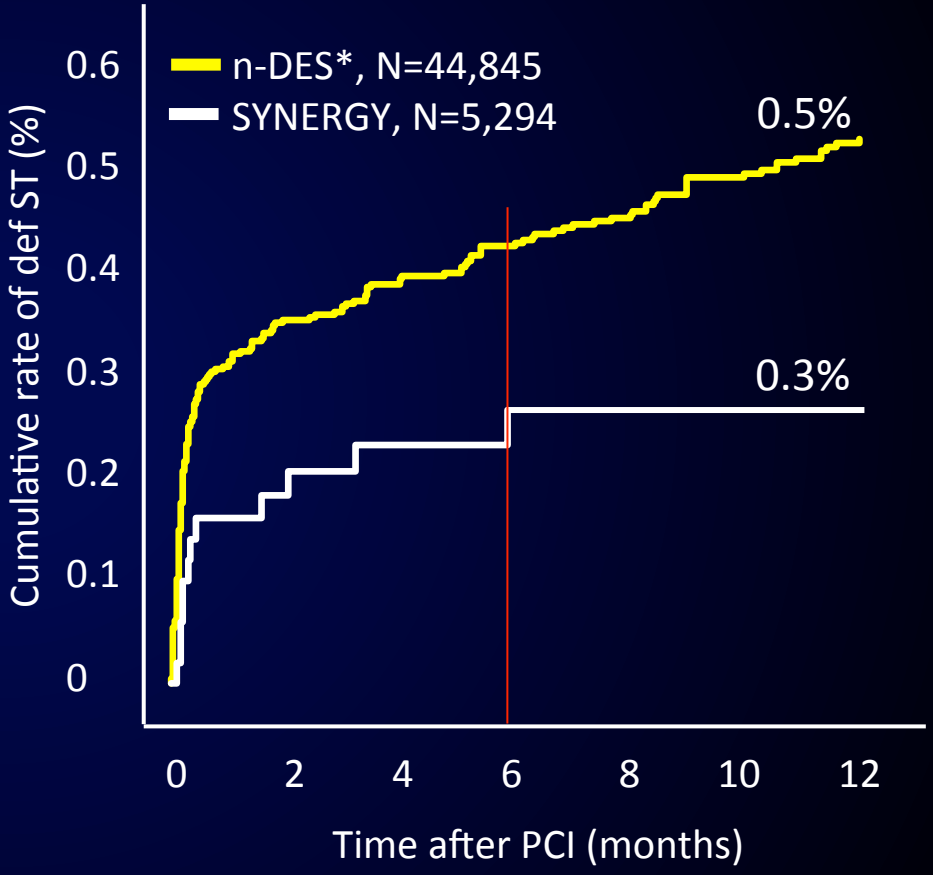
SYNERGY vs Other Current Generation DES

All Patients



0.2% vs. 0.4%, adjusted HR: 0.68; 95% CI: 0.38-1.19; p=0.17

ACS Subset



0.3% vs. 0.5%; adjusted HR: 0.69; 95% CI: 0.37-1.37; p=0.29

No additional def ST past 6 months with SYNERGY in both groups

*Other current gen DES includes: BioMatrix, Orsiro, Promus Element Plus, Promus PREMIER, Xience Xpedition, Resolute/Resolute Integrity, Ultimaster, & Resolute Onyx.

Presented by Sarno CRT 2016.

EVOLVE II Pivotal Trial Design

Patients with ≤3 native coronary artery lesions in ≤ 2 major epicardial vessels; lesion length ≤ 34 mm, RVD ≥2.25 mm ≤ 4.0, %DS≥50<100 (excluded LM disease, CTO, SVG, ISR or recent STEMI)

Randomized Cohort (RCT)
125 global sites

- **PROMUS Element Plus N=838**
- **SYNERGY N=846**

PK Substudy
- **SYNERGY N=21**

Diabetes Substudy
- **SYNERGY N=203**

RCT Design
Multicenter noninferiority trial
Pivotal, single-blind, 1:1 randomization
Primary Endpoint: TLF (CD, TV-MI, or TLR) **at 12 mo**
Follow-up through 5 years

DAPT (ASA + clopidogrel, ticlopidine, prasugrel, ticagrelor) ≥ 6 months or longer as tolerated

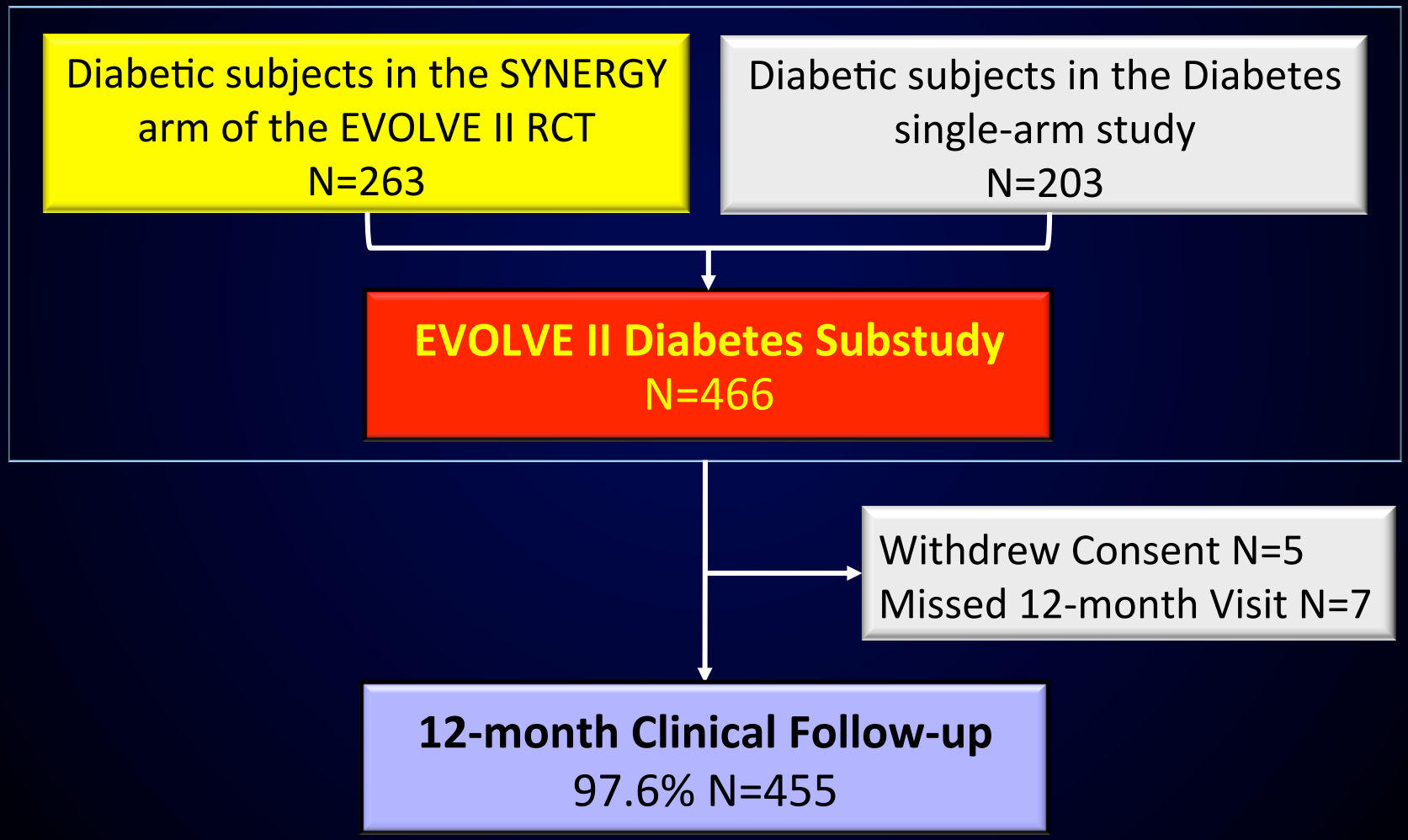
Kereiakes, et al. *Circ Cardiovasc Interv*. 2015;8:e002372. DOI: 10.1161/CIRCINTERVENTIONS.114.002372.

EVOLVE II Diabetes Substudy Design

EuroPCR 2015

Prospective, single-arm, multicentre, observational study

Primary Endpoint: Target Lesion Failure (TLF) at 12 months compared to a performance goal based on historical results in diabetic patients



Presented by Windecker at EuroPCR 2015.

TLF defined as cardic death, MI related to target vessel (based on CK-MB >3x URL), or ID-TLR

EVOLVE II DM Primary Endpoint

12-month TLF

EuroPCR 2015

P-value from the one-sided Clopper-Pearson test is <0.025, the 12-month TLF rate from SYNERGY is concluded to be less than the performance goal (14.5%)

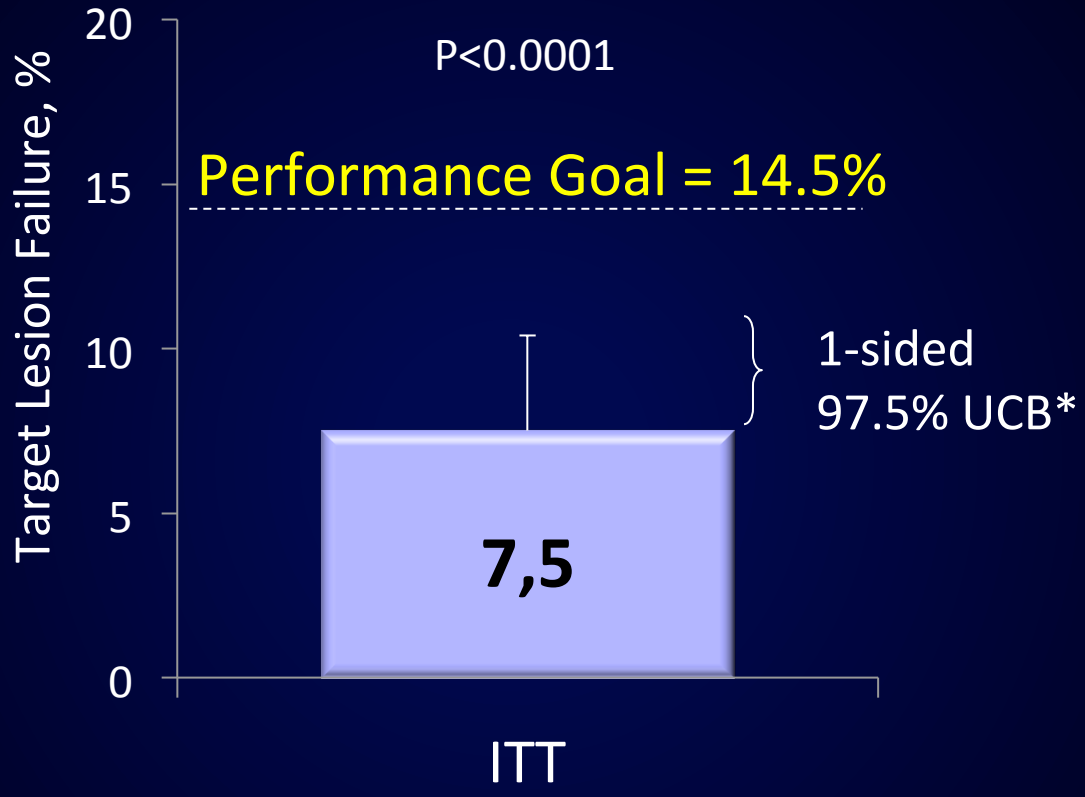
*One-sided 97.5% Clopper Pearon Upper Confidence Bound (UCB)

Presented by Windecker at EuroPCR 2015.

EVOLVE II DM Primary Endpoint

12-month TLF

EuroPCR 2015



P-value from the one-sided Clopper-Pearson test is <0.025, the 12-month TLF rate from SYNERGY is concluded to be less than the performance goal (14.5%)

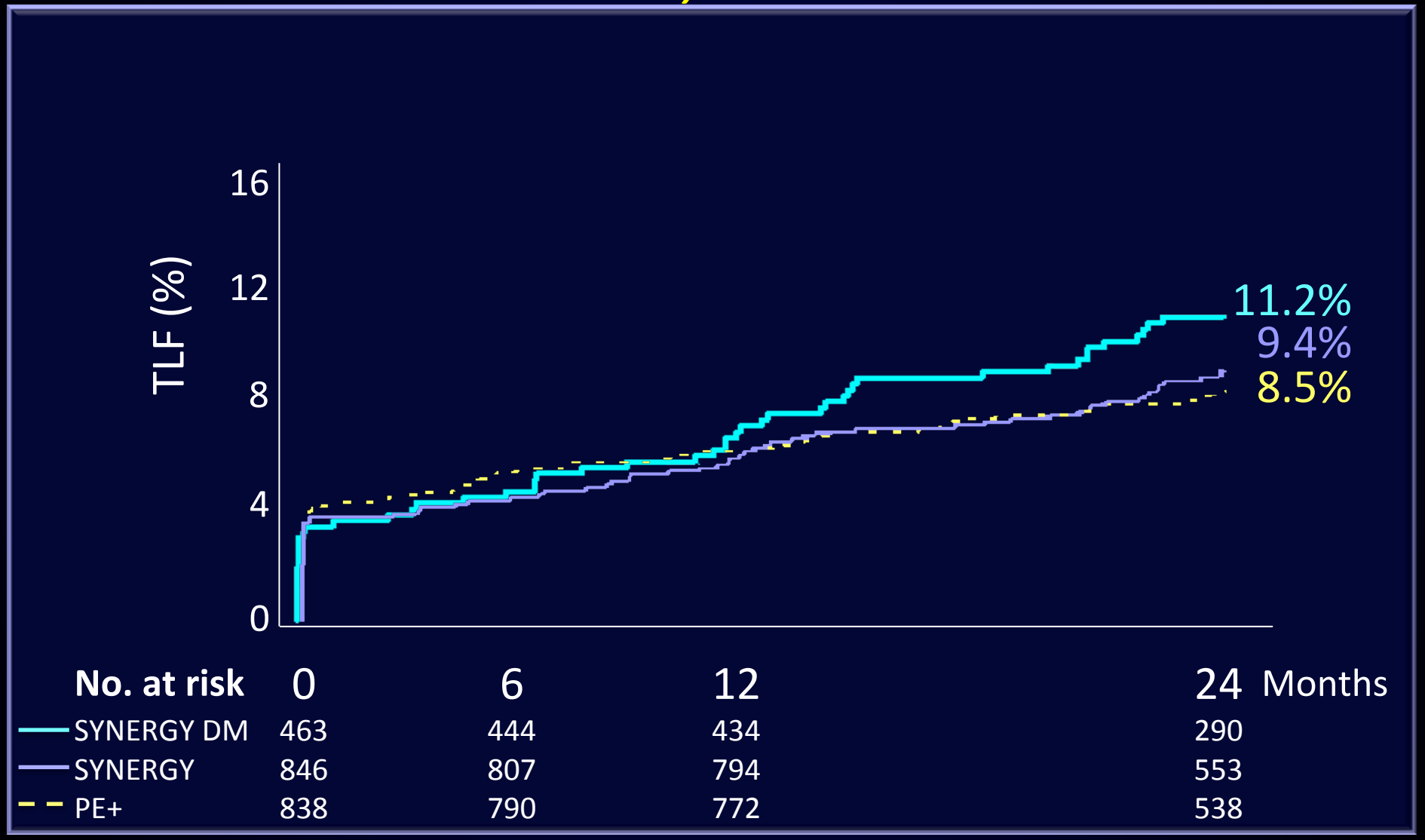
*One-sided 97.5% Clopper Pearon Upper Confidence Bound (UCB)

Presented by Windecker at EuroPCR 2015.

EVOLVE II Diabetes 2-year TLF

EVOLVE II RCT & DM Substudy

EuroPCR 2016

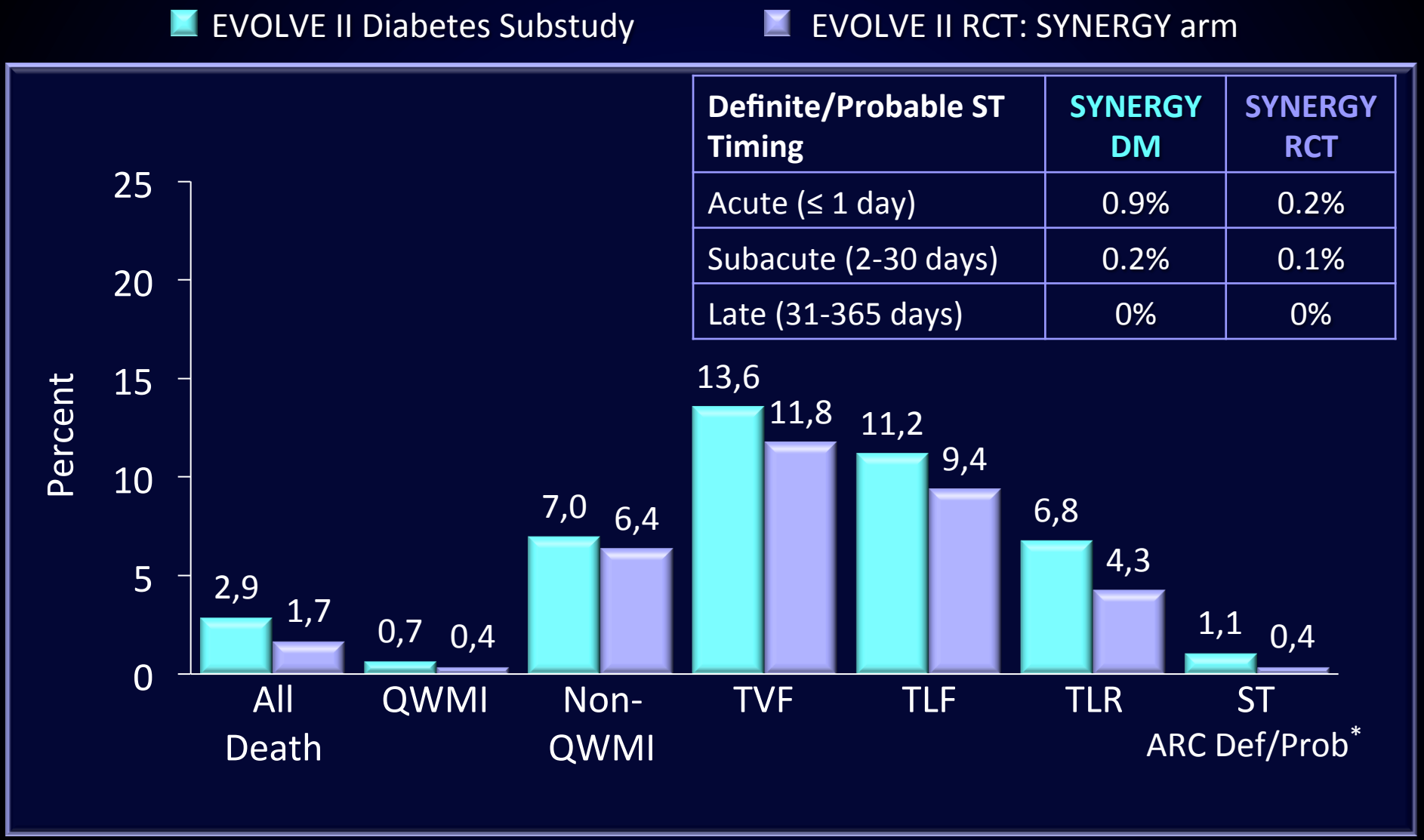


Safety Population : Patients who did not receive a study stent were censored at 1 year

Presented by Meredith at EuroPCR 2016; 2y EVOLVE II RCT data presented by Kereiakes ACC 2016; ITT population

Clinical Outcomes at 2 years

EuroPCR 2016



Definite/Probable ST Timing	SYNERGY DM	SYNERGY RCT
Acute (≤ 1 day)	0.9%	0.2%
Subacute (2-30 days)	0.2%	0.1%
Late (31-365 days)	0%	0%

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

Contrôle à J30

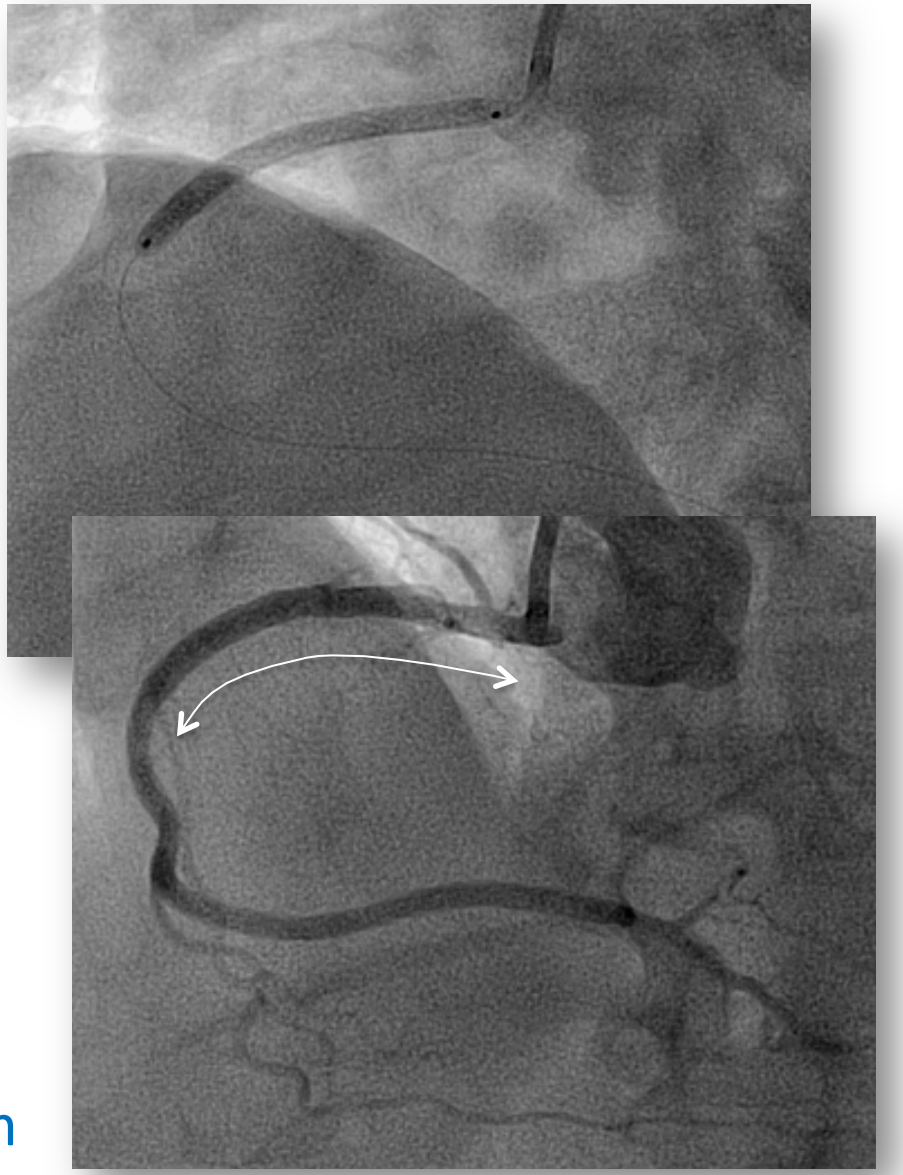
Bon résultat angioplastie IVA

Complément revasc. CD et Cx

La difficulté n'est pas toujours ou on l'attend…

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

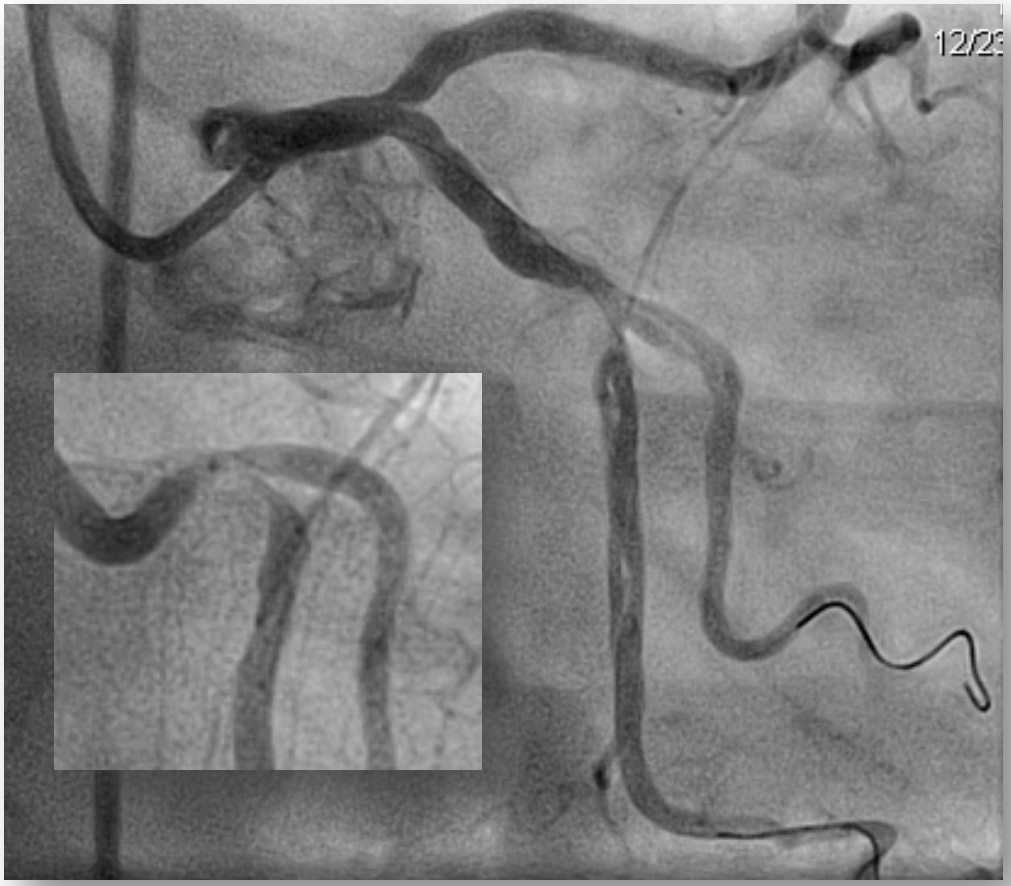
Contrôle à J30



Synergy® 3.0 x 38mm

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

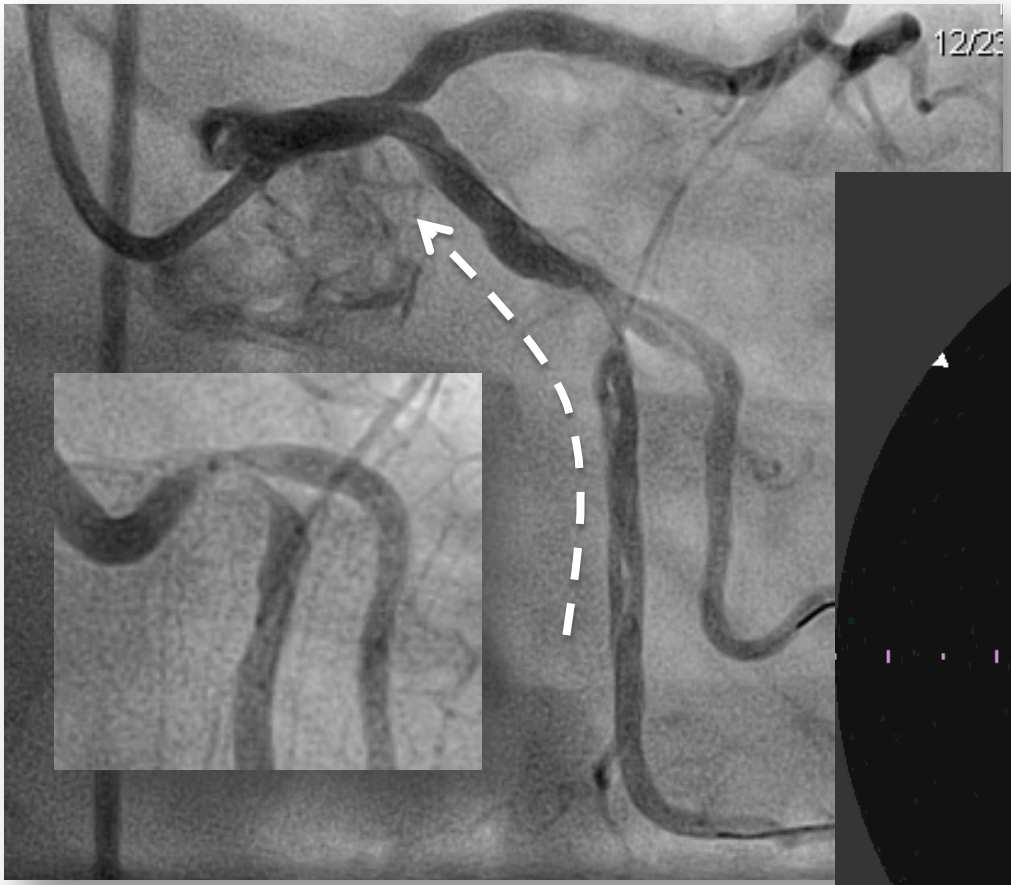
Contrôle à J30

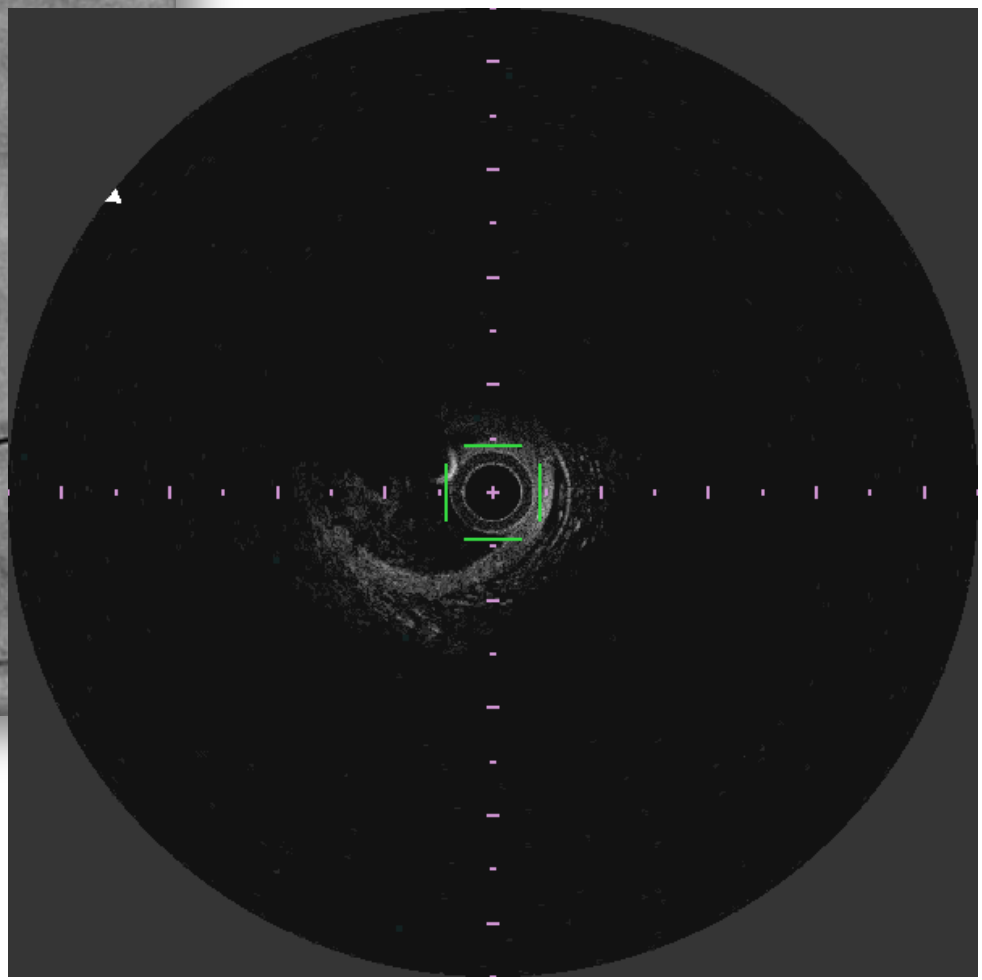


- Grosses difficultés de franchissement au guide
- Prédilatation Cx
- Doute….
- Imagerie endocoronaire

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

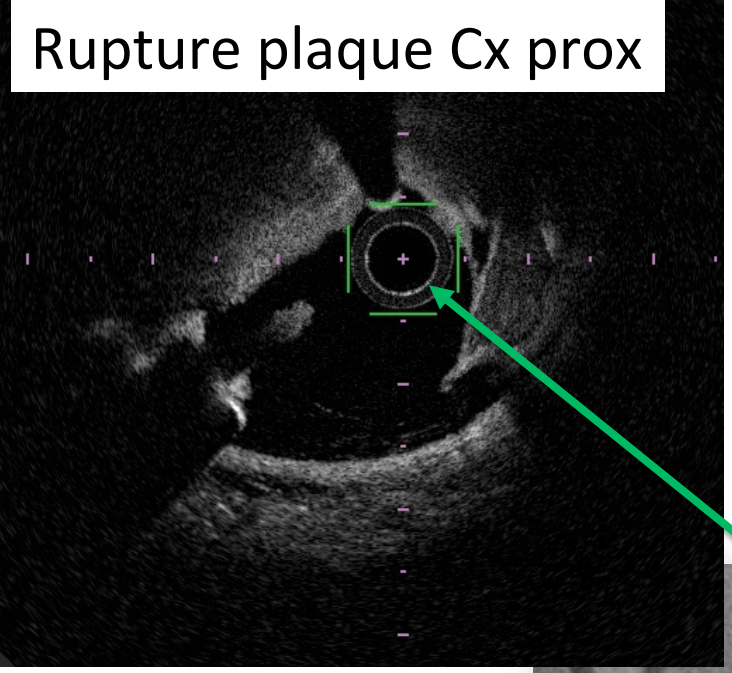
Contrôle à J30



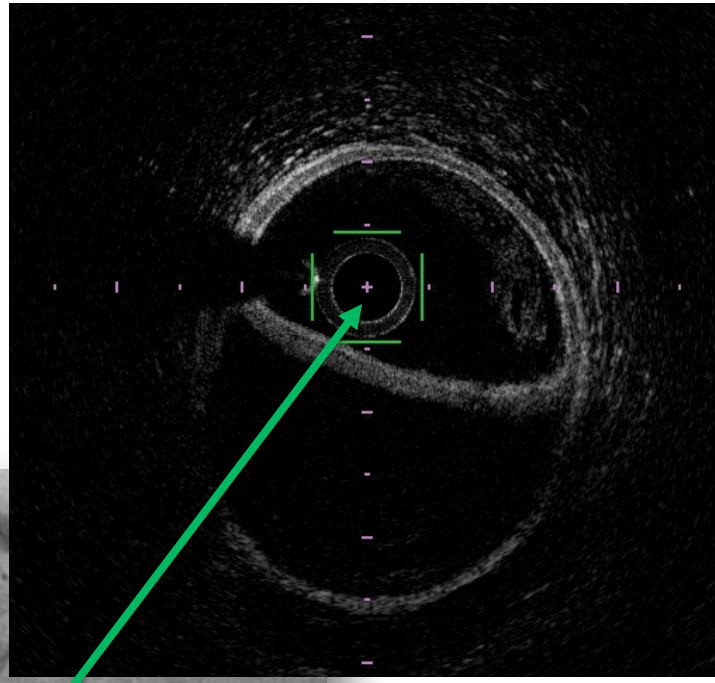


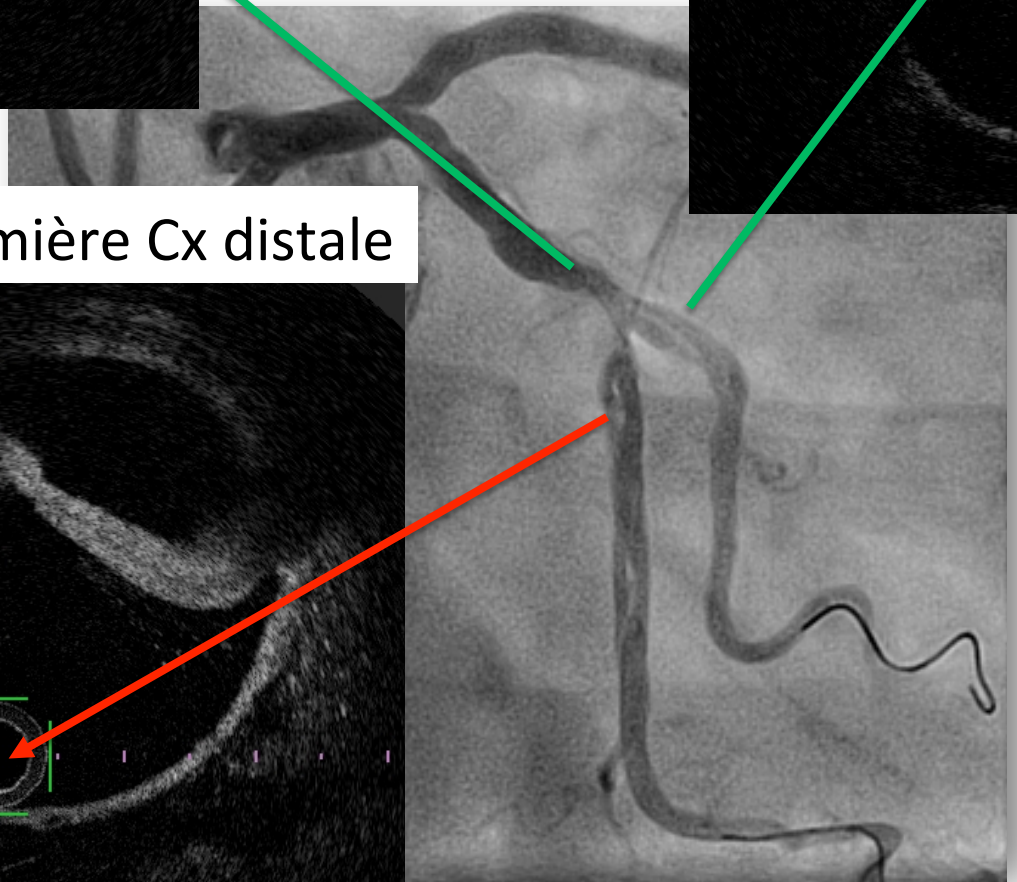
OFDI, Terumo® 20mm/s

Rupture plaque Cx prox

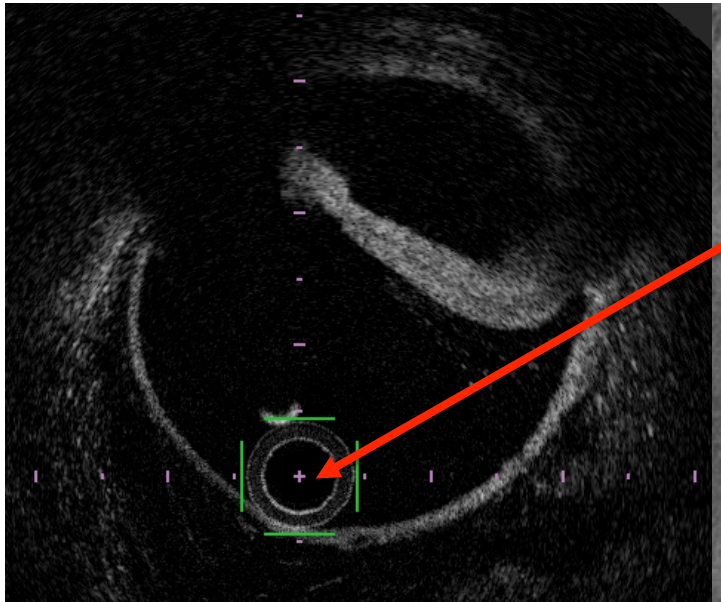


Guide vrai lumière marginale



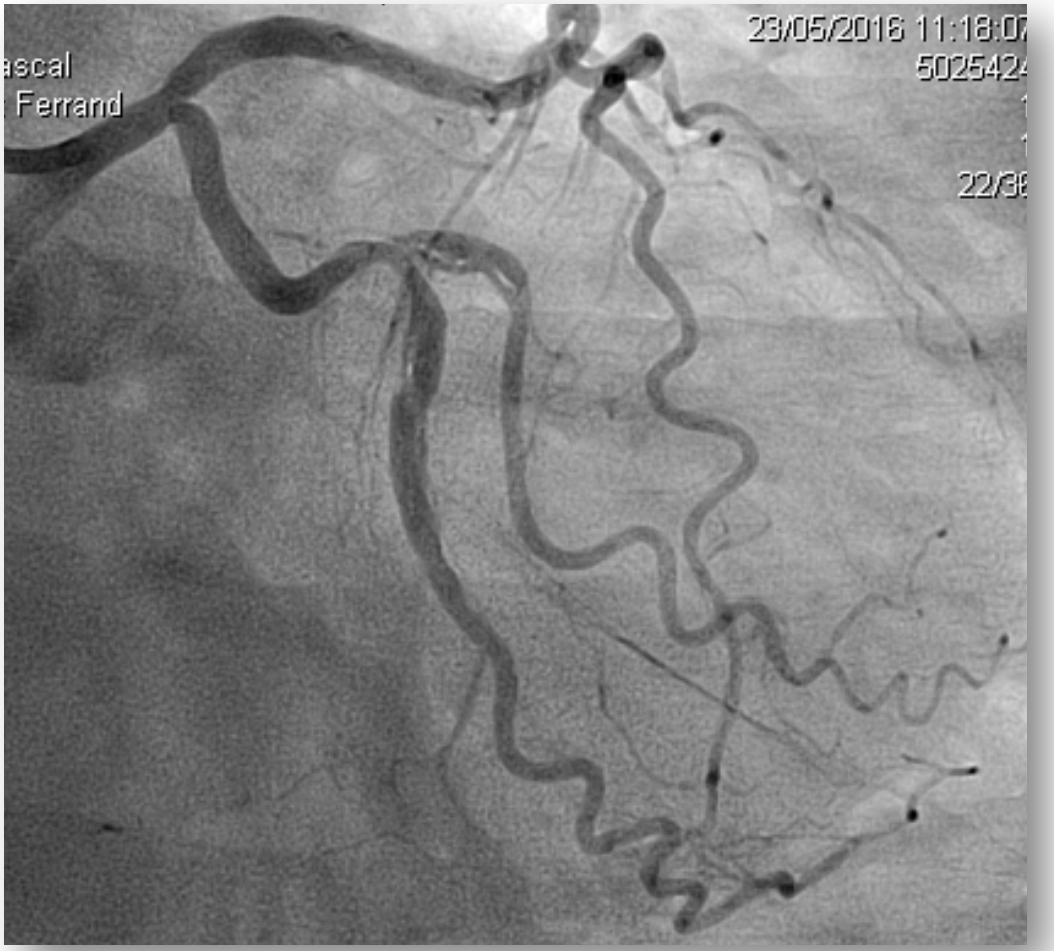


Guide fausse lumière Cx distale

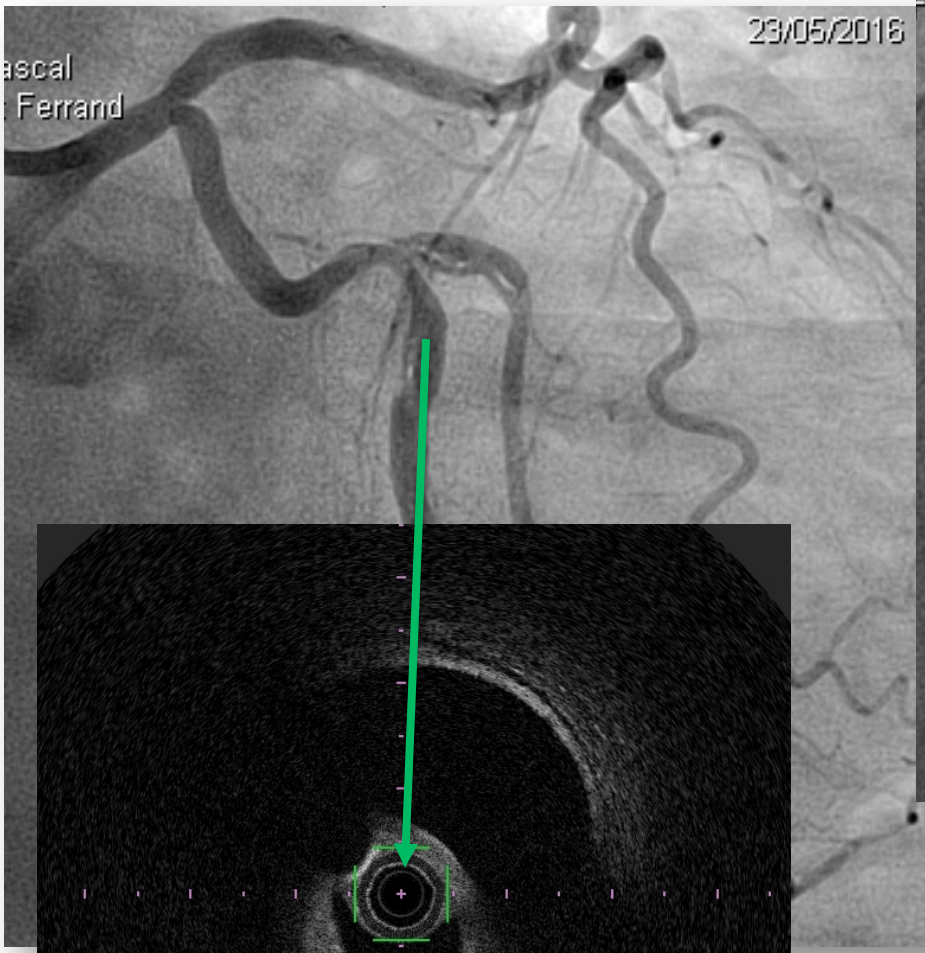


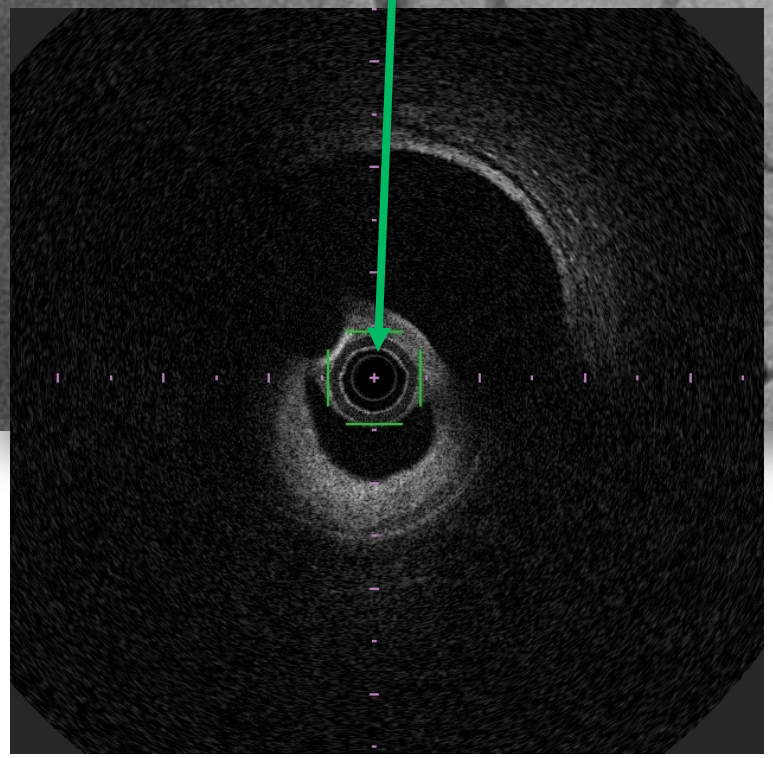
Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

Contrôle 3 semaines plus tard…

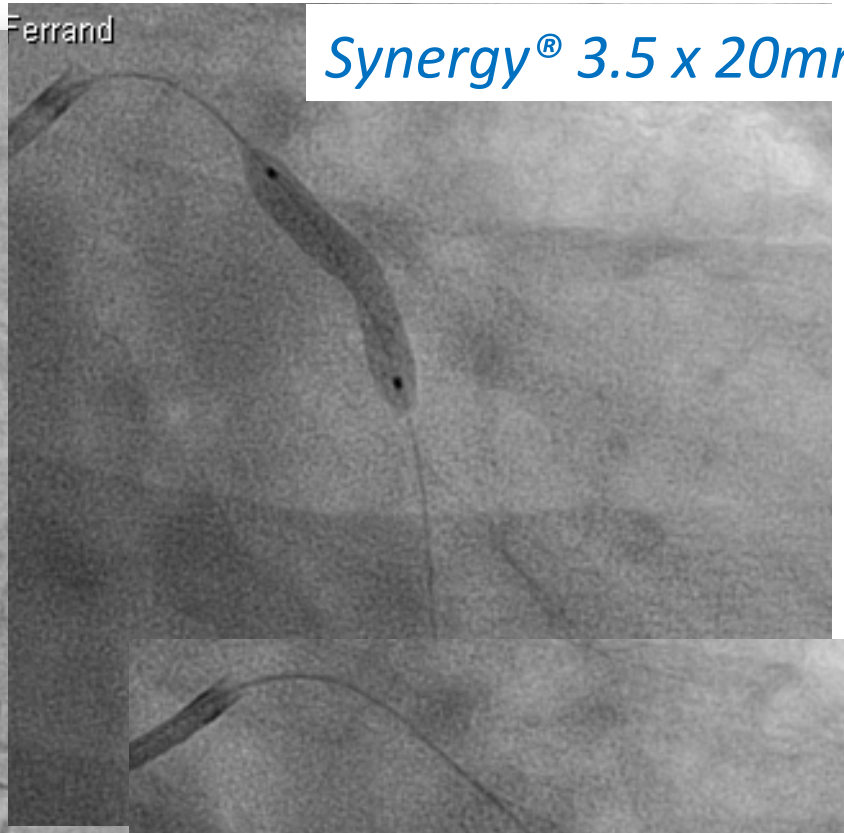


- Franchissement simple au guide
- Imagerie endocoronaire

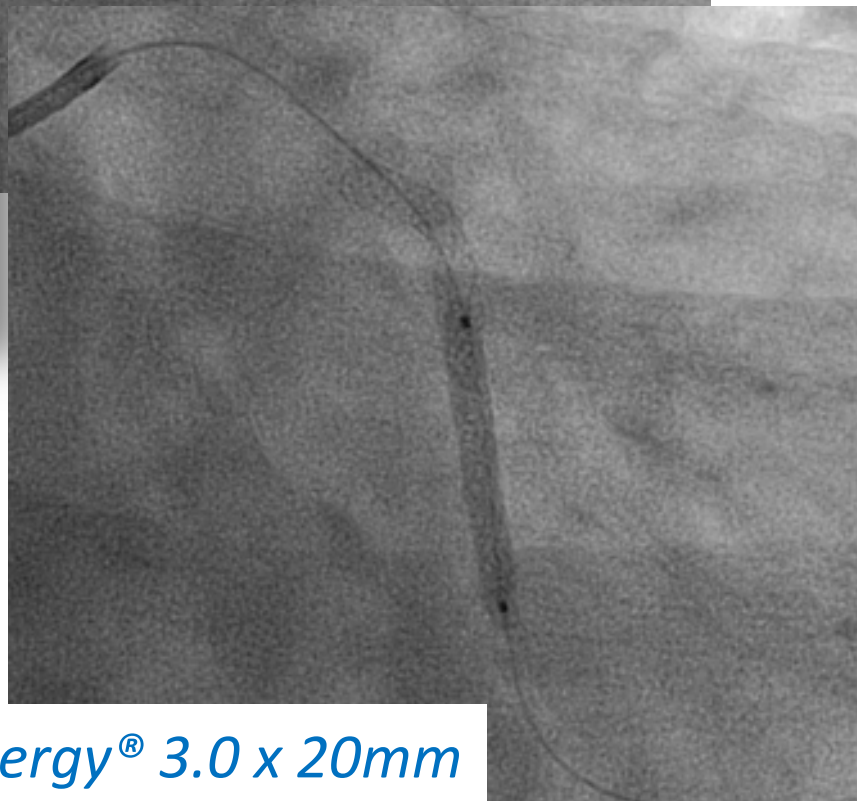




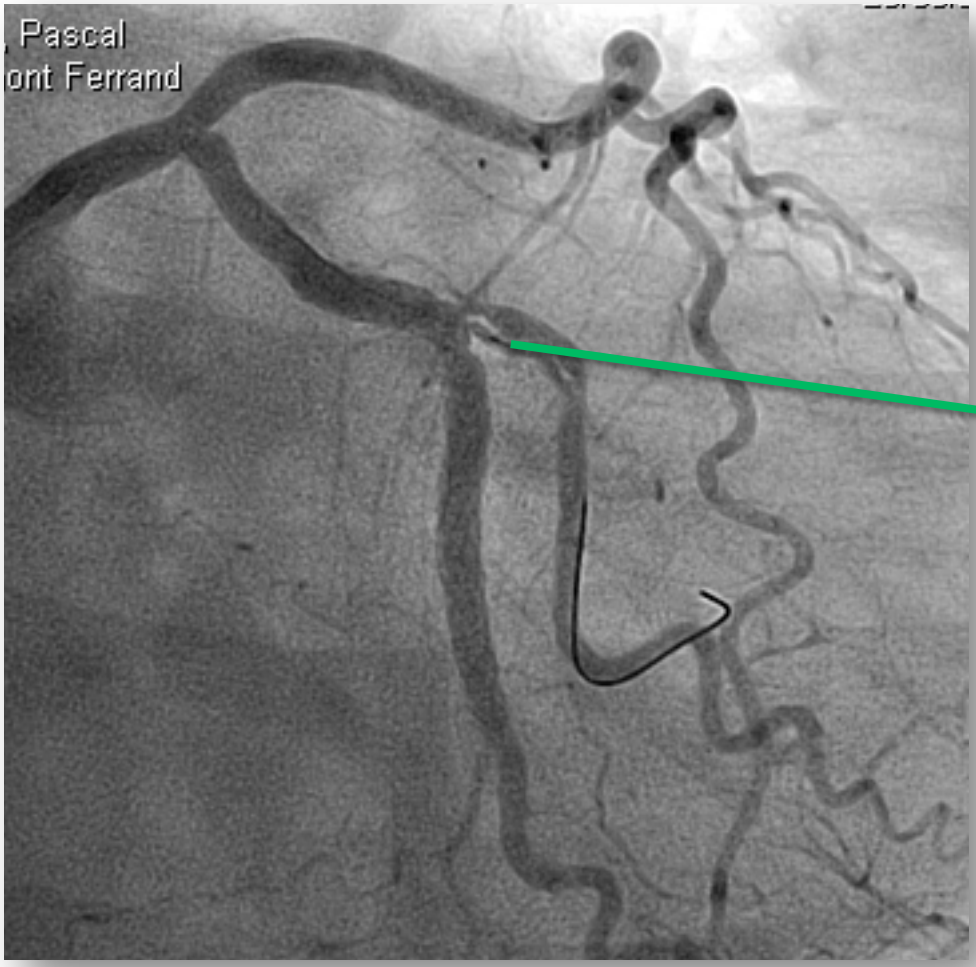
Guide vraie lumière Cx distale



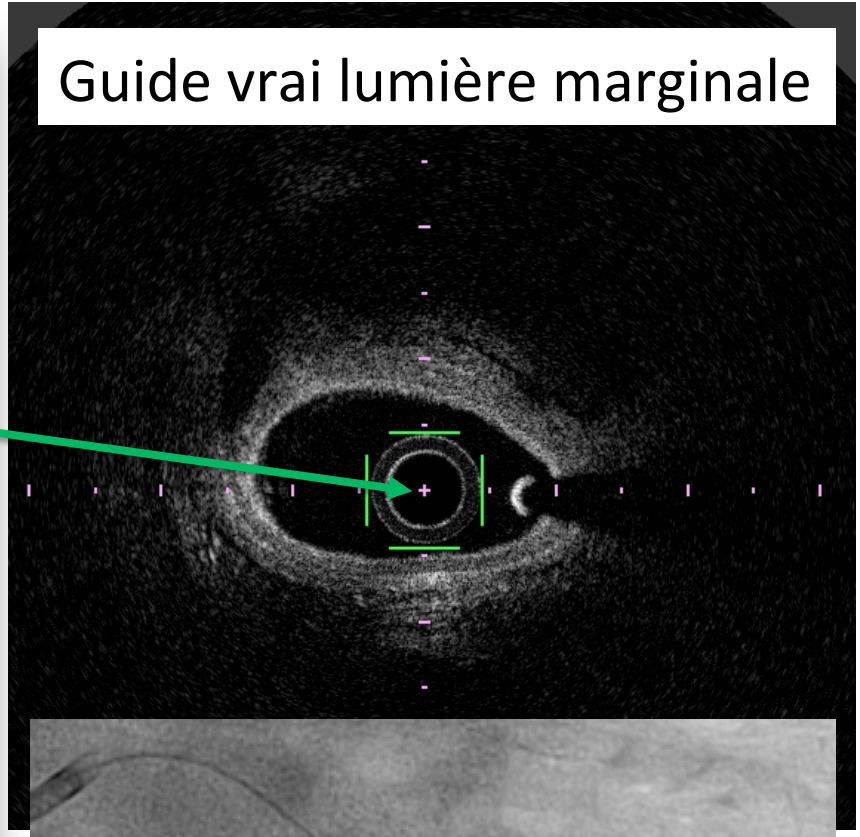
Synergy® 3.5 x 20mm

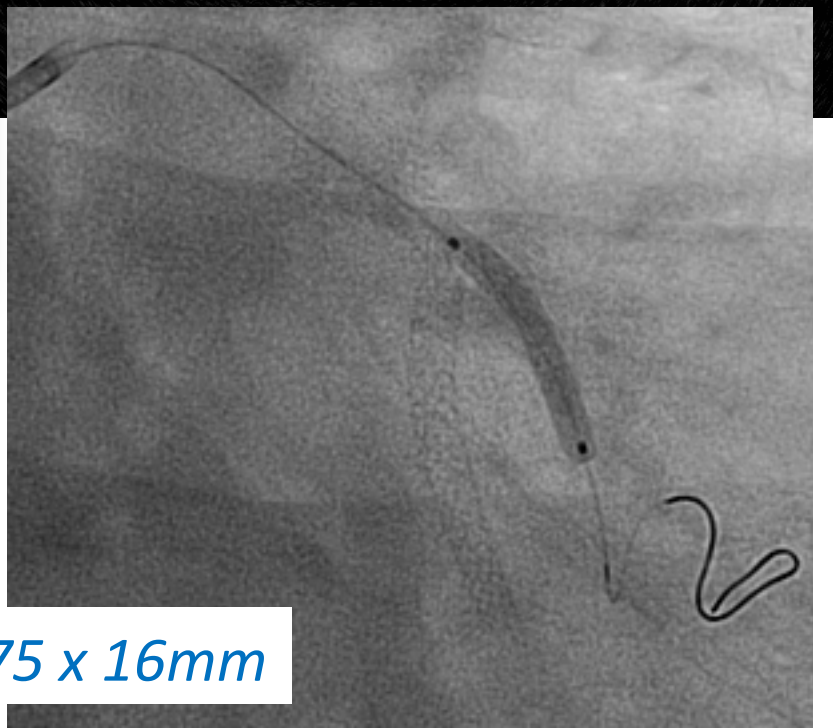


Synergy® 3.0 x 20mm



Guide vrai lumière marginale



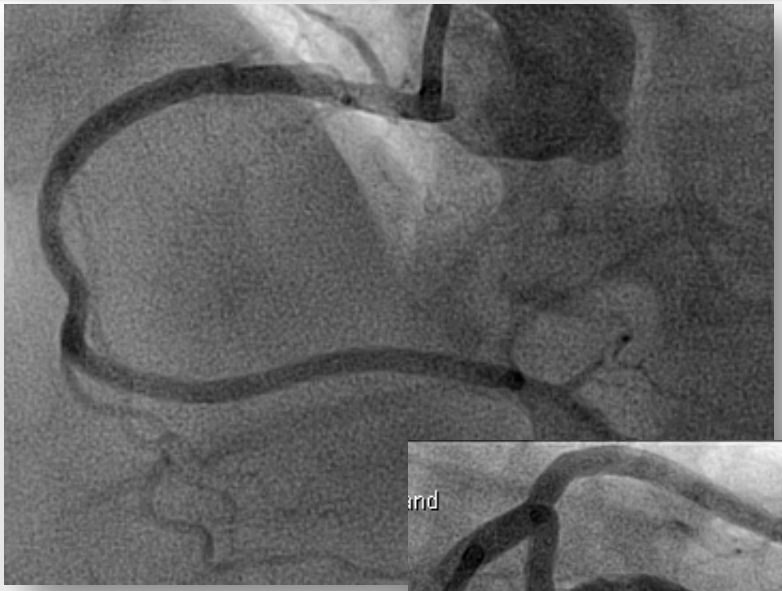


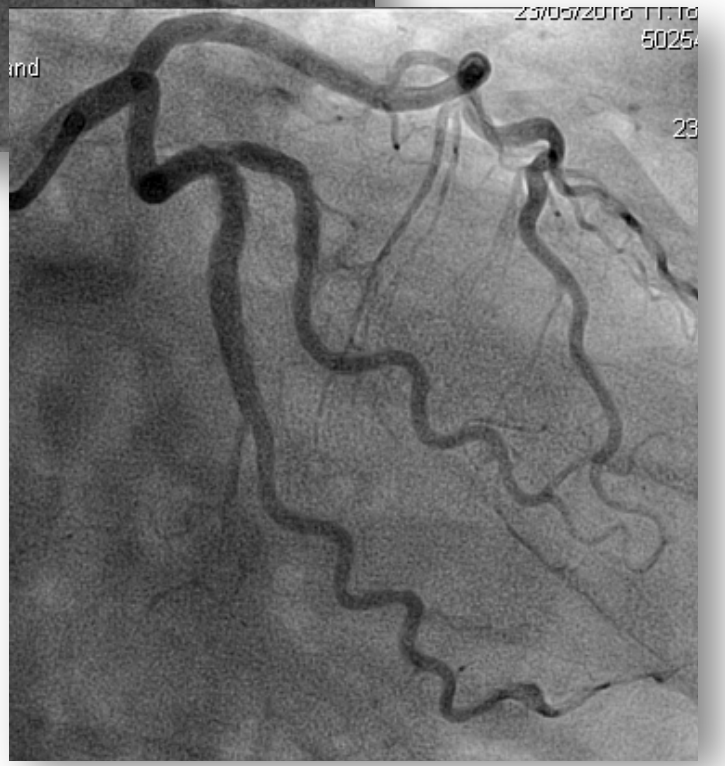
Technique REPOT,
T stenting guidé par OFDI

Synergy® 2,75 x 16mm

Mme D. 60 ans, DNID, SCA ST+ antérieur inaugural

Résultat final, 3 procédures, 5 EES





Conclusion

- **Diabétique = moins bon pronostic**
- Doit profiter des meilleures techniques de revascu.
- Hors SCA ST+, réflexion médico-chirurgicale
- Recommandations, études récentes = **plutôt CABG**
- **<u>Angioplastie avec DES dernière génération</u>** = alternative

pmotreff@chu-clermontferrand.fr