

# **SYNTAX II:**

## **Impact of Physiology and Imaging on PCI Outcome**

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On behalf of the SYNTAX II Investigators

# Components of the SYNTAX II strategy

- Major technical and procedural advances, influencing PCI outcomes, have taken place since the completion of SYNTAX I trial:
  1. New risk stratification tool: SYNTAX Score II (incorporating clinical and anatomical variables) to guide Heart Team decisions on myocardial revascularization.
  2. Physiology-based revascularisation (hybrid use of iFR and FFR).
  3. Second generation DES (thin strut, biodegradable polymer, everolimus-eluting Synergy™ stent [EES]).
  4. IVUS-guided optimisation of stent deployment (modified MUSIC criteria).
  5. Contemporary CTO revascularization techniques.
- Guideline-directed medical therapy (LDL cholesterol  $\leq 1.8$  mmol/L).

# Design and eligibility

- Multicenter, prospective, single-arm, open-label trial of patients with *de-novo* 3VD without left-main stem involvement
- **Inclusion** if the SYNTAX score II (anatomic SYNTAX score, LM, age, CrCl, LVEF, gender, COPD, and PVD) recommends either CABG or PCI (equipoise in 4-year mortality) or PCI, irrespective of anatomic SYNTAX score.
- Sample size: 450 patients (90% power to show superiority in terms of use of 2<sup>nd</sup> generation EES over PES + attrition).

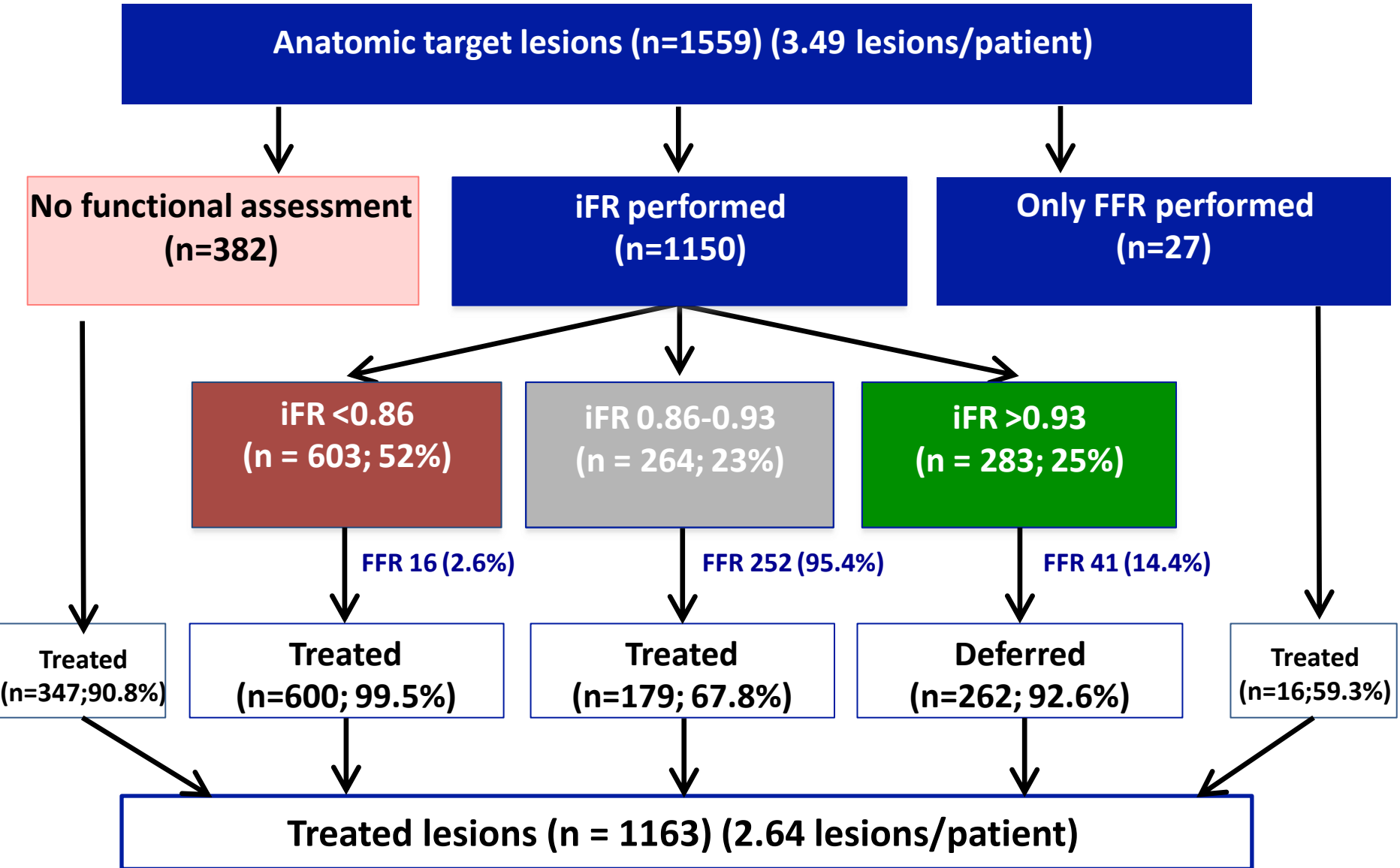
## Primary endpoint: comparison with PCI

- **Primary endpoint:** Composite of major adverse cardiac and cerebrovascular events (MACCE) at two-year follow-up. To allow comparison, MACCE was **adjudicated using SYNTAX I trial definitions**. Of note, periprocedural MI was defined as CK-MB  $\geq 5 \times \text{ULN}$  (Troponin  $\geq 35 \times \text{ULN}$ ) and new pathological Q-waves in the ECG.
- **Comparator:** Predefined PCI cohort (n=315) from the original SYNTAX-I trial selected on the basis of equipoise 4-year mortality between CABG and PCI (matching on identical SYNTAX score II).

## Exploratory endpoint: comparison with CABG

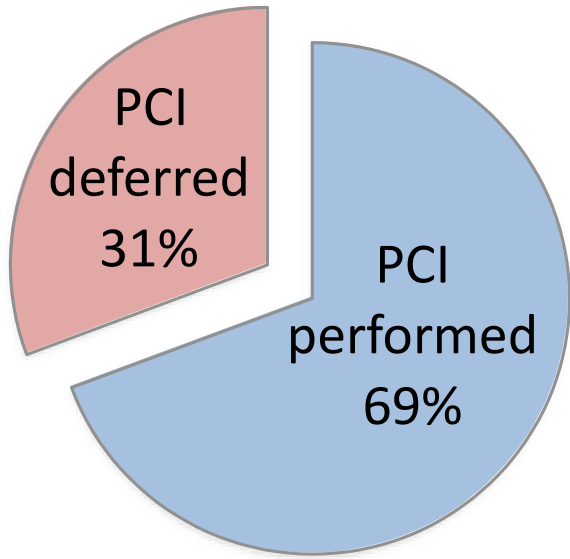
- **Exploratory endpoint:** Composite of major adverse cardiac and cerebrovascular events (MACCE) at two-year follow-up.
- **Comparator:** Predefined CABG cohort (n=334) from the original SYNTAX-I trial selected on the basis of equipoise 4-year mortality between CABG and PCI (matching on identical SYNTAX score II).

# Physiological stenosis interrogation



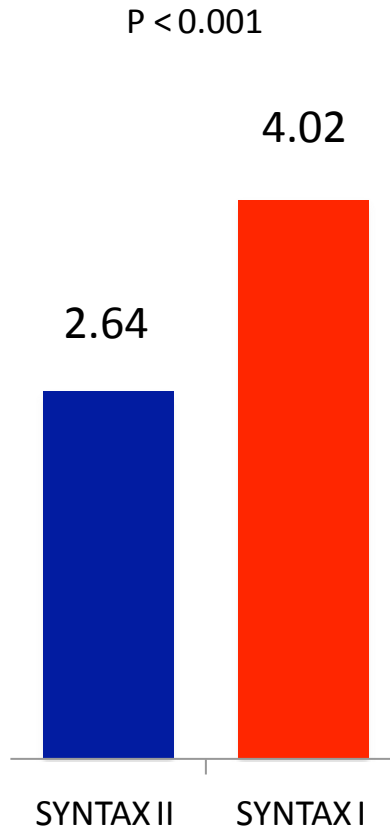
# Impact of intracoronary physiology on PCI

Lesion evaluated by iFR/FFR interrogation (n=1177)

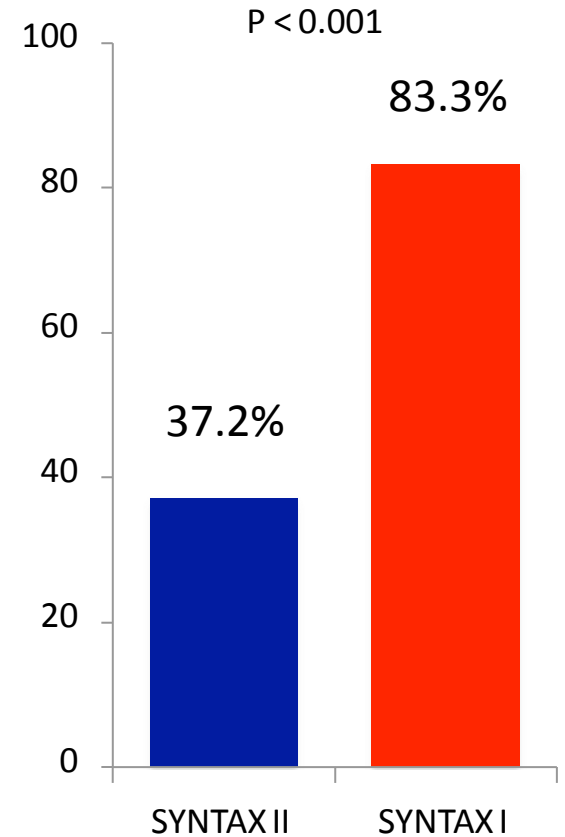


SYNTAX II

Lesions treated per patient (n) in SYNTAX II and SYNTAX I

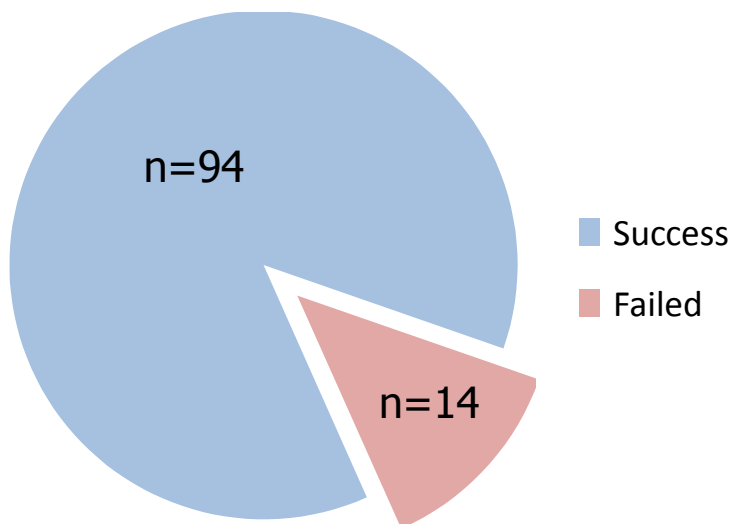


Cases of three-vessel PCI (%) in SYNTAX II and SYNTAX I



# Treatment of chronic total occlusions (CTO)

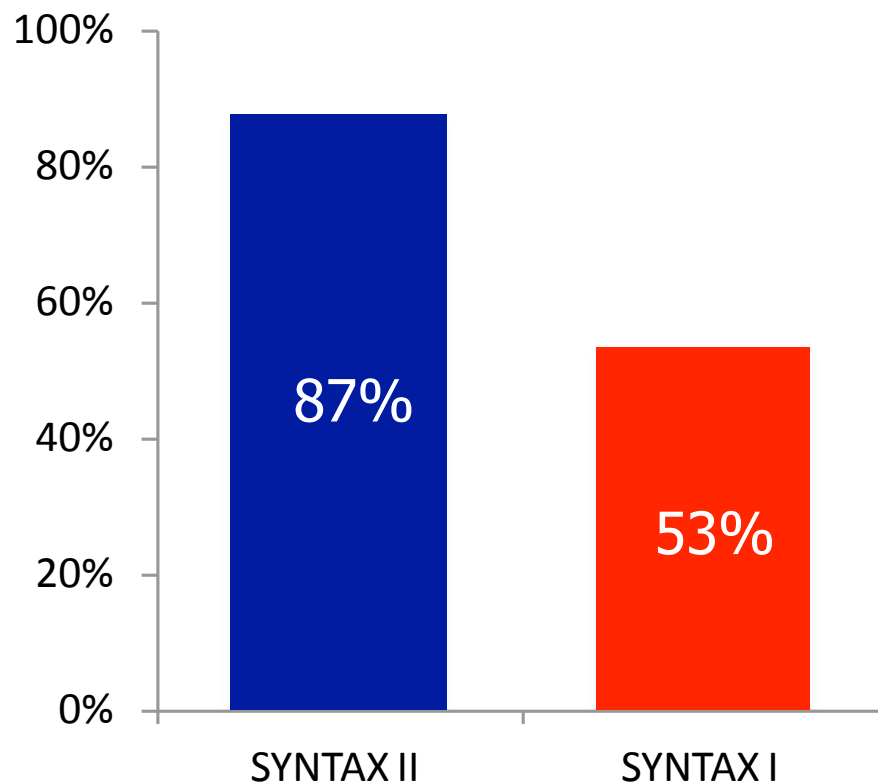
CTO PCI procedural success rate in SYNTAX II: **87%** (n = 108)



SYNTAX II CTO PCI

CTO revascularisation in SYNTAX II and SYNTAX I

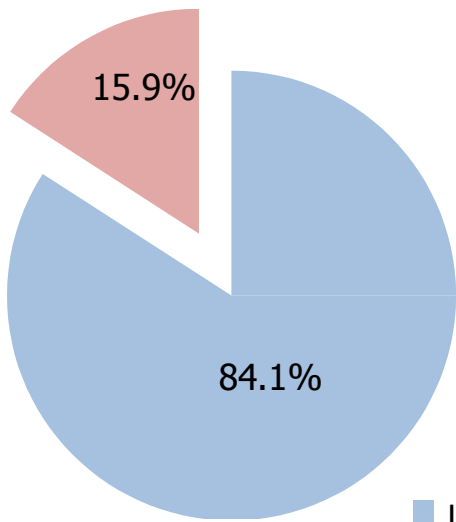
p<0.0001



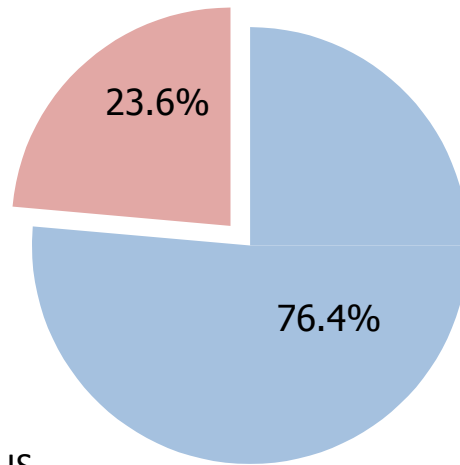
# Use of intravascular ultrasound (IVUS)

SYNTAX II

Patient level

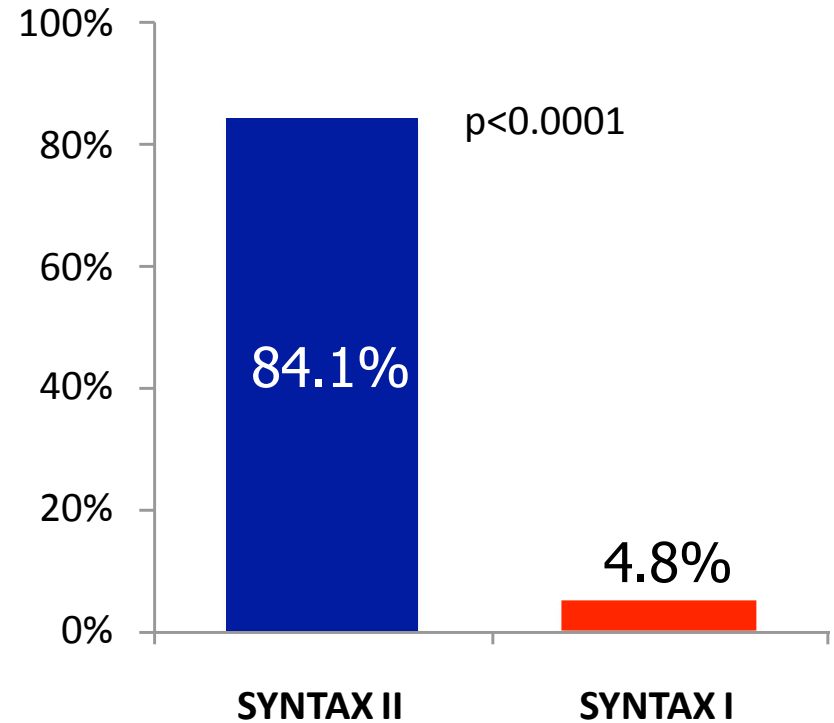


Lesion level



■ IVUS  
■ no IVUS

IVUS use in SYNTAX II and SYNTAX I (patient level, % of cases)



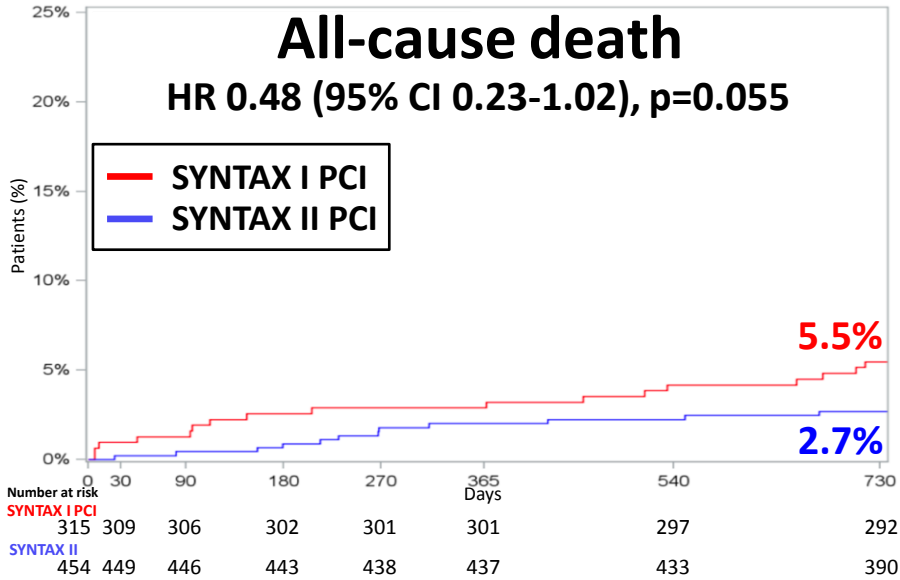
Post-implantation IVUS led to further optimisation of the stented lesion in 30.2%.



# Components of MACCE

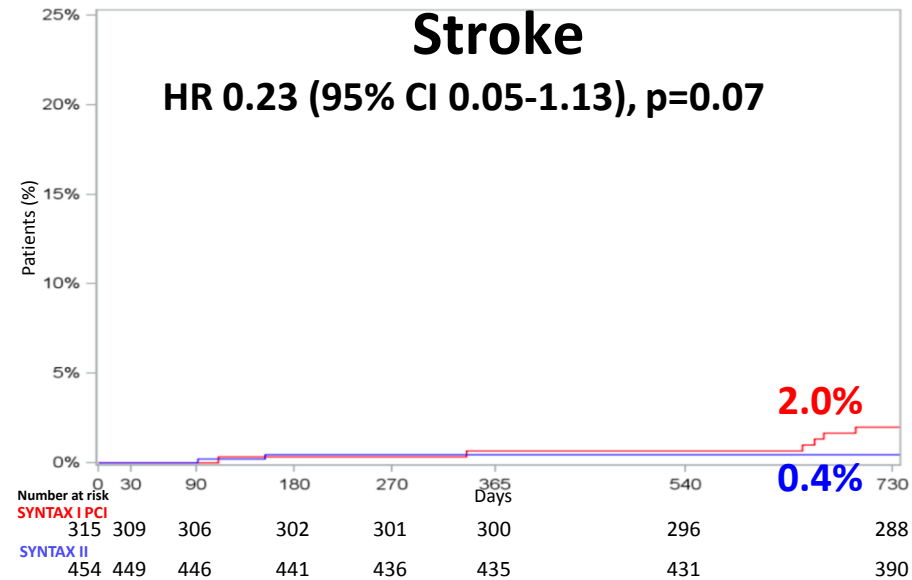
## All-cause death

HR 0.48 (95% CI 0.23-1.02), p=0.055



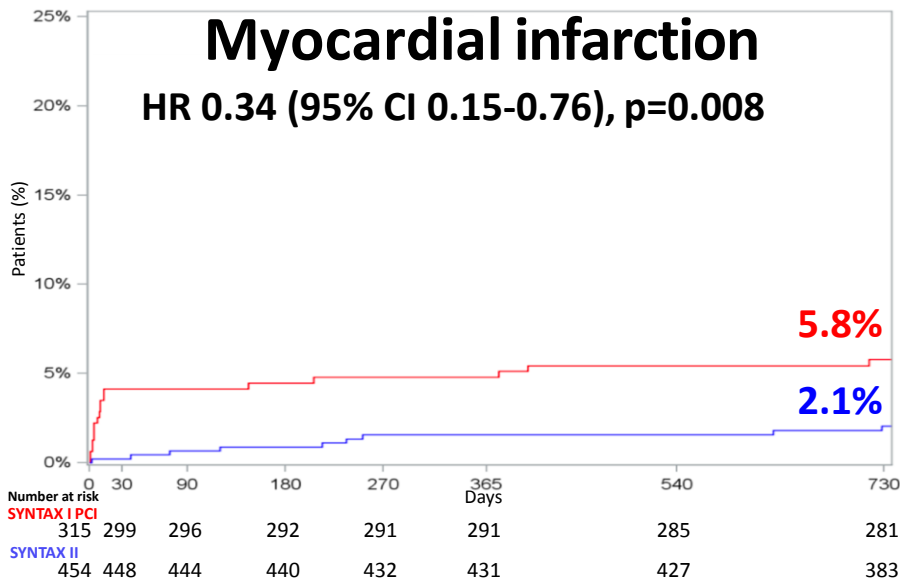
## Stroke

HR 0.23 (95% CI 0.05-1.13), p=0.07



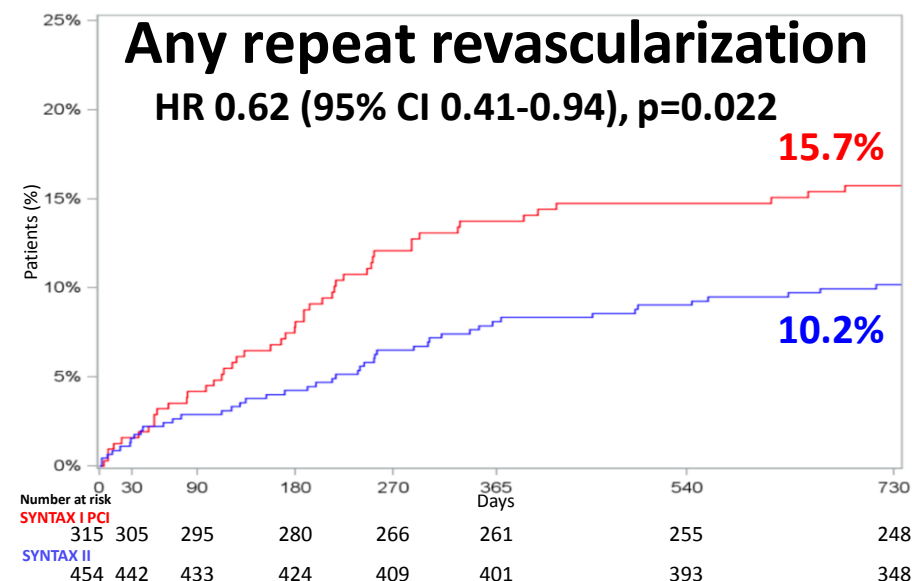
## Myocardial infarction

HR 0.34 (95% CI 0.15-0.76), p=0.008

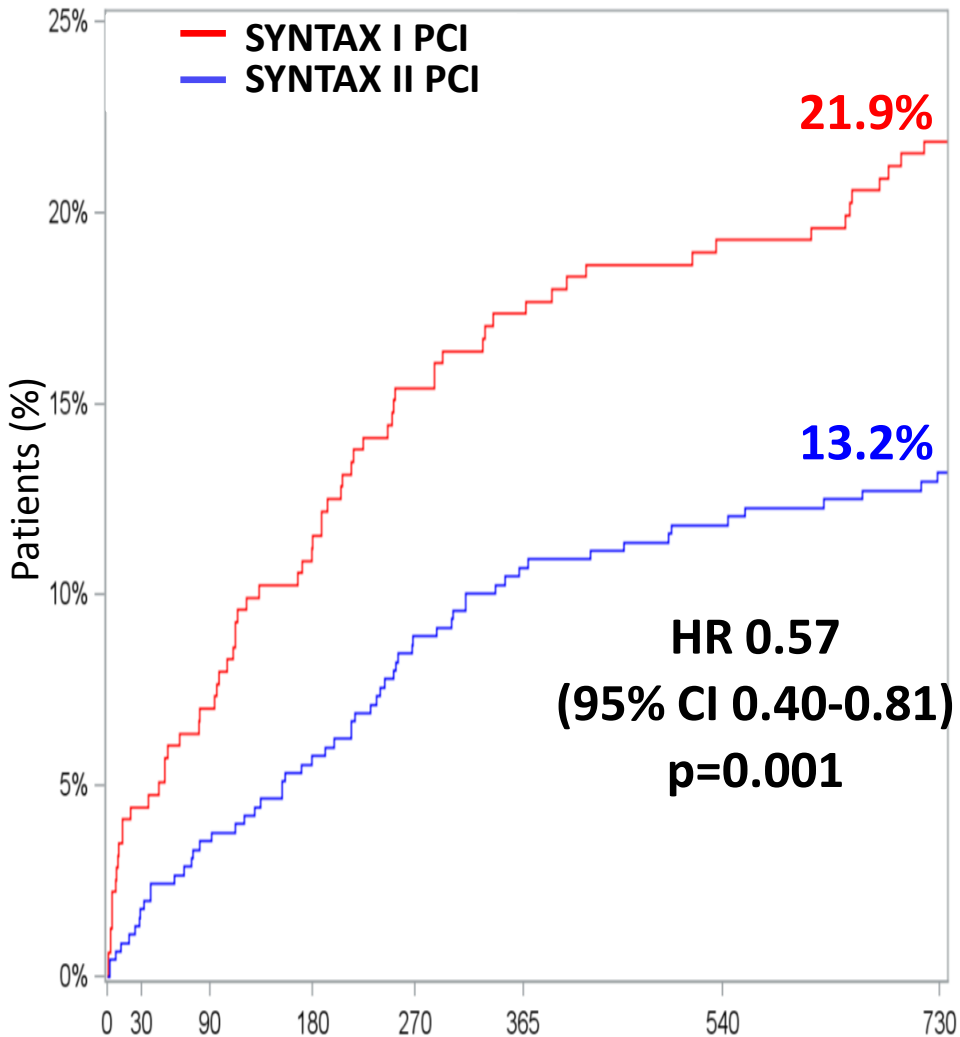


## Any repeat revascularization

HR 0.62 (95% CI 0.41-0.94), p=0.022

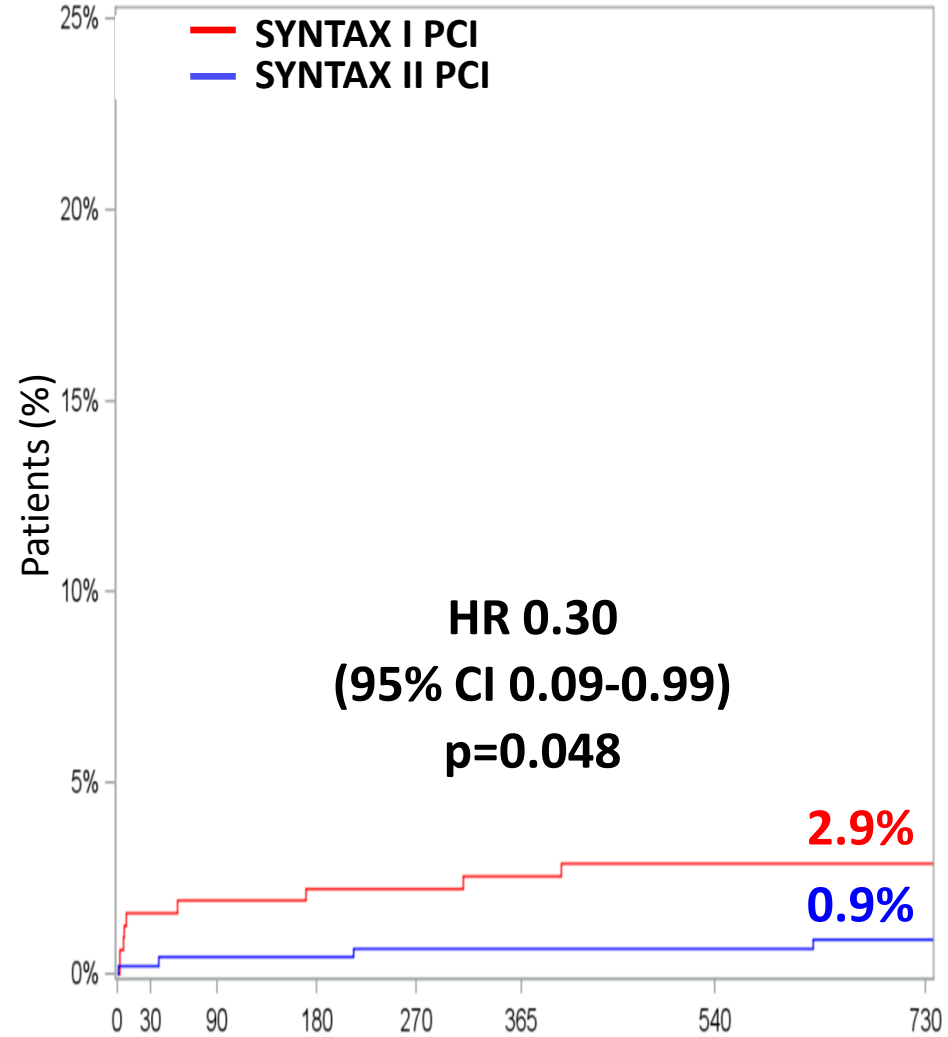


# 2Y MACCE



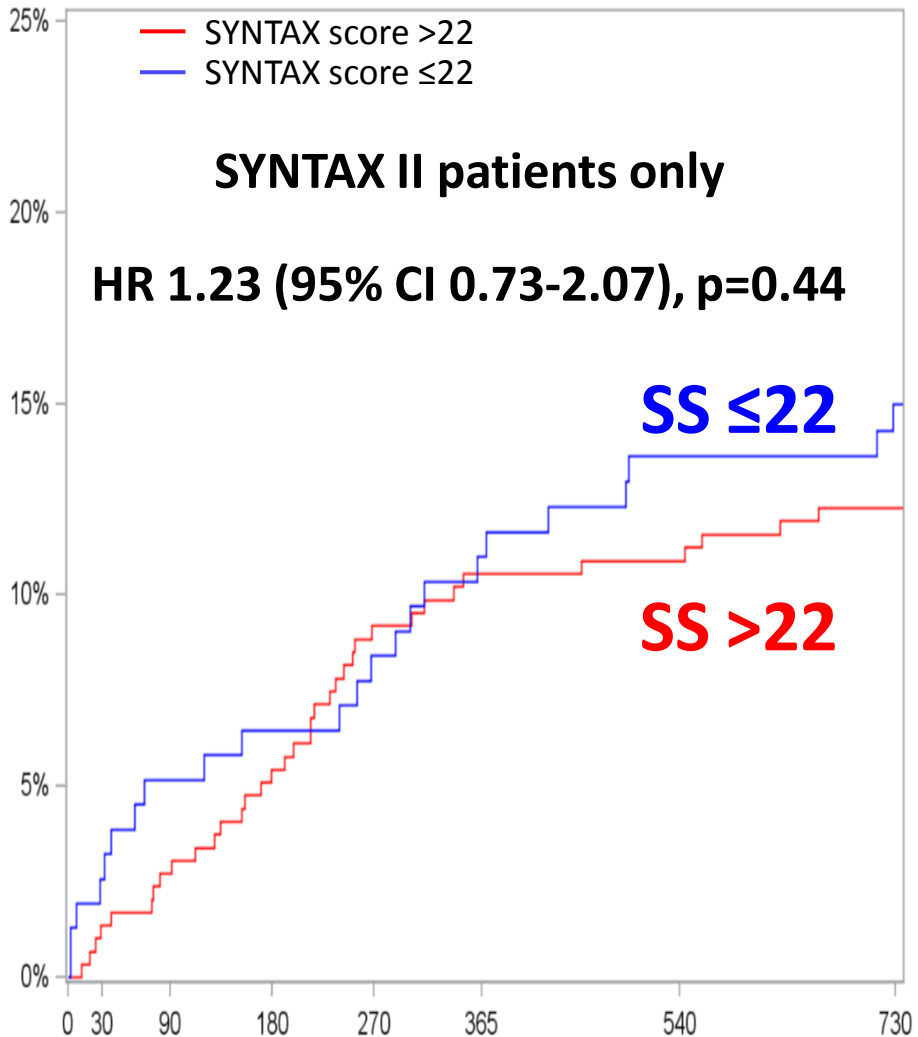
Number at risk	0	30	90	180	270	365	540	730
<b>SYNTAX I PCI</b>	315	275	256	250	242			
<b>SYNTAX II PCI</b>	454	422	399	391	347			

# Definite ST



Number at risk	0	30	90	180	270	365	540	730
<b>SYNTAX I PCI</b>	315	296	294	289	285			
<b>SYNTAX II PCI</b>	454	441	434	430	386			

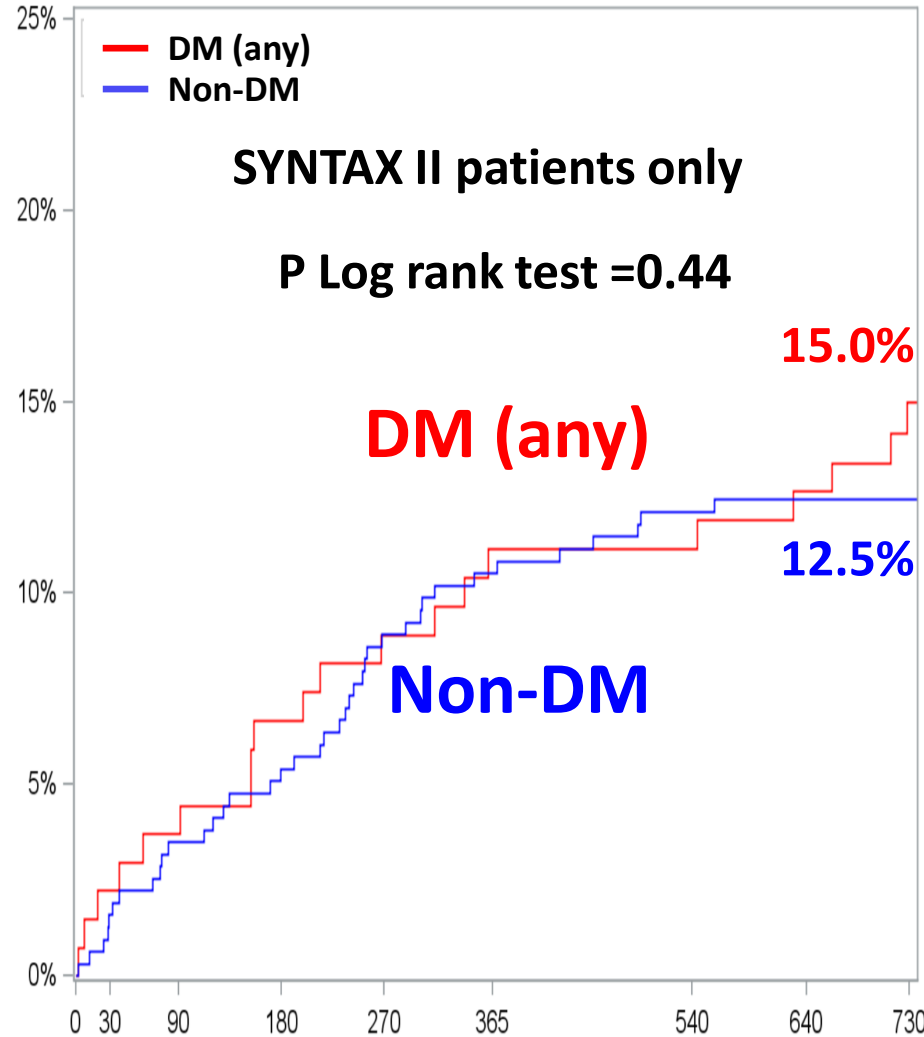
# MACCE in SS I $\leq 22$ and $>22$



Number at risk

<b>SYNTAX score <math>&gt;22</math></b>					
156	144	137	132	118	
<b>SYNTAX score <math>\leq 22</math></b>					
298	278	262	259	229	

# MACCE in DM and non-DM



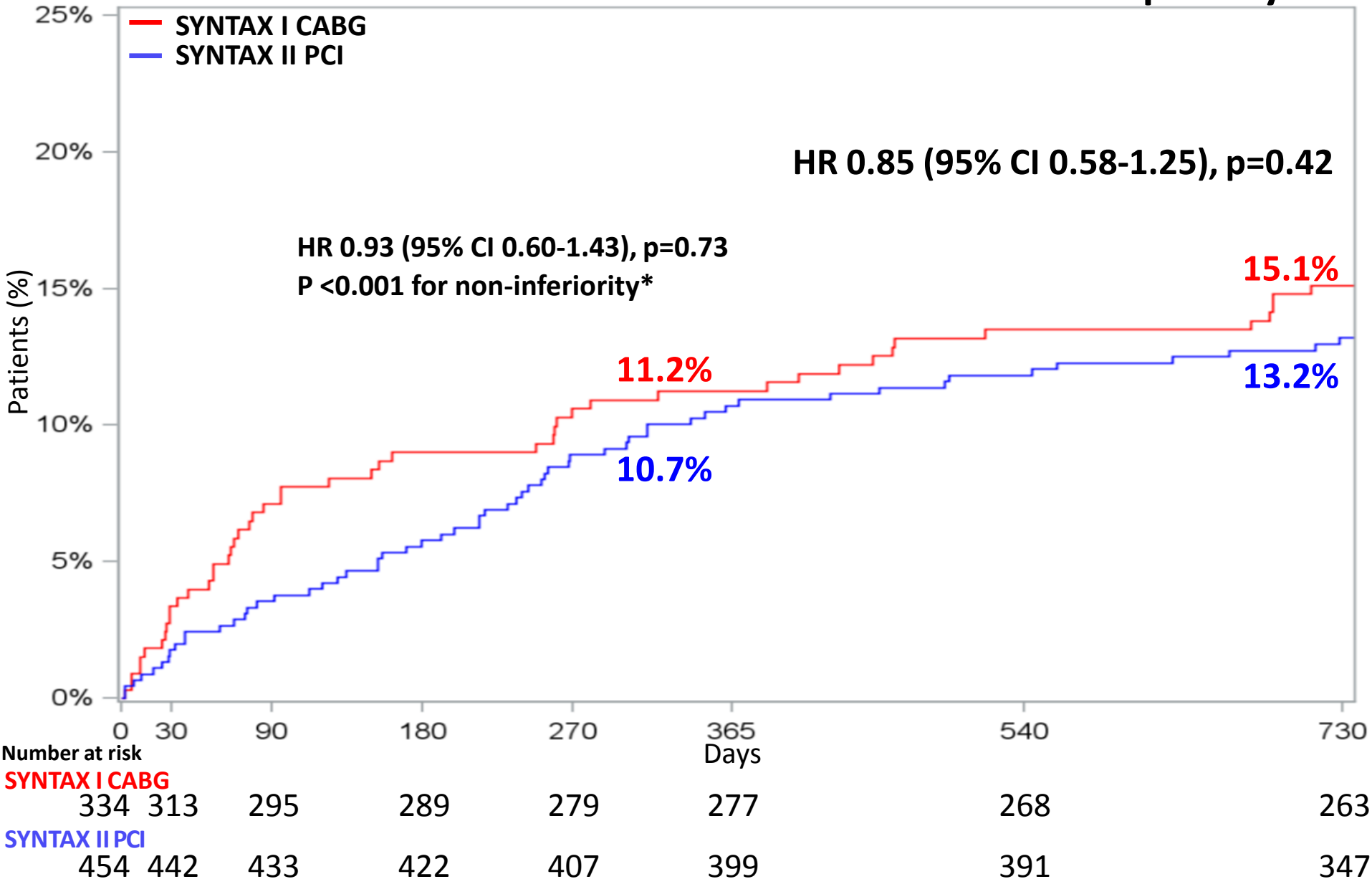
Number at risk

<b>DM (any)</b>					
135	126	119	118	99	
<b>Non-DM</b>					
319	296	280	273	248	



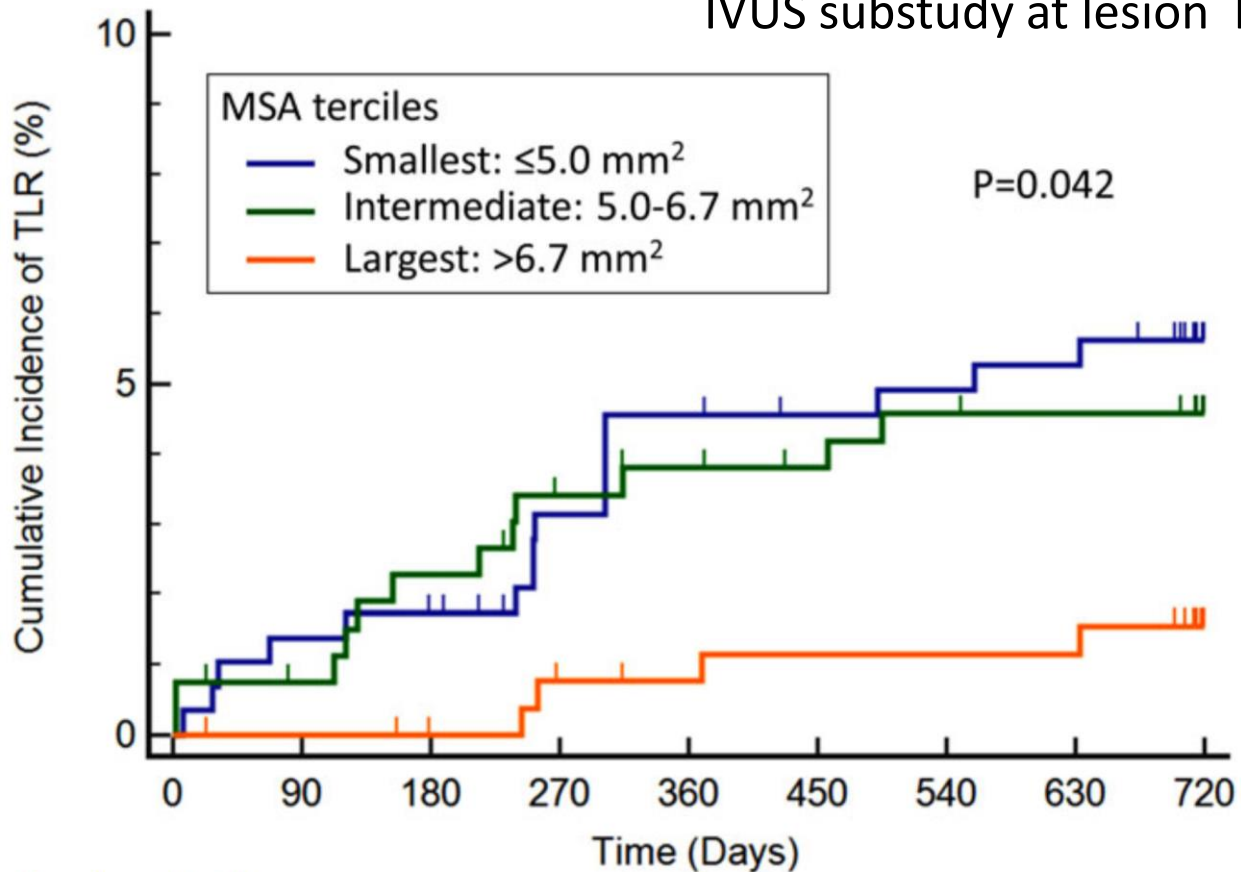
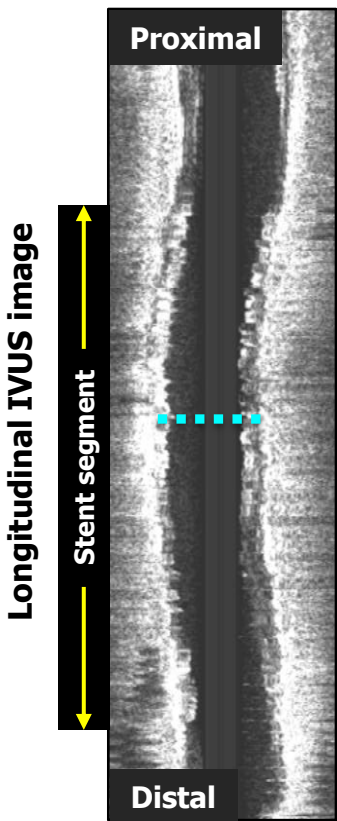
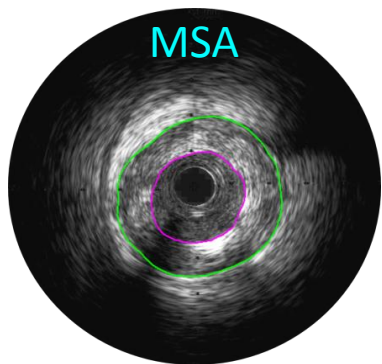
# Exploratory End-Point: MACCE PCI vs. CABG

up to 2 years



# 2-Y TLR stratified by MSA tercile

IVUS substudy at lesion level



Number at risk

Smallest MSA tercile:  $\leq 5.0 \text{ mm}^2$

288	284	282	275	271	268	267	266	246
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Intermediate MSA tercile:  $5.0-6.7 \text{ mm}^2$

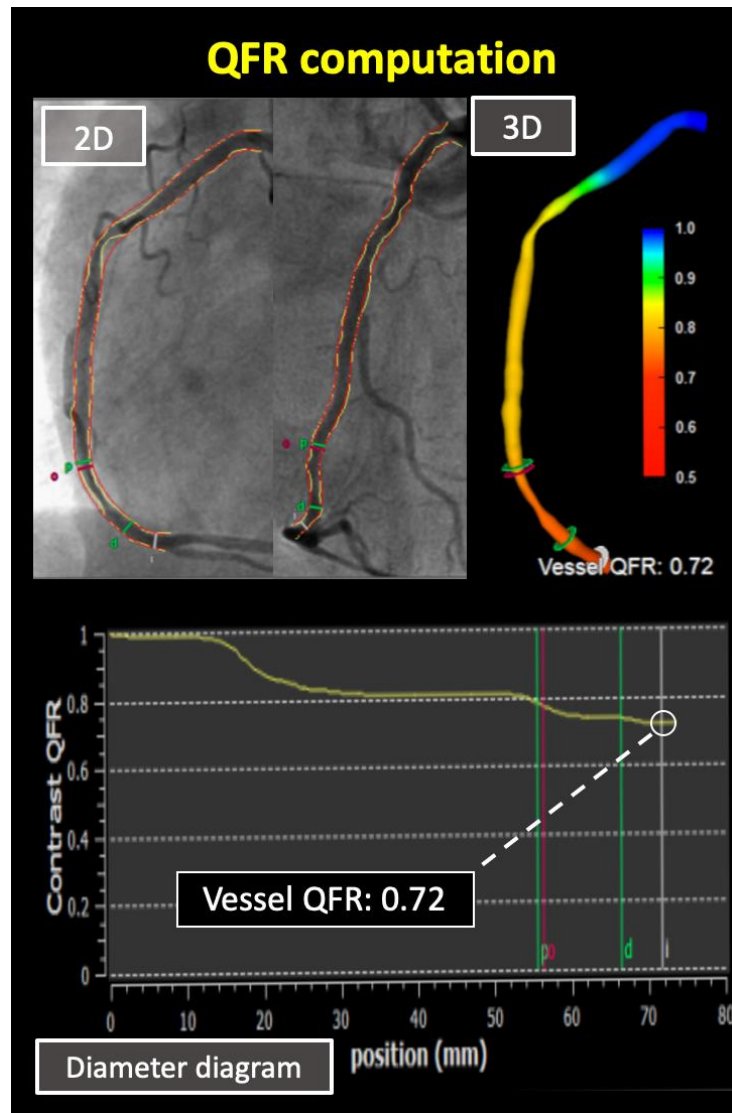
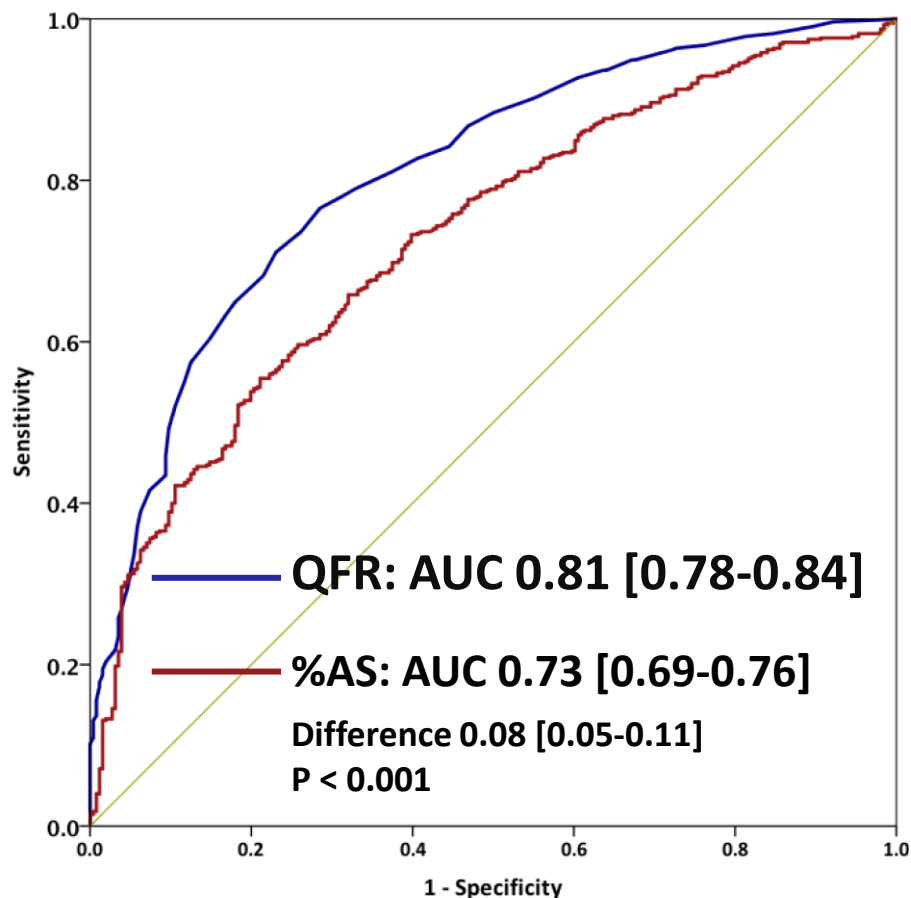
265	261	257	251	249	247	245	242	237
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Largest MSA tercile:  $>6.7 \text{ mm}^2$

266	264	261	257	255	254	254	254	241
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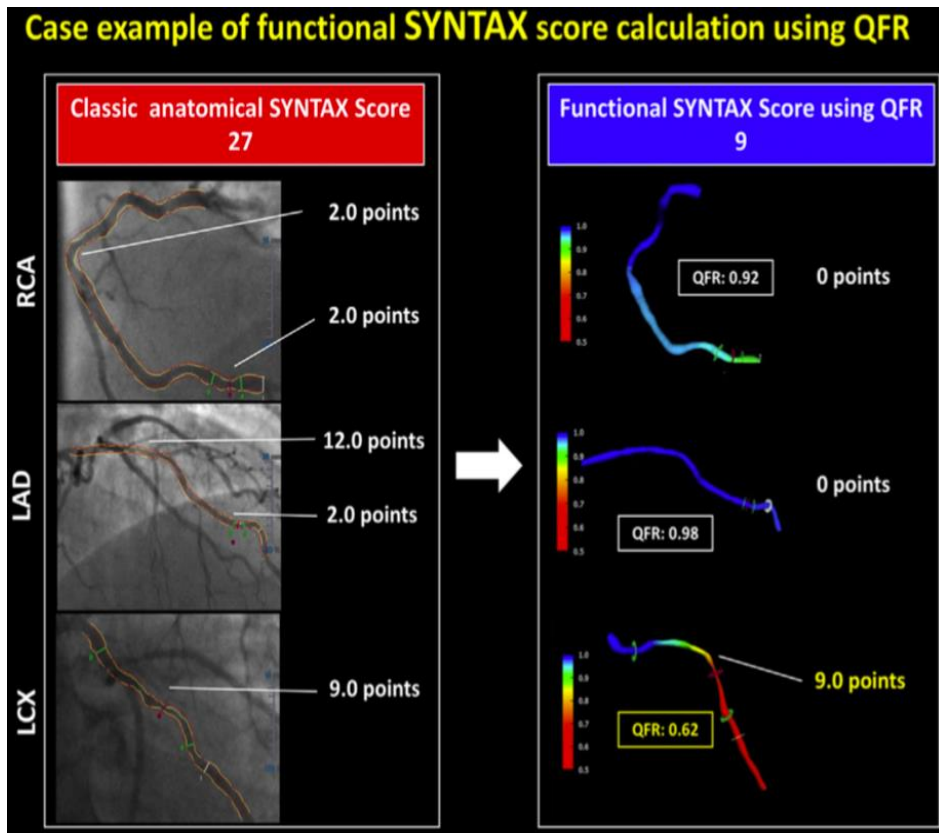
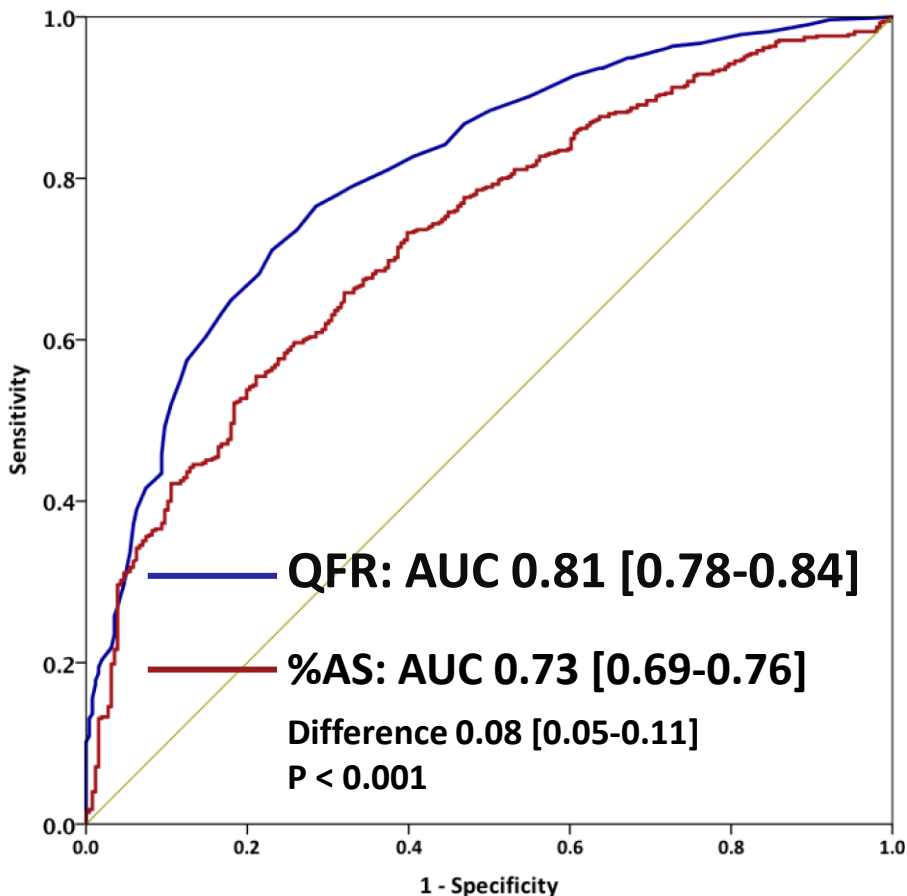
# Diagnostic performance of QFR for predicting physiologically significant ischemia identified with hybrid iFR/FFR

836 lesions were analyzable for QFR (71.0%)



# Diagnostic performance of QFR for predicting physiologically significant ischemia identified with hybrid iFR/FFR

836 lesions were analyzable for QFR (71.0%)



# Conclusions

- Compared to SYNTAX I, **physiology guidance** led to significantly fewer lesions treated with PCI.
- In patients with 3VD the use of the **SYNTAX-II strategy** was associated with improved clinical outcomes at two years, compared to matched patients treated percutaneously in the original SYNTAX-I trial.
- The two-year exploratory comparison between SYNTAX II and matched CABG patients from the original SYNTAX-I trial suggests equivalent outcome of PCI with CABG when the **SYNTAX-II strategy** is followed.
- Two-year outcomes of patients with SYNTAX score >22, treated with PCI using the SYNTAX score II risk stratification, were similar to those observed in patients with low anatomical risk (SYNTAX score ≤22).
- Larger **MSA measured by IVUS** was associated with the lower rate of 2Y-TLR.
- **QFR** demonstrated a substantial diagnostic performance with high positive predictive value and may be used as a surrogate of iFR in the future trial in patients with 3VD.



*Thank you for your attention!*



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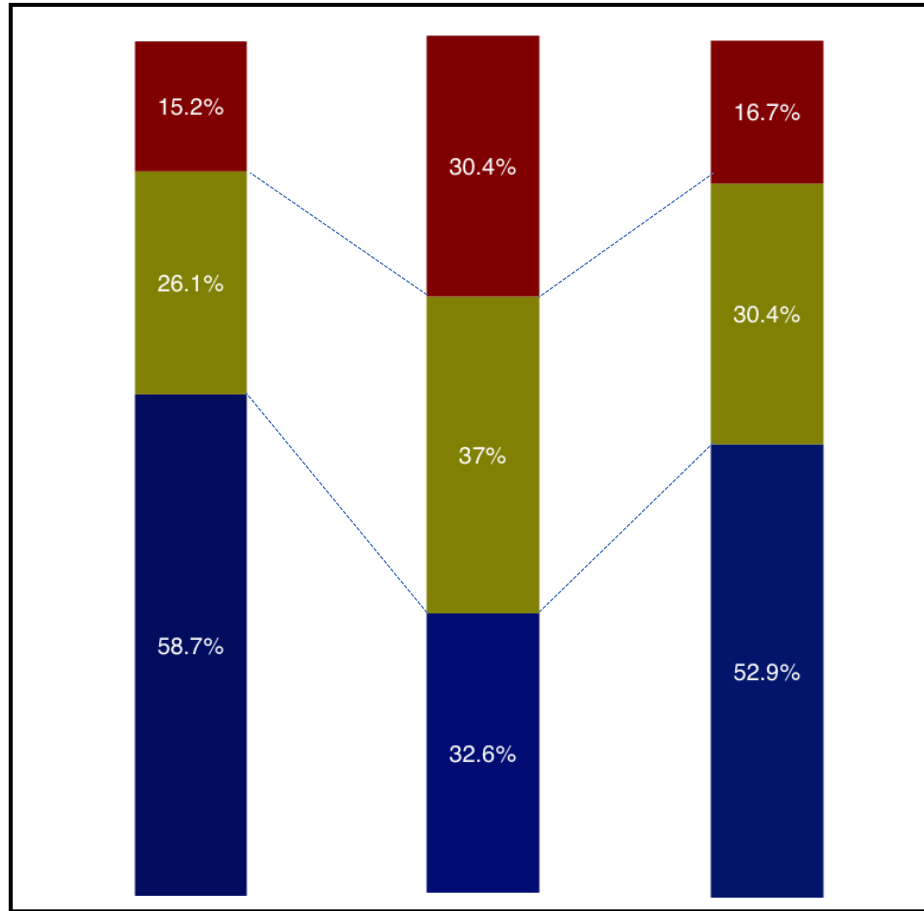
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Back up slides

# Reclassification of functional SYNTAX score derived from QFR and iFR/FFR (N=138)



Functional SYNTAX score  
QFR  
14.8±7.0

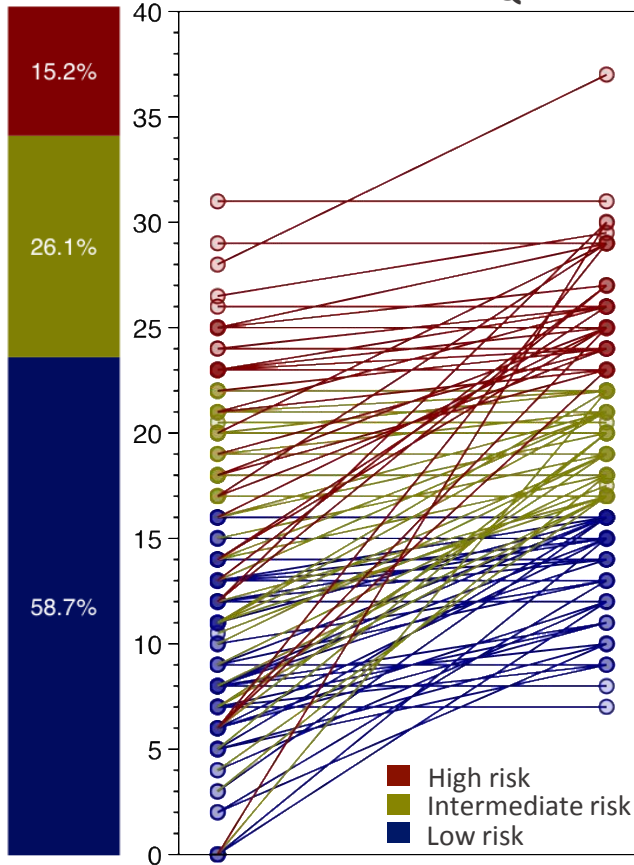
Anatomic SYNTAX score  
N=138  
19.5±5.6

Functional SYNTAX score  
iFR/FFR  
16.0±6.5

- High risk
- Intermediate risk
- Low risk

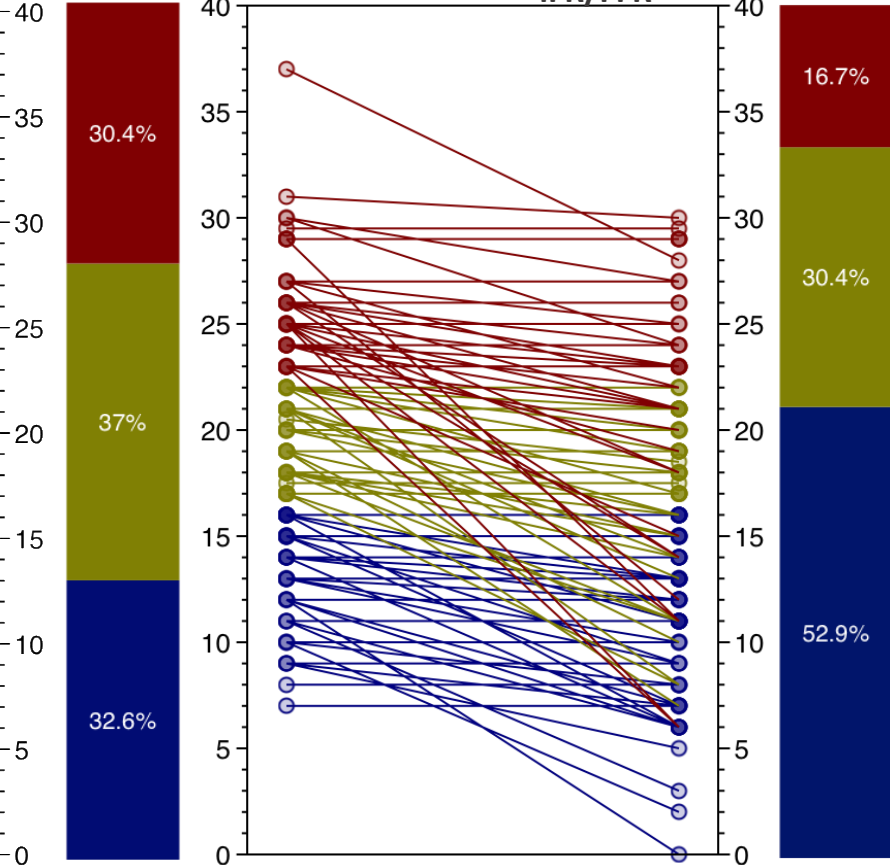
# Reclassification of functional SYNTAX score derived from QFR and iFR/FFR (N=138)

Reclassification  
aSS to fSS<sub>QFR</sub>



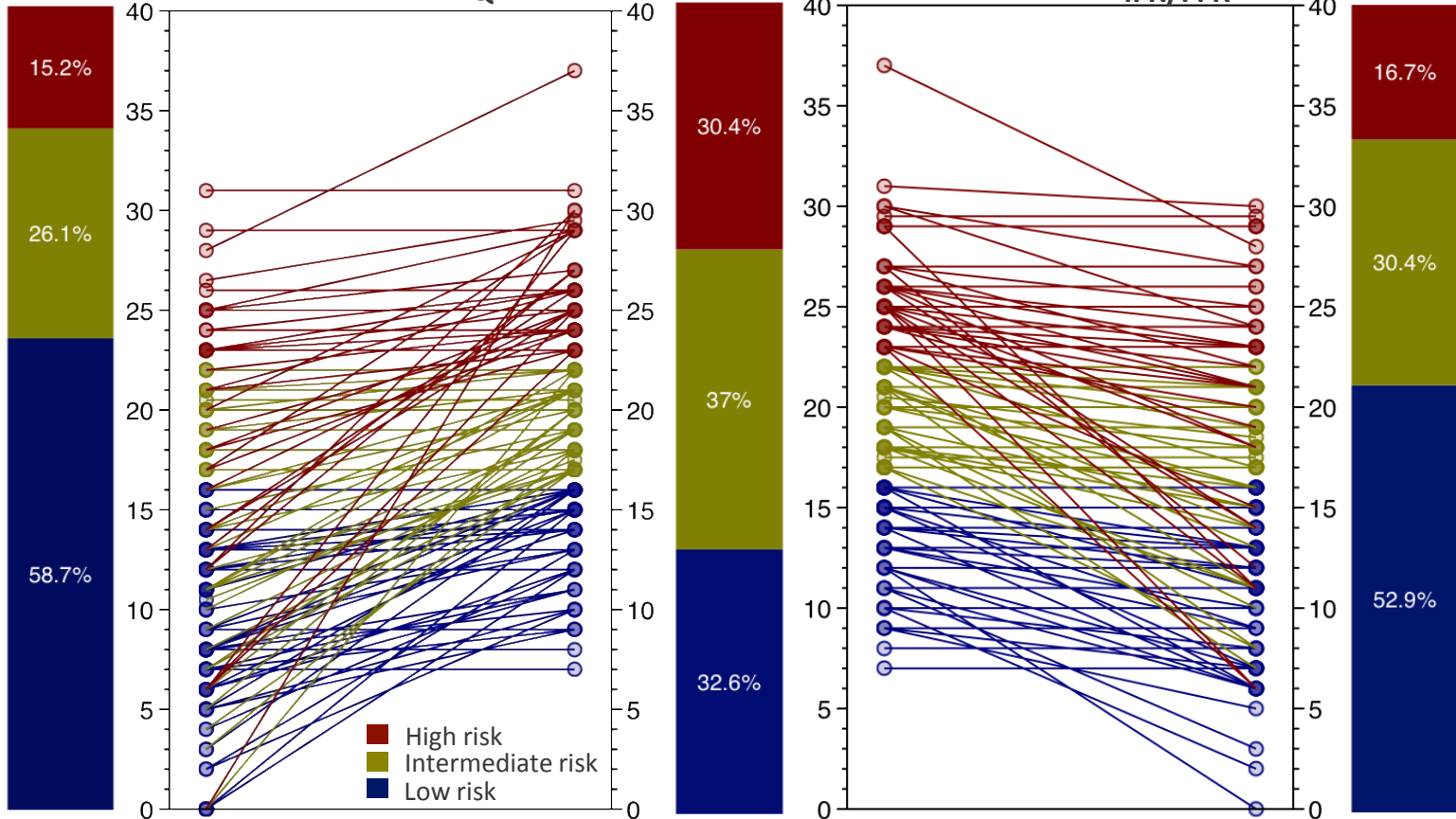
Functional SYNTAX score  
**QFR**  
 14.8±7.0

Reclassification  
aSS to fSS<sub>iFR/FFR</sub>



Anatomic SYNTAX score  
 N=138  
 19.5±5.6

Functional SYNTAX score  
**iFR/FFR**  
 16.0±6.5



# Reclassification table of functional SYNTAX score derived from QFR and iFR/FFR (N=138)

Reference event: 2-year MACE

			Functional SYNTAX Score derived from QFR			
			<17	17-22	>22	%Reclassified
Anatomic SYNTAX Score	<17	Event	6	0	0	0
		non-Event	39	0	0	0
	17-22	Event	1	4	0	20
		non-Event	25	21	0	54
	>22	Event	0	0	1	0
		non-Event	10	11	20	51

**NRI**  
0.28 [0.10 to 0.46]  
P = 0.002

			Functional SYNTAX Score derived from iFR/FFR			
			<17	17-22	>22	%Reclassified
Anatomic SYNTAX Score	<17	Event	6	0	0	0
		non-Event	39	0	0	0
	17-22	Event	1	4	0	20
		non-Event	19	27	0	41
	>22	Event	0	0	1	67
		non-Event	8	11	22	46

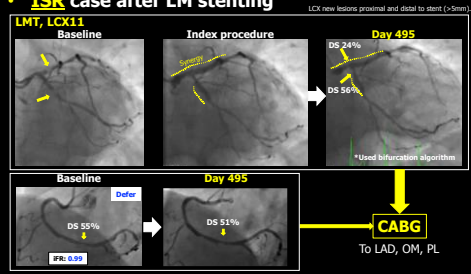
**NRI**  
0.22 [0.05 to 0.39]  
P = 0.014

**Functional SYNTAX score derived from QFR yielded significantly improved risk classification compared to anatomic SYNTAX Score.**

# Conclusions

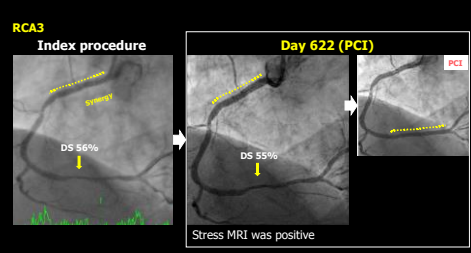
- ❖ QFR demonstrated a substantial diagnostic performance with high positive predictive value whereas low negative predictive value was observed especially in the lesions in a small vessel (RVD  $\leq 2.25$  mm) and bifurcation/trifurcation.
- ❖ The functional SYNTAX score derived from QFR has a potential to offer a discriminative decision-making tool taking into account of coronary physiology as well as functional SYNTAX score derived from a pressure wire.

Triggered by investigator  
Confirmed by CEC as **TLR (ISR)** by **CABG**

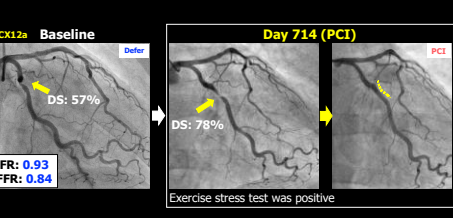


# All revascularization from 1 year to 2 years in 20 lesions out of 1559 lesions in 14 patients out of 454 patients

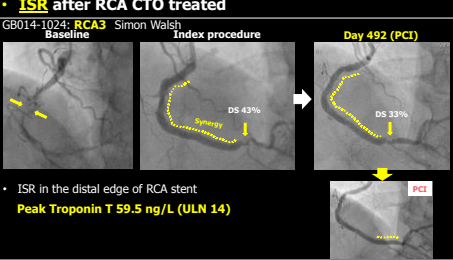
Triggered by investigator  
Confirmed by CEC as **TVR (non-TLR)**



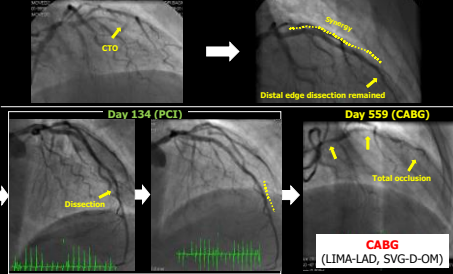
Triggered by investigator  
Confirmed by CEC as **Non-TVR**



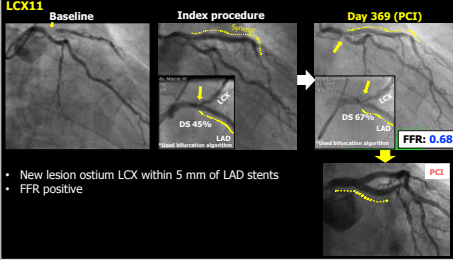
Triggered by investigator as MI  
Not confirmed by CEC as MI, confirmed as **TLR (ISR)**



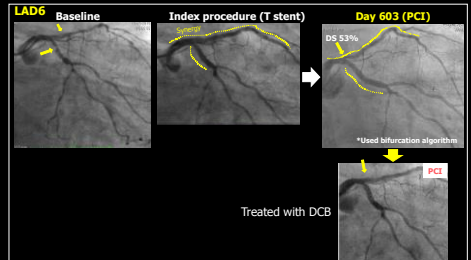
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)** by **CABG**



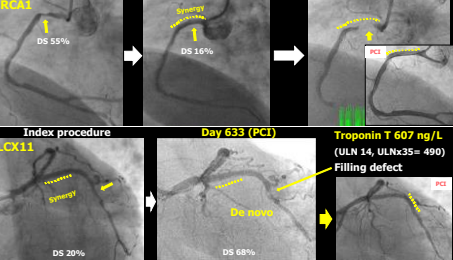
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)**



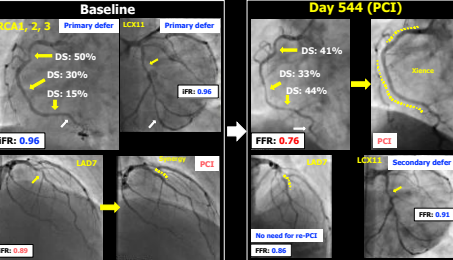
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)**



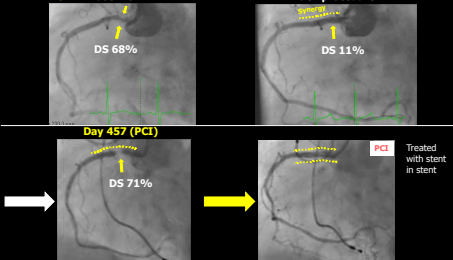
Triggered by investigator as MI and ST  
Confirmed by CEC as **Non-Q-wave MI (TV-MI), Definite ST, and TLR (ISR)**



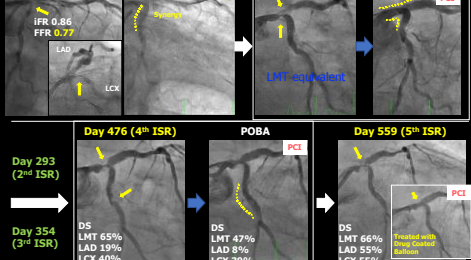
Triggered by investigator as MI (No biomarkers measured, based on source presented with heart failure)  
Re-adjudicated and confirmed by CEC as **non-TVR of RCA on 16th Apr**



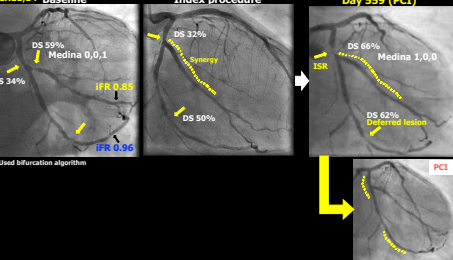
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)**



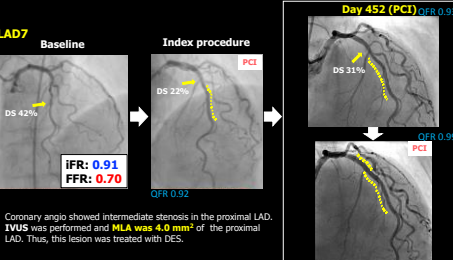
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)**



Triggered by investigator  
Confirmed by CEC as **TVR (Non-ISR)**



Triggered by investigator  
Re-adjudicated and confirmed by CEC as **TLR (ISR)** of LAD on 16th Apr



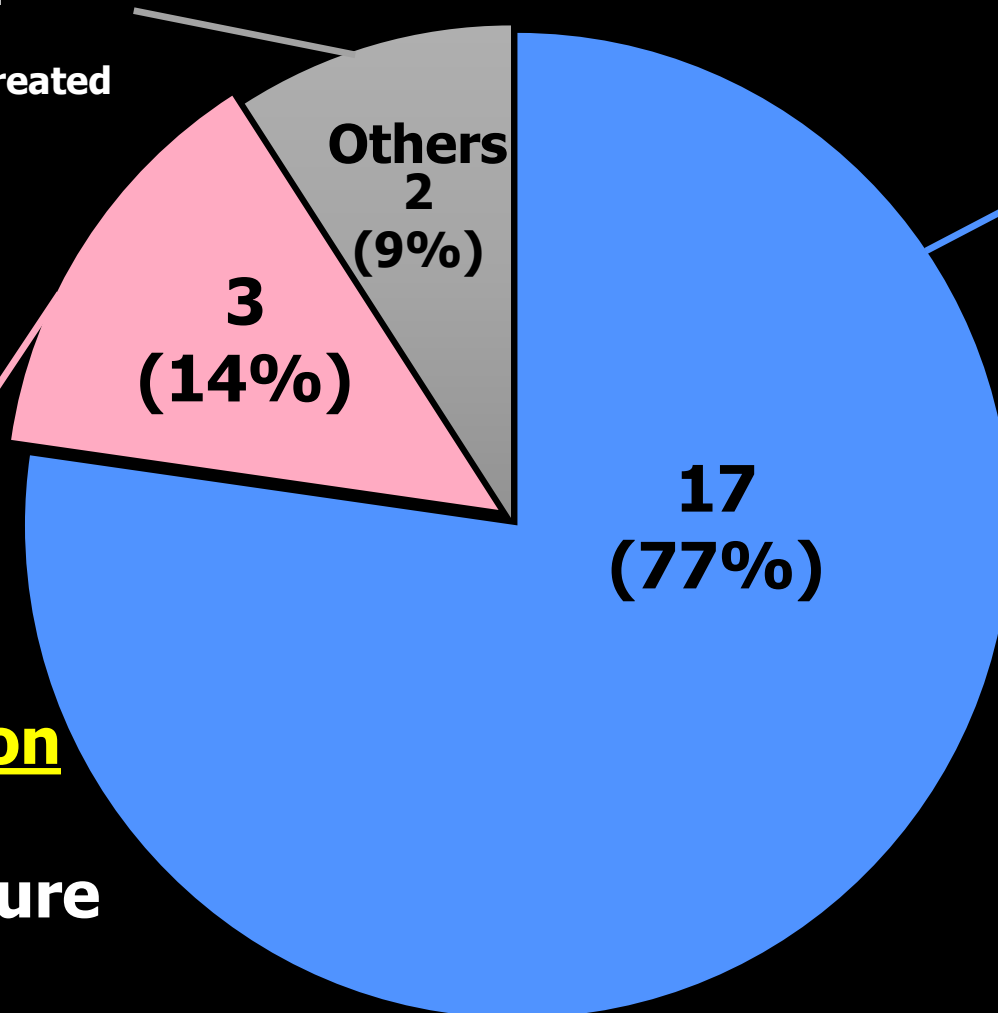
# All revascularization from 1 year to 2 years in 20 lesions out of 1559 lesions in 14 patients out of 454 patients

- Lesion level analysis -

\*2 lesions were treated two times

## TVR (non-TLR)

- Progression of far distal lesion from stented segment
- CTO that was not treated at index procedure

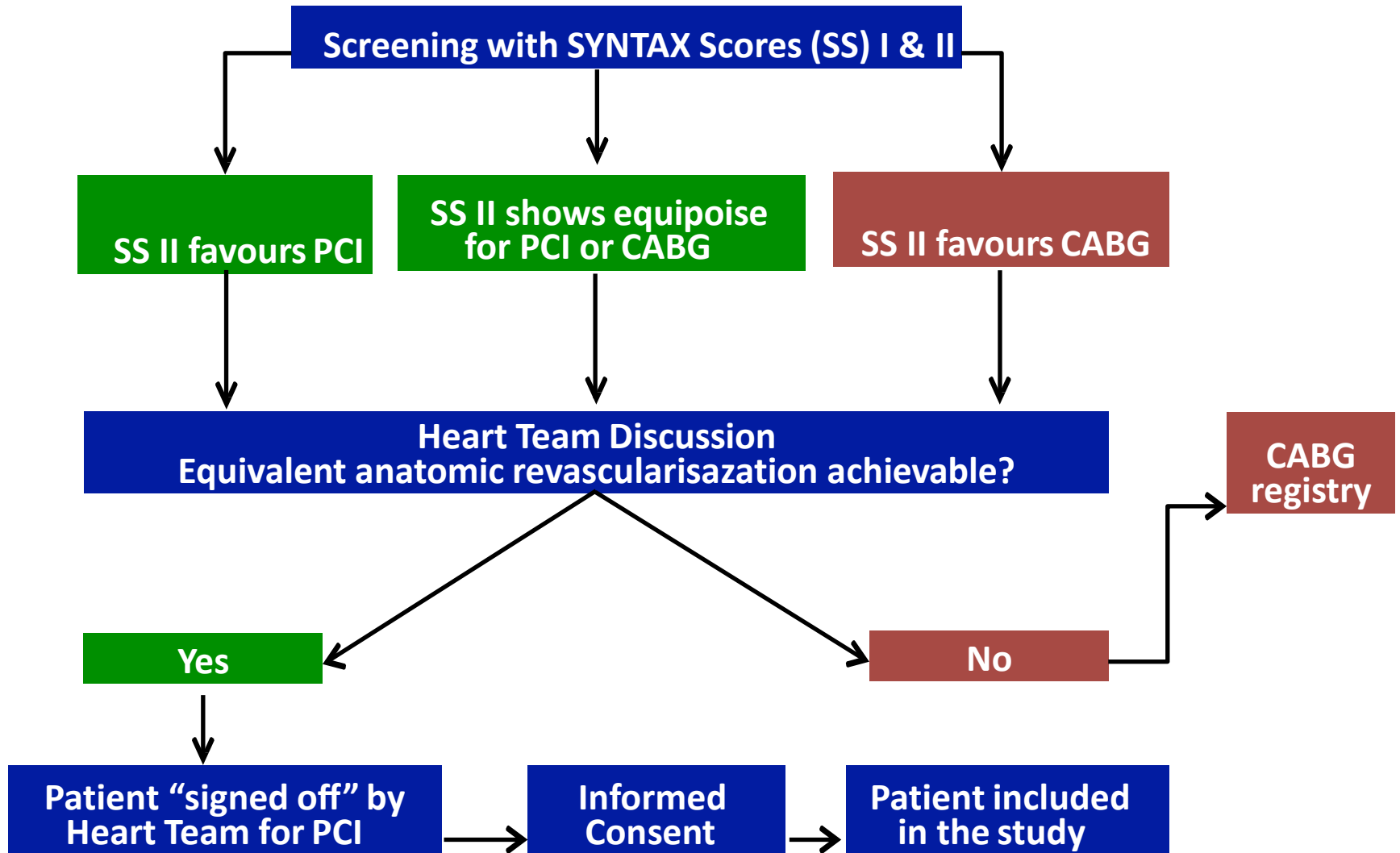


**TLR for in-stent restenosis**

**Non-TVIR in deferred lesion with iFR at index procedure**

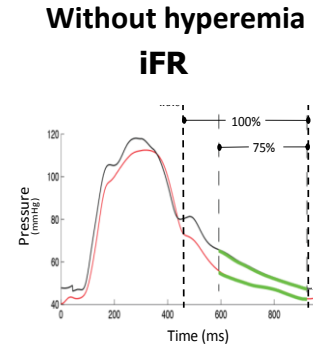
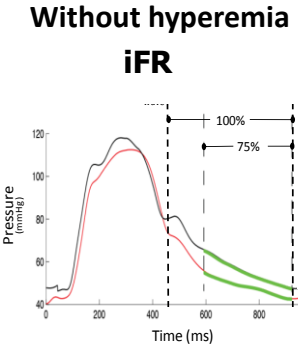


# Study flowchart: patient inclusion



# Study flowchart

**Screening with SYNTAX Score II**  
**SS II favors PCI or shows equipoise for PCI or CABG**



**iFR in all intended to treat stenoses**

**iFR < 0.86**

**iFR 0.86 – 0.93**

**iFR > 0.93**

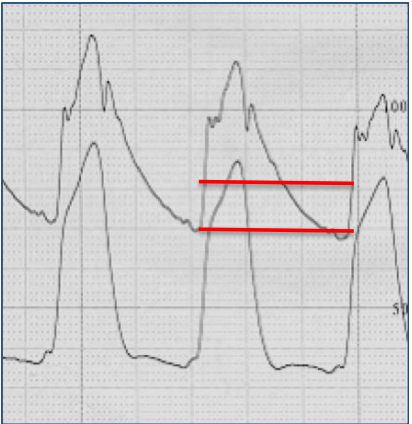
**Stenosis treated with SYNERGY™ EES**

**FFR ≤ 0.80**

**IVUS optimization**

**FFR**

**FFR Hyperemia**

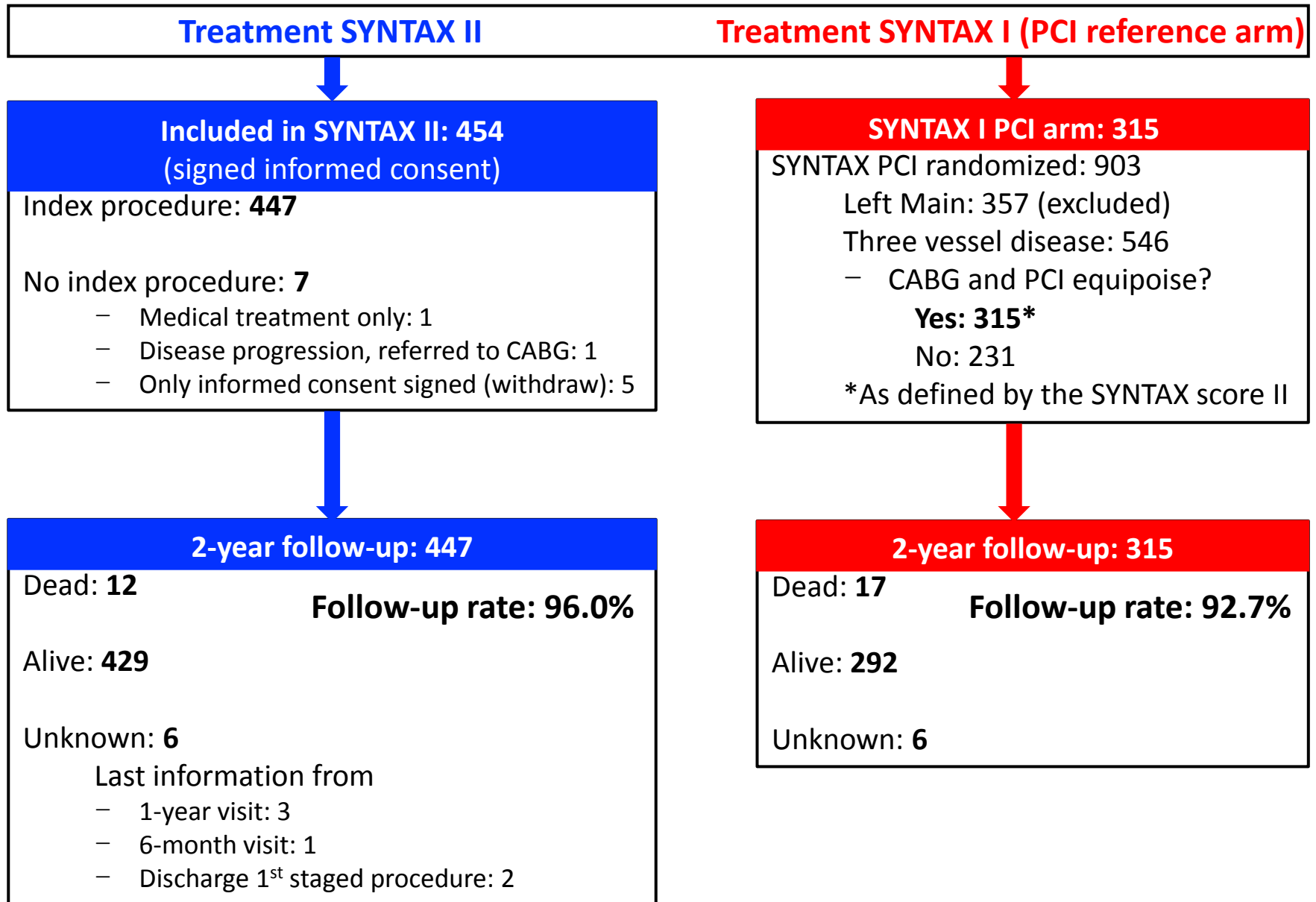


**FFR > 0.80**

**Stenosis not treated**

**Optimal medical therapy with strict LDL control (≤ 1.8mmol/L)**

# Study flowchart: patient follow-up



# SYNTAX Score II

	SYNTAX II		SYNTAX I PCI arm	P value
<b>Components of the SYNTAX Score II</b>				
Age	66.7 ± 9.7	=	66.7 ± 9.1	0.99
Gender (Male)	93.2%	=	93.0%	0.93
Cr Clearance (ml/min)	(-) 82.0 ± 26.9		87.3 ± 28.5 (+)	0.008
Ejection Fraction (%)	(-) 58.1 ± 8.3		61.8 ± 11.3 (+)	<0.001
Peripheral Vascular Disease	(+) 7.7%		9.5% (-)	0.37
COPD	(+) 10.8%		12.7% (-)	0.42
Anatomic SYNTAX Score	(+) 20.3 ± 6.4		22.8 ± 8.7 (-)	<0.001

<b>SYNTAX Score II PCI</b>	<b>30.2 ± 8.6</b>		<b>30.6 ± 8.7</b>	<b>0.528</b>
Predicted 4-yr mortality PCI (%)	8.9 ± 8.8%		9.2 ± 8.7%	0.640
<b>SYNTAX Score II CABG</b>	<b>29.1 ± 10.4</b>		<b>29.1 ± 9.6</b>	<b>1.0</b>
Predicted 4-yr mortality CABG (%)	9.0 ± 9.3		8.5 ± 8.1	0.440

**Anatomic target lesions (n=1559) (3.49 lesions/patient)**

**iFR performed  
(n=1150; 73.8%)**

**Only FFR performed  
(n=27; 1.7%)**

**Lesions not assessed with physiology (n = 382; 24.5 %)**

- **Pressure wire crossing not attempted/indicated\* : 221**
- **Unable to cross the lesion with a pressure wire\*\* : 127**
- **Other reasons: 26**

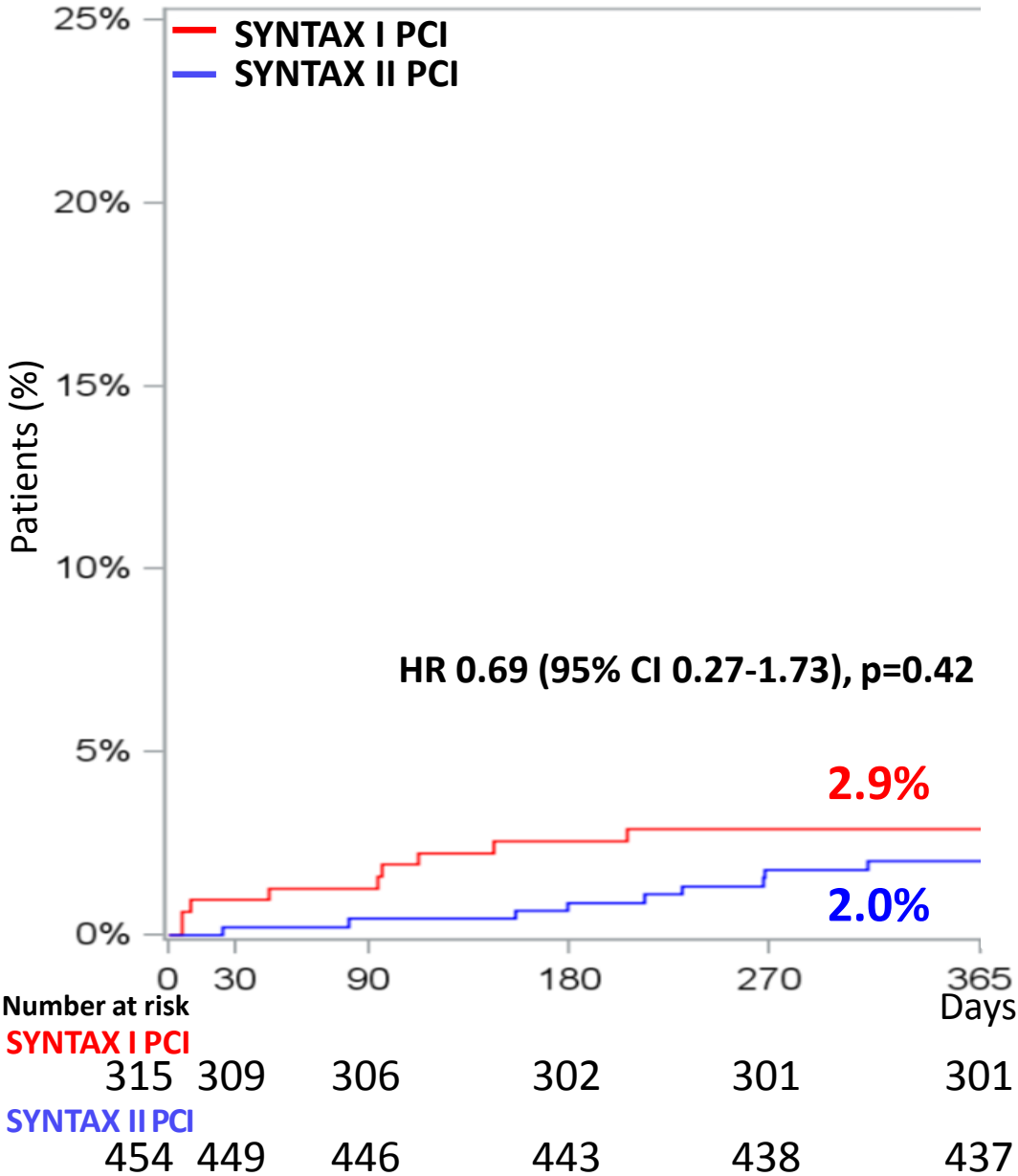
**\*Use of pressure guidewire in CTOs was not indicated.**

**\*\*Physiological interrogation was prompted irrespective of angiographic lesion severity.**

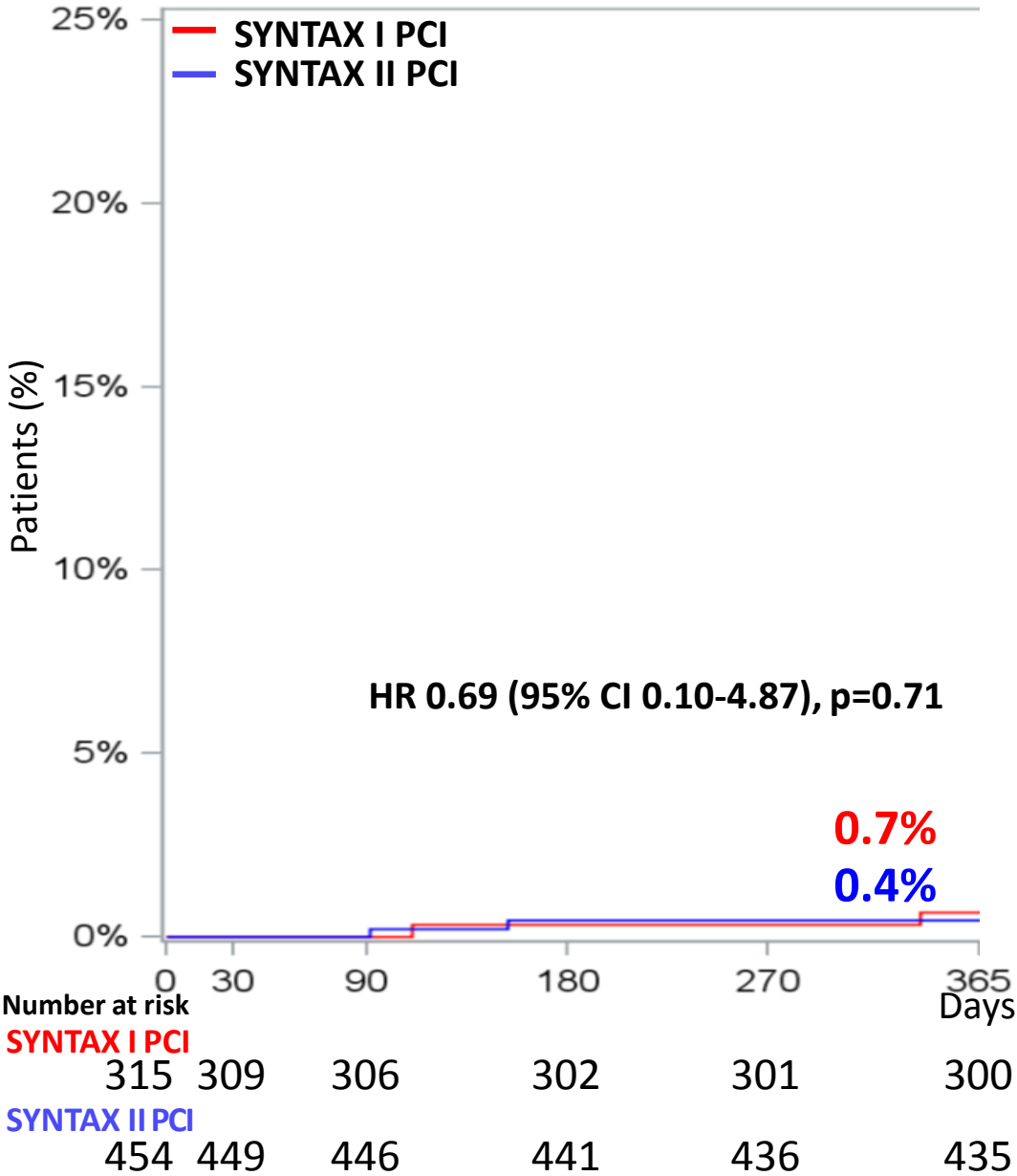
# Two year follow up results

## Comparison with SYNTAX I PCI

# All-cause death up to 2 years

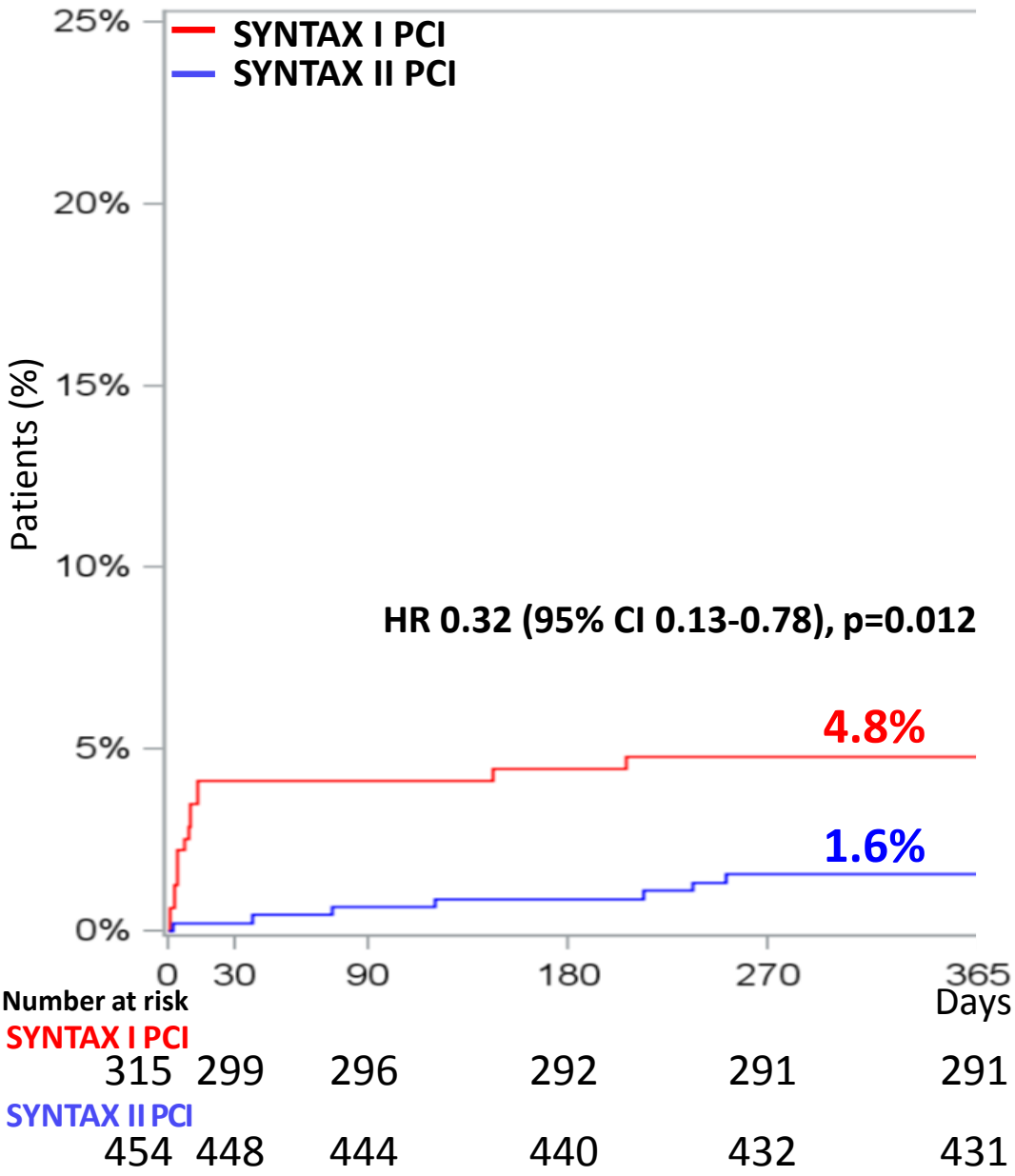


# Stroke up to 2 years

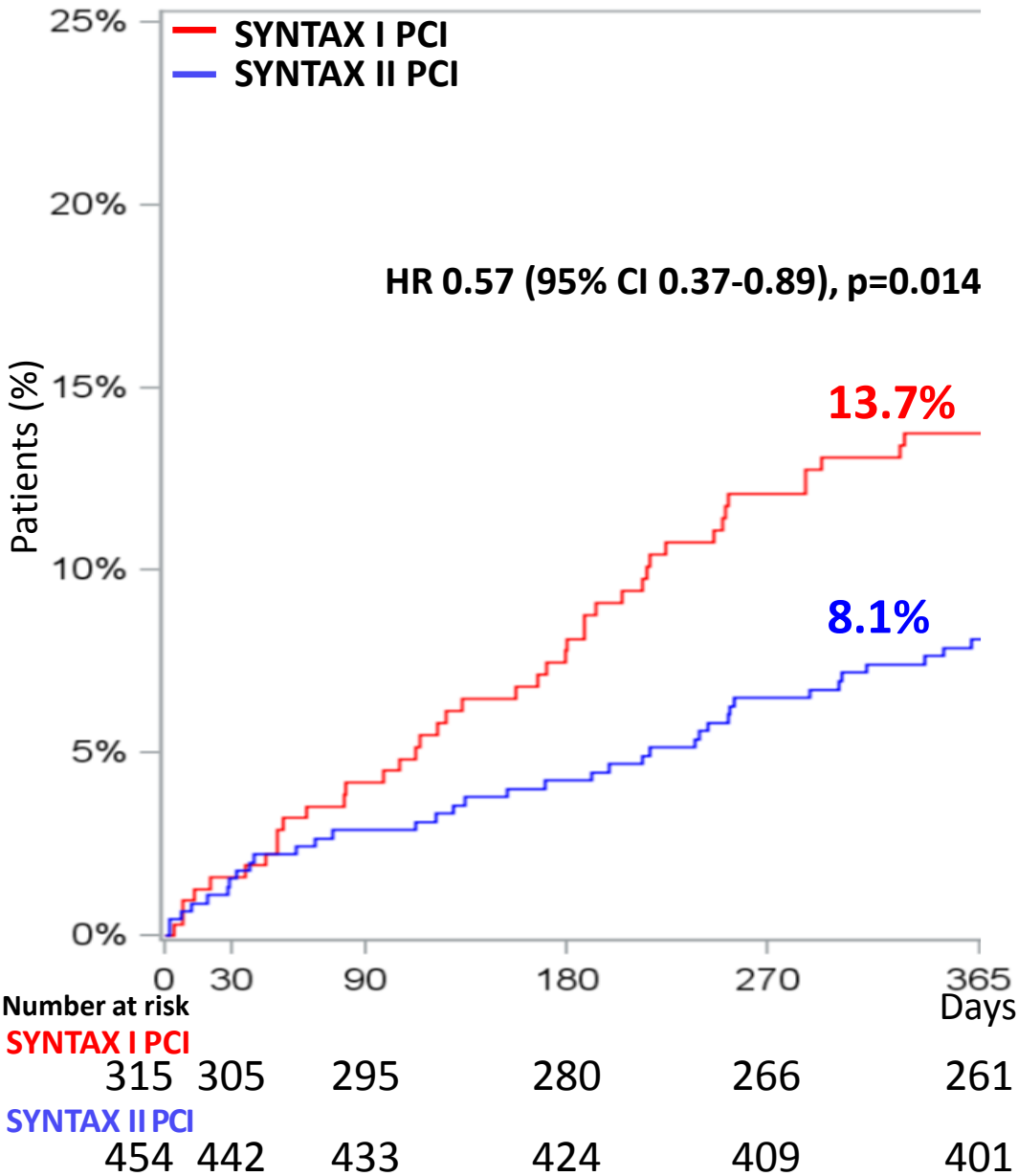




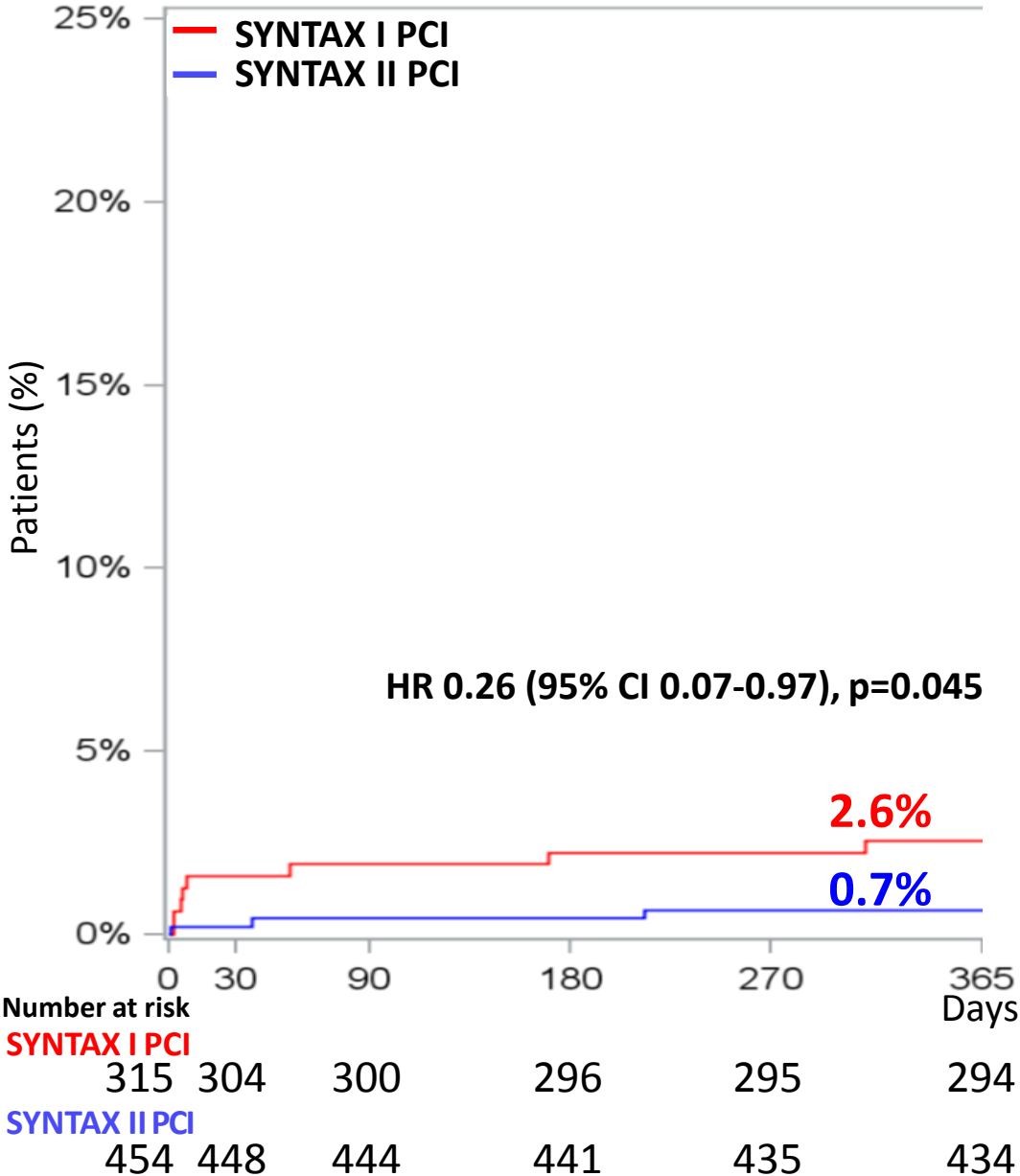
# Myocardial infarction up to 2 years



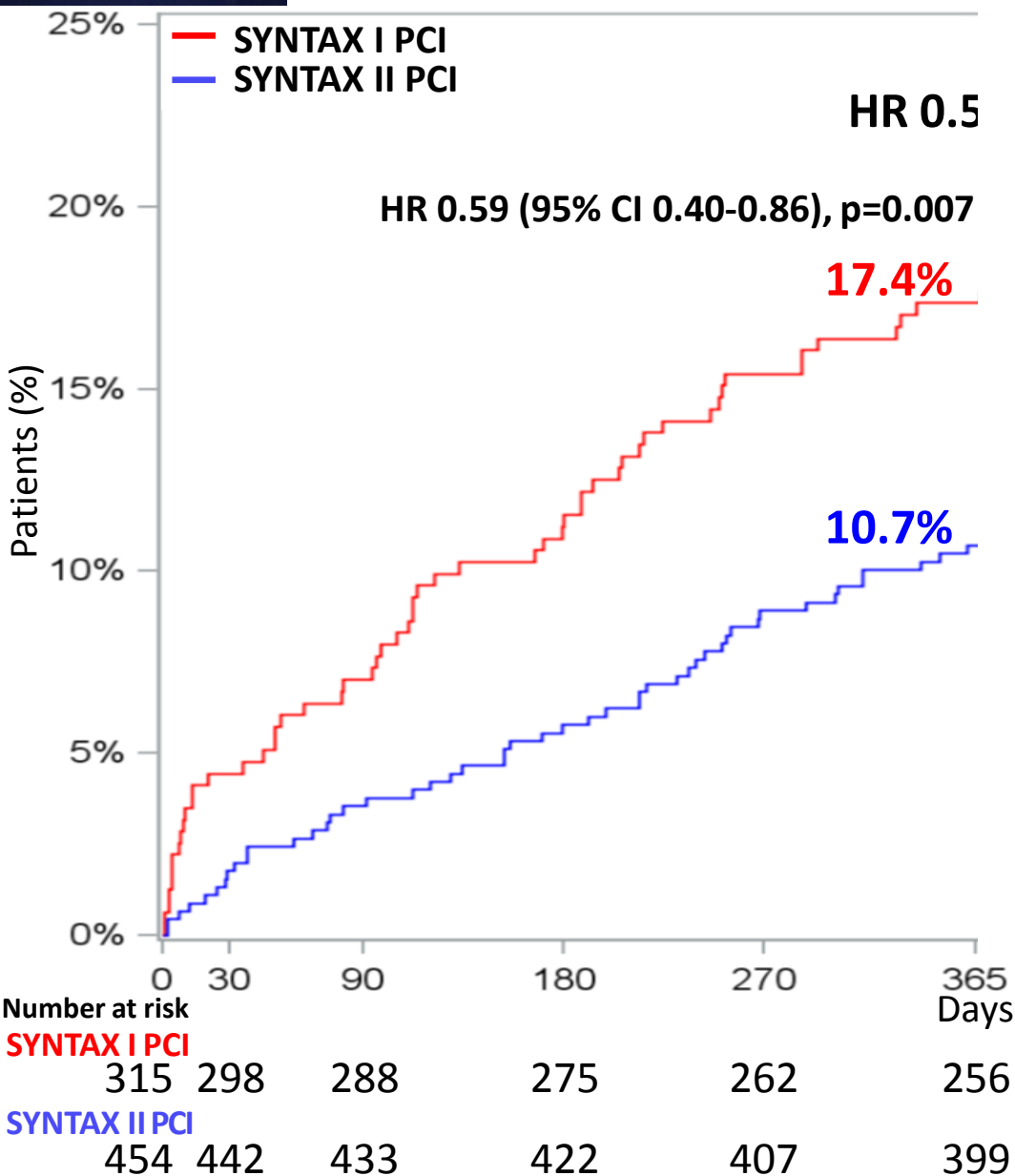
# Any repeat revascularization up to 2 years



# Definite stent thrombosis up to 2 years



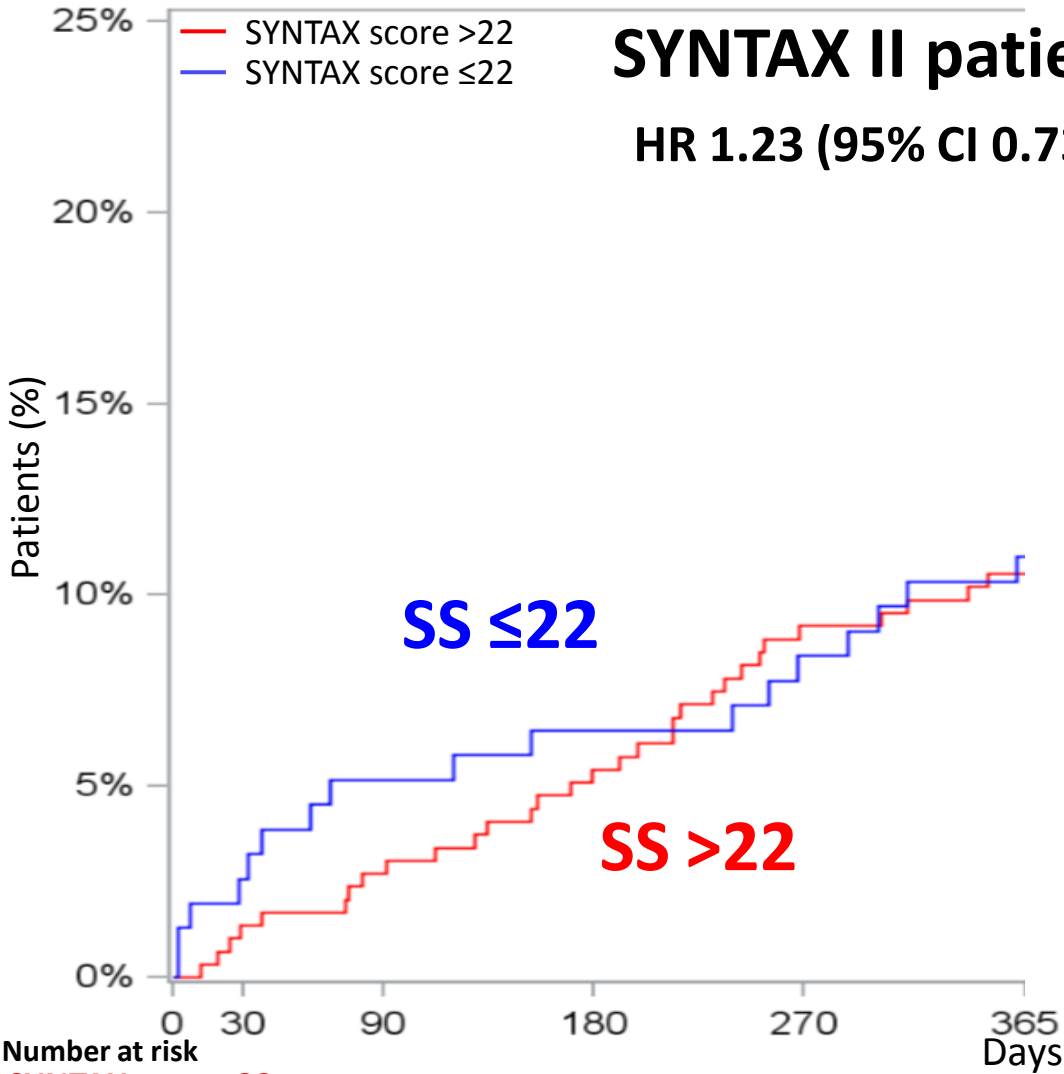
# Primary endpoint: MACCE up to 2 years



# SYNTAX II MACCE in SS I $\leq 22$ and $>22$ up to 2 years

## SYNTAX II patients only

HR 1.23 (95% CI 0.73-2.07), p=0.44



Number at risk		0	30	90	180	270	365
SYNTAX score >22		156	151	147	144	141	137
SYNTAX score $\leq 22$		298	291	286	278	266	262



Triggered by investigator

Confirmed by CEC as **TLR (ISR)**

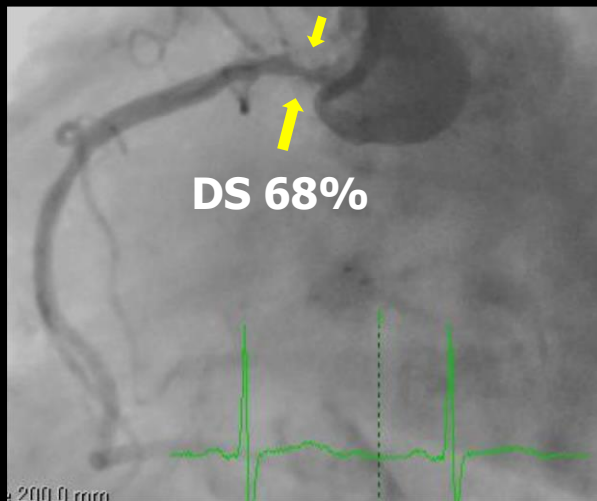
Patient level: 1TLR (ISR)

Lesion level: 1TLR (ISR)

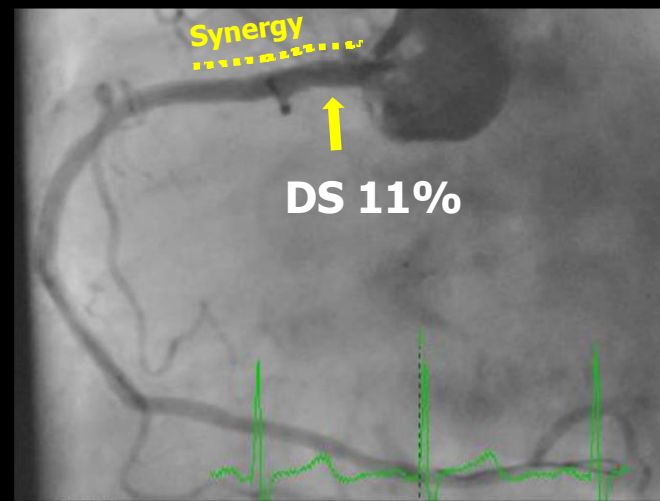
Segments	
	7
	11
	1

- **ISR** case after RCA ostium stenting

**RCA1** Baseline



Index procedure





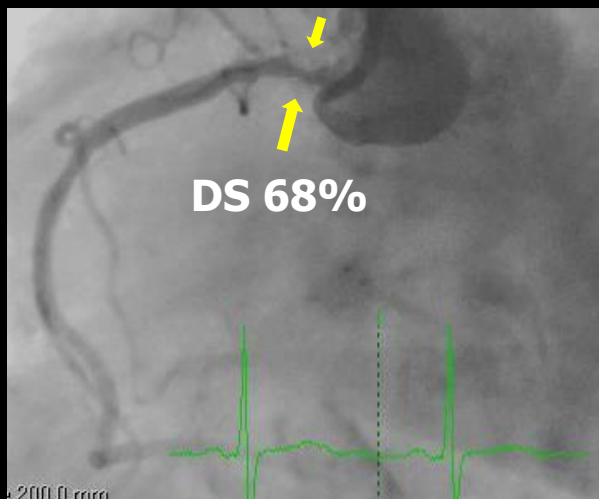
Triggered by investigator  
Confirmed by CEC as **TLR (ISR)**

Patient level: 1TLR (ISR)  
Lesion level: 1TLR (ISR)

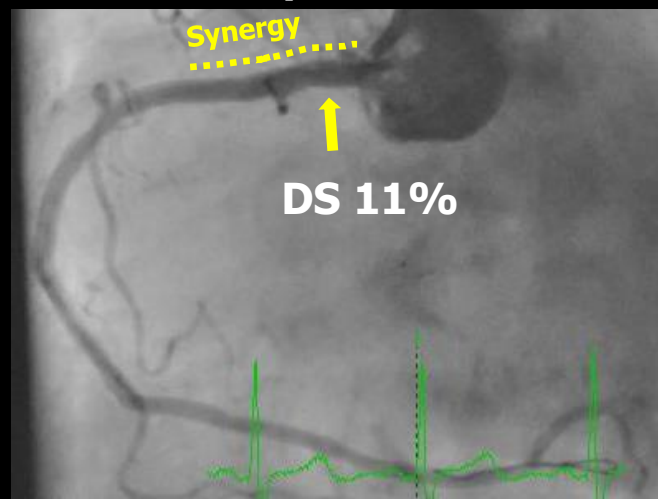
Segments	▼
	7
	11
	1

• **ISR** case after RCA ostium stenting

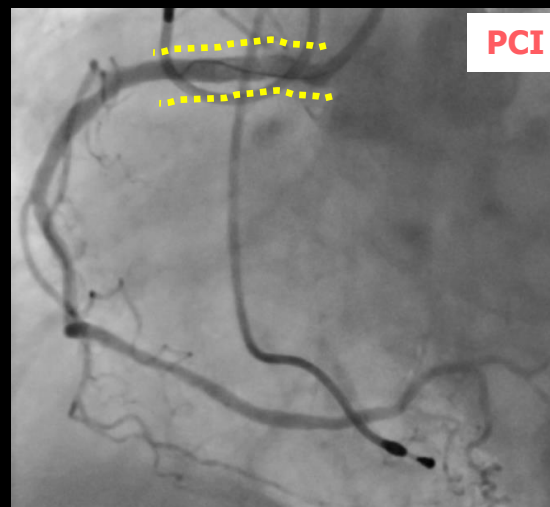
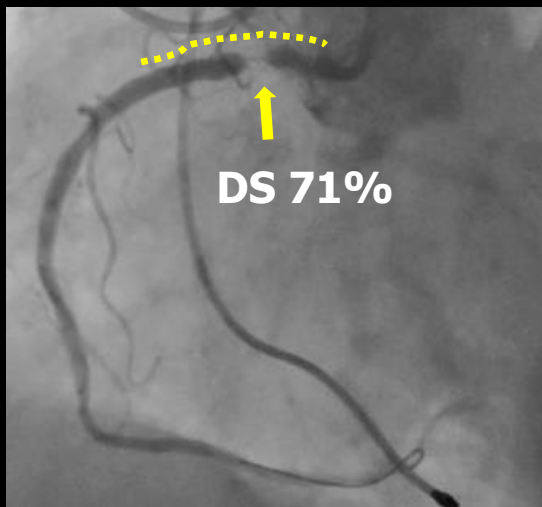
**RCA1 Baseline**



**Index procedure**



**Day 457 (PCI)**





Segments	V
1	
6	
12a	

Triggered by investigator

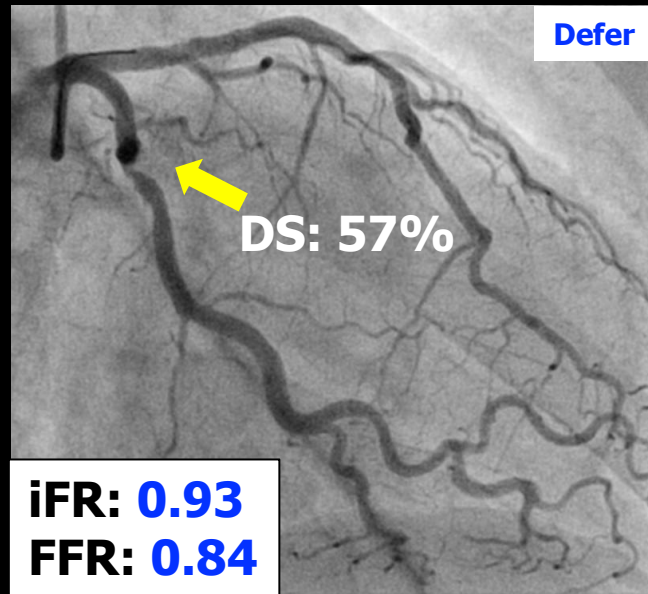
Patient level: 1non-TVR (deferred)

Confirmed by CEC as **Non-TVR**

Lesion level: 1non-TVR (deferred)

- A case with progression of **deferred lesion**

## LCX12a Baseline







Segments	▼	V
		1
		6
12a		

Triggered by investigator

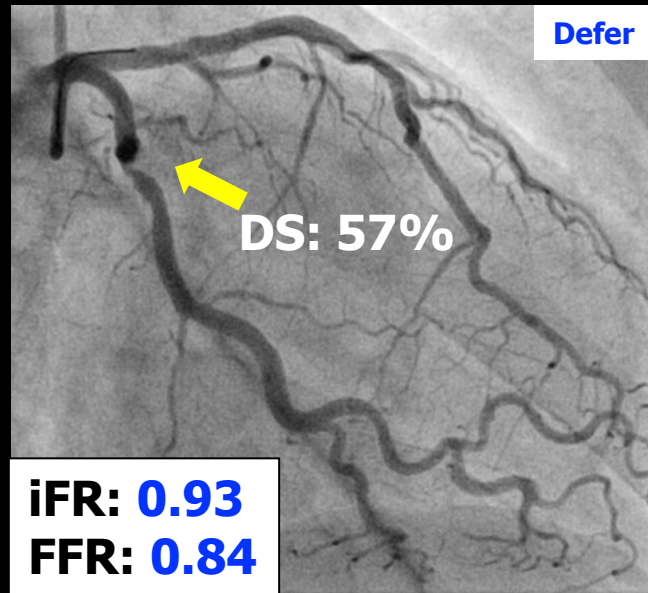
Patient level: 1non-TVR (deferred)

Lesion level: 1non-TVR (deferred)

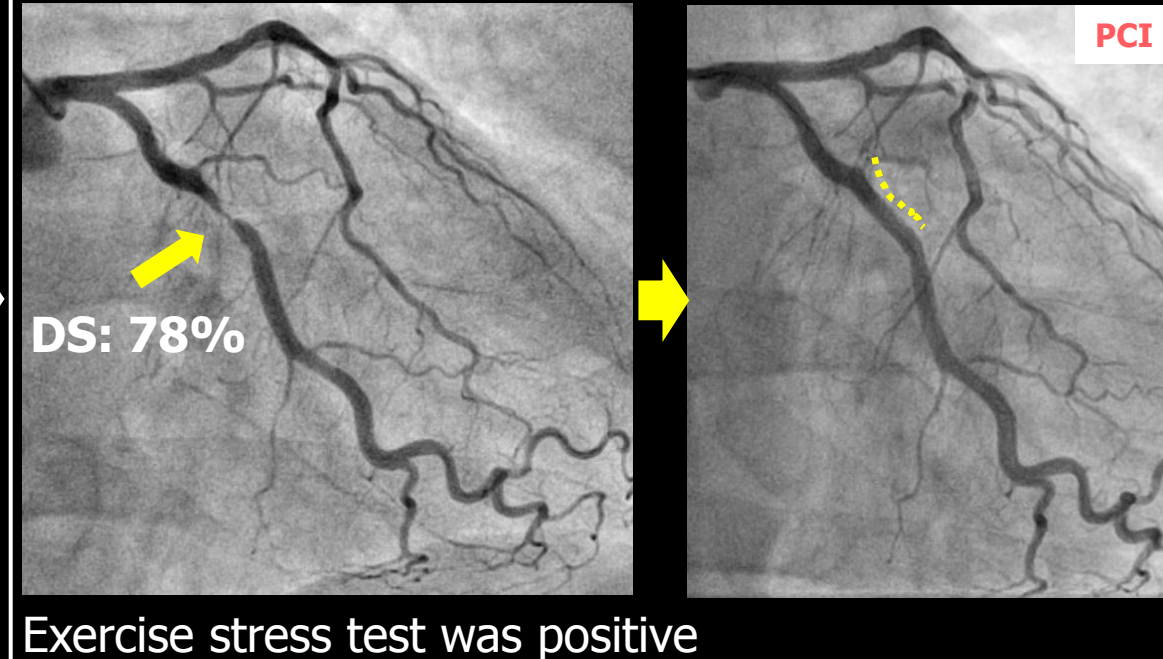
Confirmed by CEC as **Non-TVR**

- A case with progression of **deferred lesion**

### LCX12a Baseline



### Day 714 (PCI)





Segments
6 7
2
11
12a
9

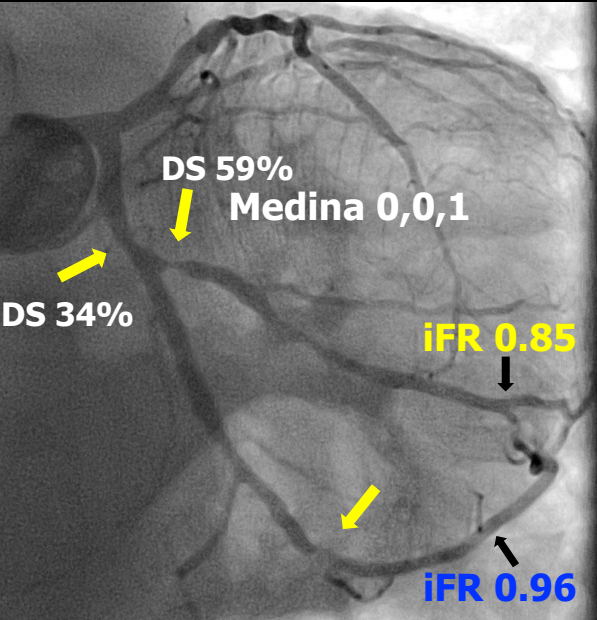
Triggered by investigator

Patient level: 1TLR (ISR)  
Lesion level: 1TLR (ISR)

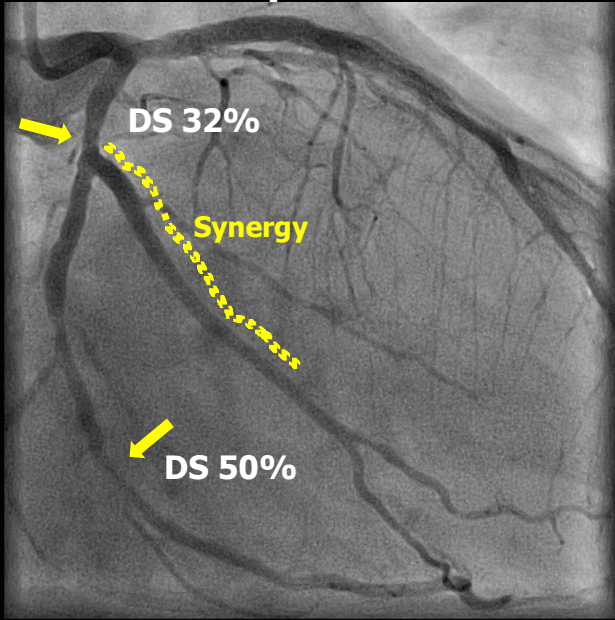
Confirmed by CEC as **TLR (ISR)**

- **Re-PCI case with ISR and progression and treatment of deferred lesion**

**LCX11,14 Baseline**



**Index procedure**



\*Used bifurcation algorithm



Segment	▼
67	
	2
	11
12a	
	9

Triggered by investigator

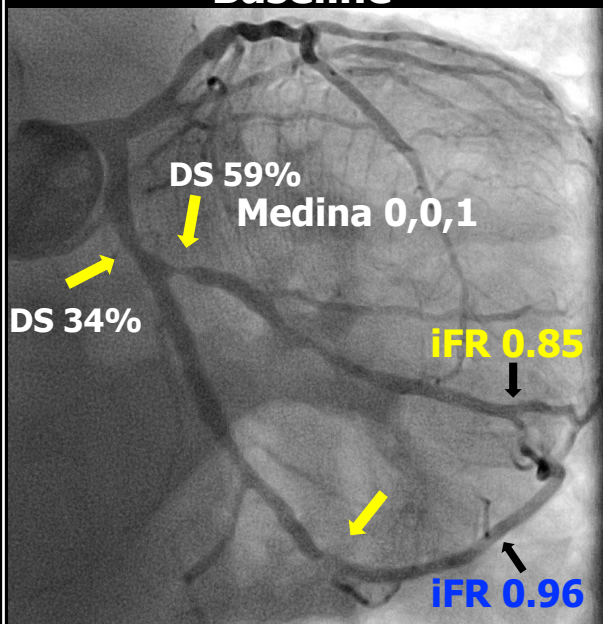
Confirmed by CEC as **TLR (ISR)**

Patient level: 1TLR (ISR)

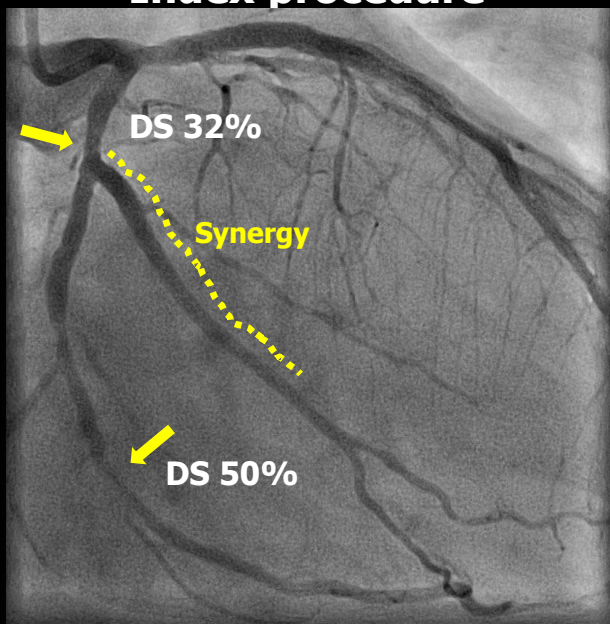
Lesion level: 1TLR (ISR)

- **Re-PCI case with ISR and progression and treatment of deferred lesion**

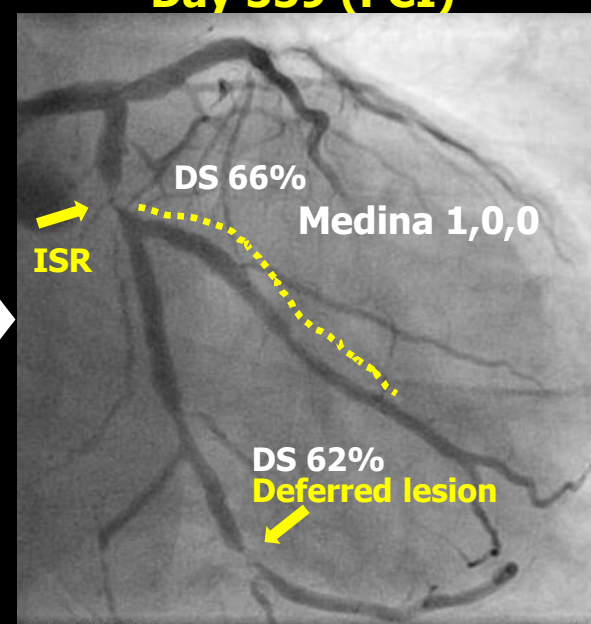
**LCX11,14 Baseline**



**Index procedure**

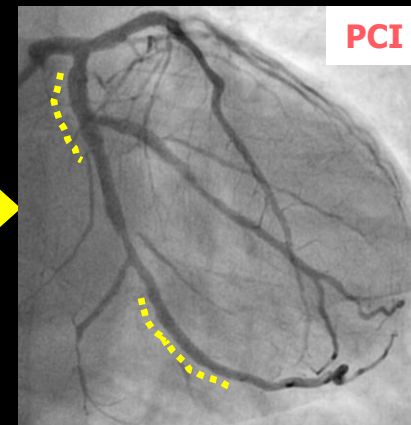


**Day 559 (PCI)**



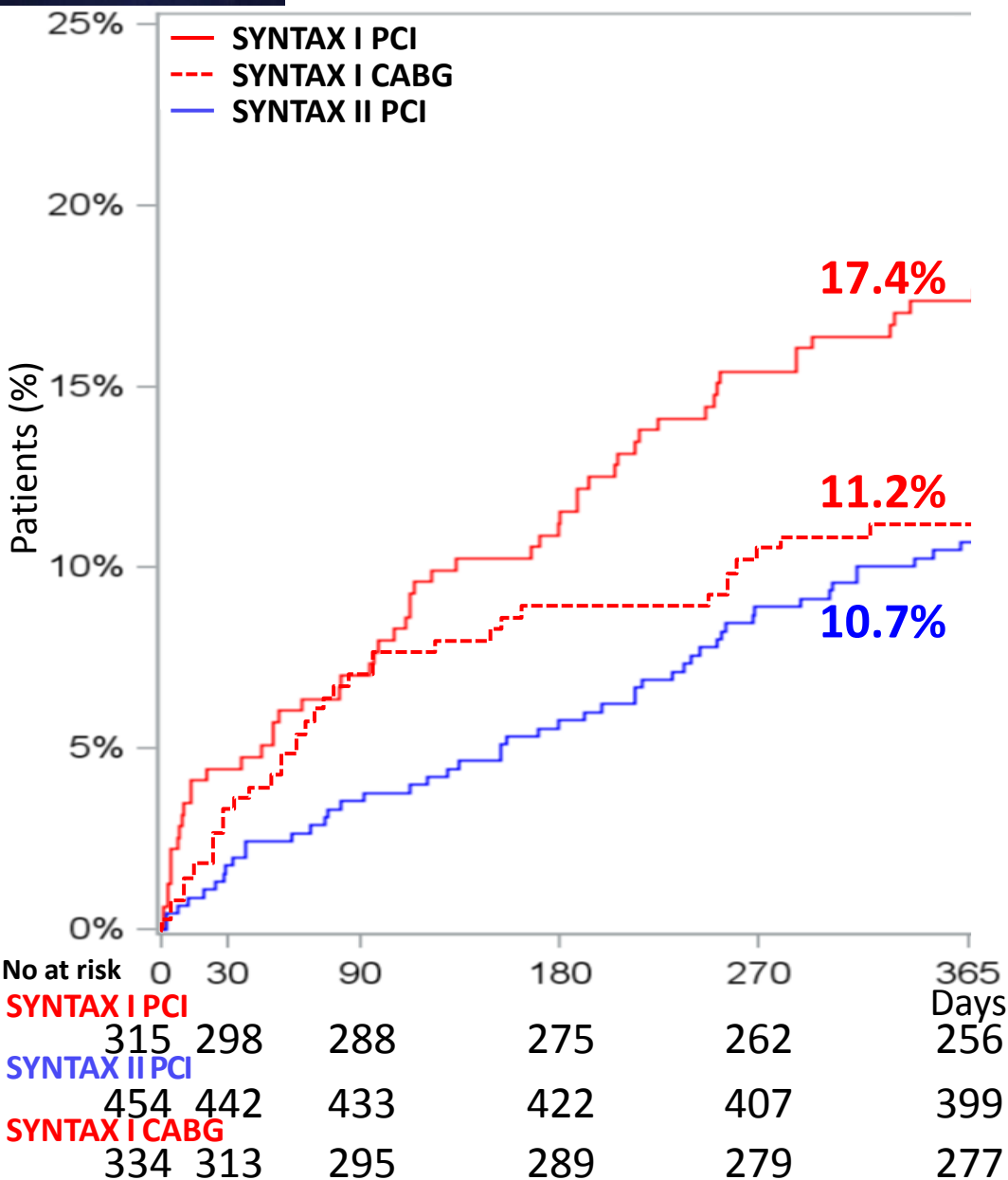
\*Used bifurcation algorithm

**PCI**



# Two year follow up results

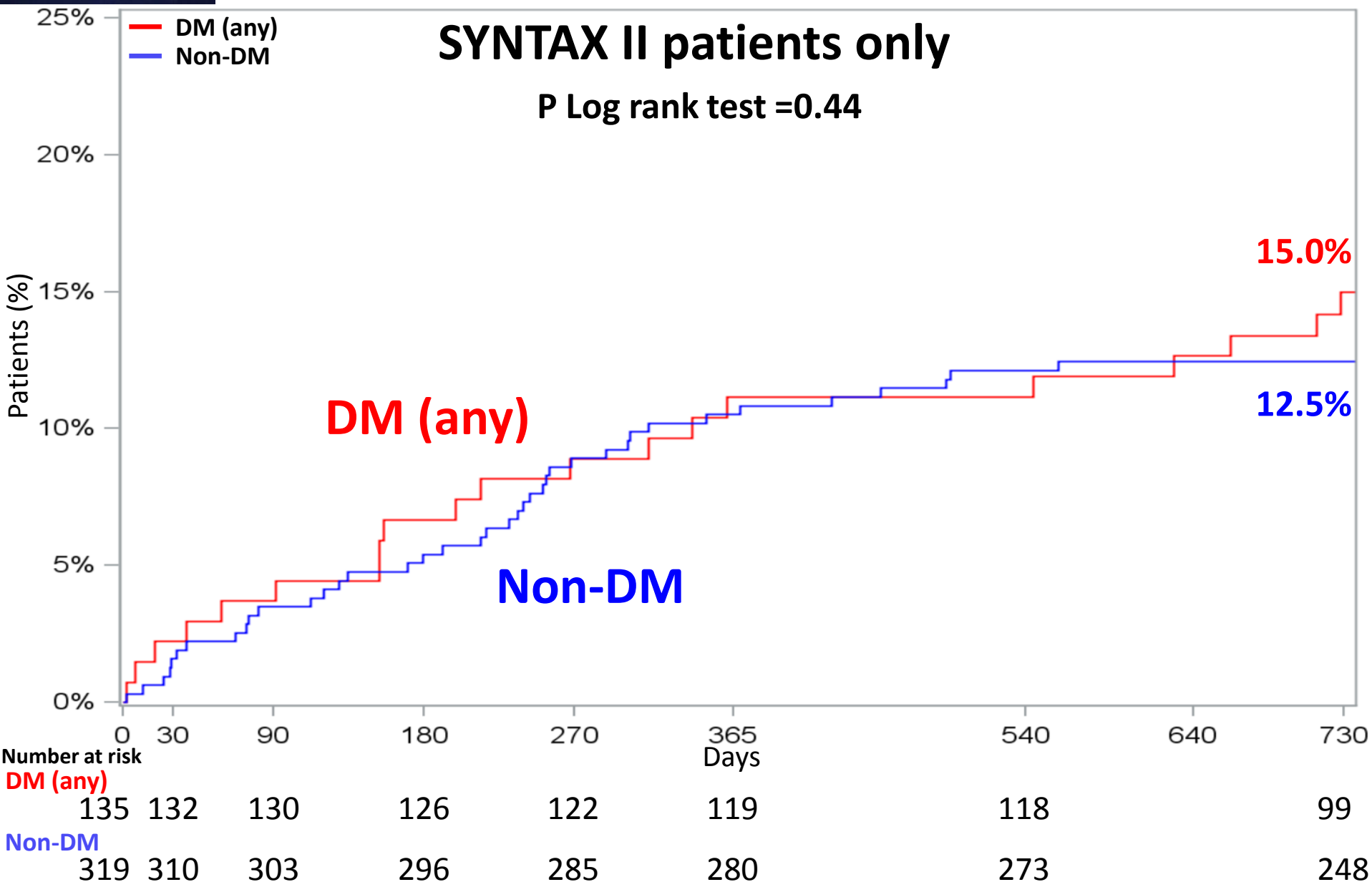
## Comparison with SYNTAX I CABG



# Two year follow up results

## Influence of DM on MACCE

# SYNTAX II MACCE with or without DM



**Two year follow up results**  
**Influence of anatomic SS**  
**on MACCE**



# Background

- The management of patients with 3-vessel disease (3VD) according to ESC guidelines is largely influenced by the results of the pivotal SYNTAX trial.

## Class I:

Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

## Level of evidence B:

Data derived from a single randomized clinical trial or large non-randomized studies.

Extent Of CAD	CABG		PCI	
3VD with a SYNTAX Score $\leq 22$	I	A	I	B
3VD with a SYNTAX Score 23-32	I	A	III	B
3VD with a SYNTAX Score $>32$	I	A	III	B

# Statistical considerations

## Sample size and Power calculation

- Observed event rate was 17.4% in the historical control group (i.e. patients in the SYNTAX I PCI arm with SYNTAX score II recommending PCI or equipoise)
- Assuming an 11.5% MACCE rate\* at 365 days from the randomized EXECUTIVE trial:
  - A sample size of 416 analysable patients would provide a power of 90% to show superiority of EES over PES
  - Considering attrition, final sample size should be 450 patients

# Use of coronary stents

	<b>SYNTAX II</b>	<b>SYNTAX I PCI arm</b>	<b>P value</b>
<b>Stents per patient</b>	3.78±1.92 (440)	5.19±2.04 (308)	<b>&lt;0.001</b>
<b>Stents per lesion</b>	1.43±0.76 (1165)	1.28±0.65 (1251)	<b>&lt;0.001</b>
<b>Mean stent length (per stent, mm)</b>	24.43±9.18 (1663)	18.82±7.04 (1599)	<b>&lt;0.001</b>
<b>Total stent length (per patient, mm)</b>	92.32±52.78 (440)	97.71±43.66 (308)	0.13

## Principal Investigators

PIs: A Banning, J Escaned

Study Chairman: PW Serruys

Deputy Chairman: V Farooq

Co-PIs: AP Kappetein, D Taggart (Surgeons)

## Steering Commiuee

A Banning, J Escaned, V Farooq, AP Kappetein,  
PW Serruys, D Taggart, GA van Es

## Sponsor

ECRI - European Cardiovascular Research  
Institute

## Grant givers

Volcano and Boston Scientific

## Data & Safety Monitoring Board

FW Mohr, K Oldroyd, J Tijssen

## Clinical Events Commiuee

JP Herrman, E McFadden, V Thijs, P Vranckx

## Clinical Research Organization

Cardialysis BV, Rotterdam, The Netherlands  
Trial Manager: S. Leeflang

Statistics: T de Vries, C. Collet, R. Cavalcante

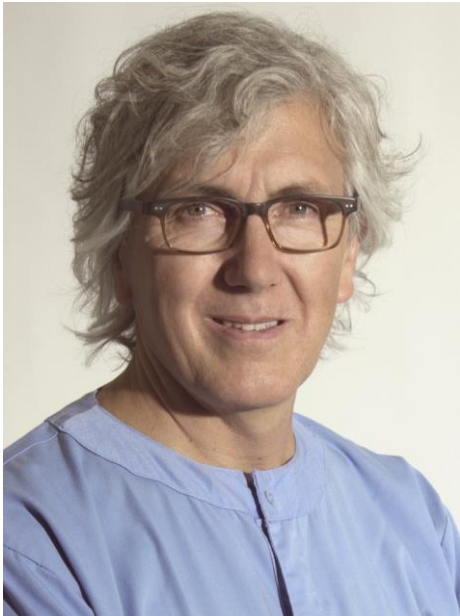
## Core Laboratory

Coronary physiology: N. Ryan

IVUS: G. De Maria

Coronary CTA: C. Collet, Y. Miyazaki

*Thank you for your attention!*



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Deputy Chairman*



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doi:10.1093/eurheartj/ehv512

**FASTTRACK CLINICAL RESEARCH**  
**ESC Late Breaking Science in PCI 1**

*Interventional cardiology*

## Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with *de novo* three vessel disease: 1-year results of the SYNTAX II study

Javier Escaned<sup>1</sup>, Carlos Collet<sup>2</sup>, Nicola Ryan<sup>1</sup>, Giovanni Luigi De Maria<sup>3</sup>, Simon Walsh<sup>4</sup>, Manel Sabate<sup>5</sup>, Justin Davies<sup>6</sup>, Maciej Lesiak<sup>7</sup>, Raul Moreno<sup>8</sup>, Ignacio Cruz-Gonzalez<sup>9</sup>, Stephan P. Hoole<sup>10</sup>, Nick Ej West<sup>10</sup>, J. J. Piek<sup>2</sup>, Azfar Zaman<sup>11</sup>, Farzin Fath-Ordoubadi<sup>12</sup>, Rodney H. Stables<sup>13</sup>, Clare Appleby<sup>13</sup>, Nicolas van Mieghem<sup>14</sup>, Robert Jm. van Geuns<sup>14</sup>, Neal Uren<sup>15</sup>, Javier Zueco<sup>16</sup>, Pawel Buszman<sup>17</sup>, Andres Iniguez<sup>18</sup>, Javier Goicolea<sup>19</sup>, David Hildick-Smith<sup>20</sup>, Andrzej Ochala<sup>21</sup>, Dariusz Dudek<sup>22</sup>, Colm Hanratty<sup>4</sup>, Rafael Cavalcante<sup>14</sup>, Arie Pieter Kappetein<sup>14</sup>, David P. Taggart<sup>3</sup>, Gerrit-Anne van Es<sup>23,24</sup>, Marie-Angele Morel<sup>23</sup>, Ton de Vries<sup>23</sup>, Yoshinobu Onuma<sup>14,23</sup>, Vasim Farooq<sup>12</sup>, Patrick W. Serruys<sup>6\*</sup>, and Adrian P. Banning<sup>3</sup>

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your attention*

# Centres, site investigators and enrolled patients

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	Hospital Clinico San Carlos Javier Escaned	50		Freeman Hospital Newcastle Azfar Zaman	19
	John Radcliffe Hospital Adrian Banning	35		Erasmus Medical Center Nicolas van Mieghem	16
	Hospital Clinic I Provincial Manel Sabaté	32		The Royal Infirmary of Edinburgh Neal Uren	15
	Imperial College Healthcare Justin Davies	27		Hospital Universitario Valdecilla Javier Zueco	12
	Holy Transfiguration Hospital Maciej Lesiak	20		American Heart of Poland (PAK), Pawel Buszman	10
	Hospital Universitario La Paz Raul Moreno	20		Hospital Meixoeiro Andres Iñiguez	8
	Hospital Clinico Salamanca Ignacio Cruz	20		Hospital Puerta de Hierro Javier Goicolea	8
	Papworth Hospital Nick West	20		Brighton & Sussex University Hospitals David Hildick-Smith	6
	Academisch Medisch Centrum Jan Piek	20		Gornoslaskie Centrum Medycnze, Andrzej Ochala	4
	Liverpool Heart and Chest Hospital Clare Appleby & Rod Stables	19		St Raphael Hospital Dariusz Dudek	3