# Lessons from SYNTAX II: Improving Decision Making in the SYNTAX III Trial

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# Components of the SYNTAX II strategy

- Major technical and procedural advances, influencing PCI outcomes, have taken place since the completion of SYNTAX I trial:
- New risk stratification tool: SYNTAX Score II (incorporating clinical and anatomical variables) to guide Heart Team decisions on myocardial revascularization.
- Physiology-based revascularisation (hybrid use of iFR and FFR).
- Second generation DES (thin strut, biodegradable polymer, everolimus-eluting Synergy™ stent [EES]).
- IVUS-guided optimisation of stent deployment (modified MUSIC criteria).
- Contemporary CTO revascularization techniques.
- Guideline-directed medical therapy (LDL cholesterol ≤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 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 2nd generation EES over PES + attrition).
- **Control group: Matched patients with 3VD from the SYNTAX I trial with a SYNTAX Score II showing equipoise between PCI and CABG (315 out of 1100 3VD in SYNTAX I trial).**

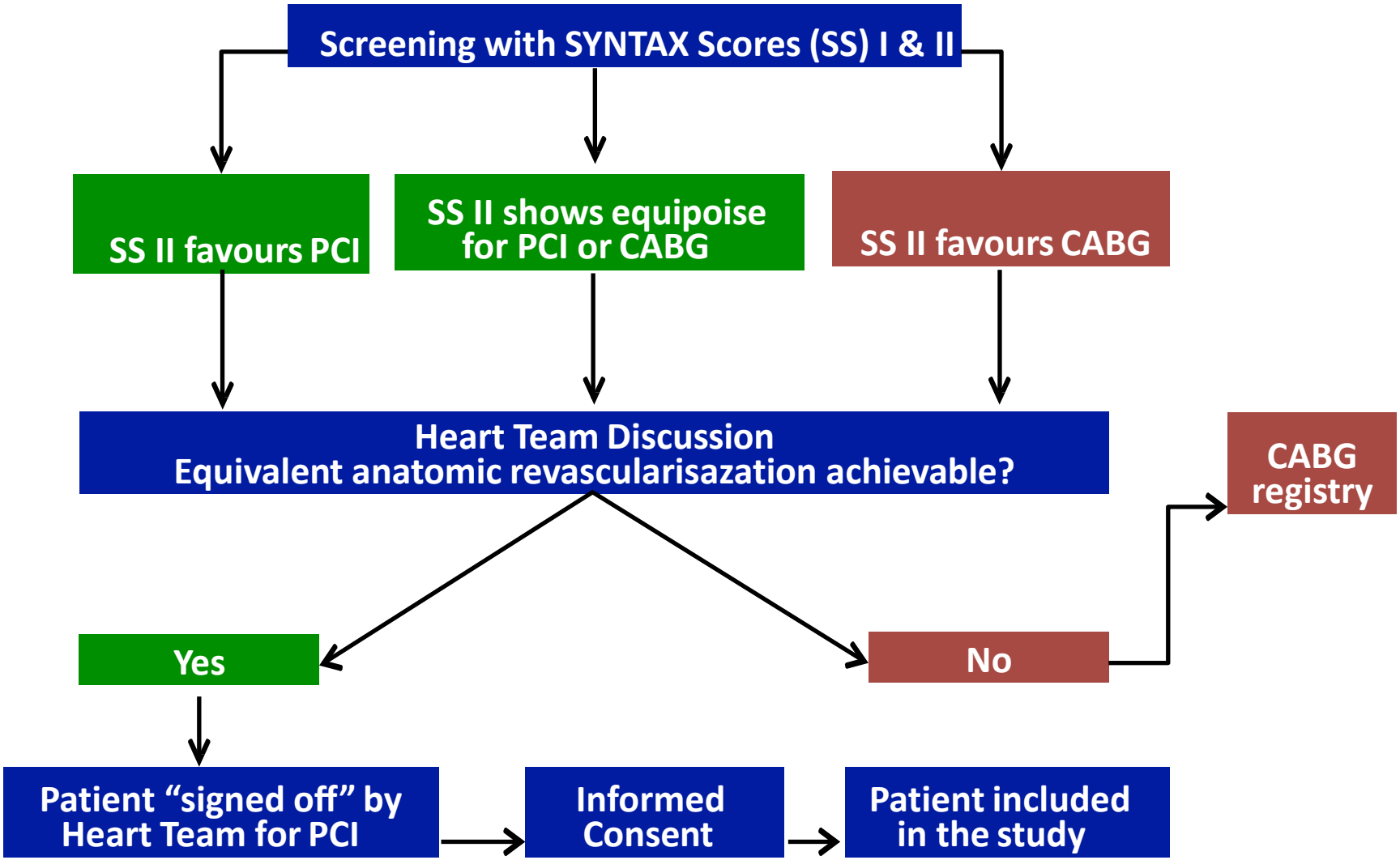
Study design: Escaned J et al. EuroIntervention. 2016 Jun 12;12(2):e224-34. ClincalTrials.gov identifier: NCT02015832.

# Statistical considerations

## Sample size and Power calculation

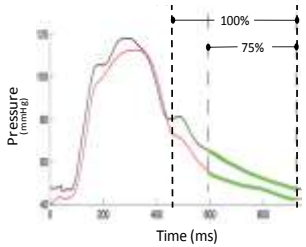
- Observed event rate was 17.4% in the historical control group (i.e. patients in the SYNTAX I PCI arm with SYNTAX score II recommending PCI or equipoise)
- Assuming an 11.5% MACCE rate* at 365 days from the randomized EXECUTIVE trial:
  - A sample size of 416 analysable patients would provide a power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

# Study flowchart: patient inclusion



# Study flowchart: PCI procedure

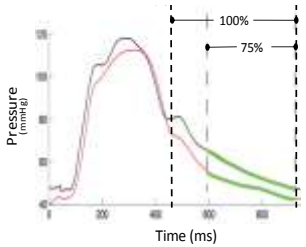
Without hyperemia
iFR




Patient included in the SYNTAX II study

iFR in all intended to treat stenoses

Without hyperemia
iFR




iFR < 0.86

iFR 0.86 – 0.93

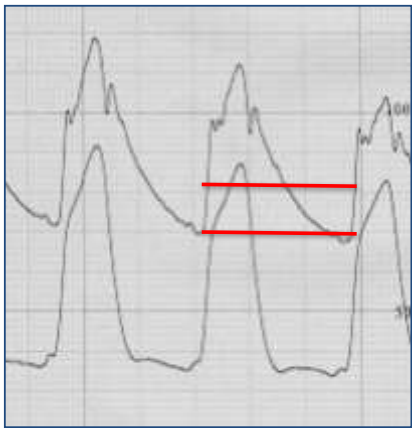
iFR > 0.93

FFR

FFR ≤ 0.80

FFR > 0.80

FFR
Hyperemia



Stenosis treated with SYNERGY™ EES

IVUS optimization

Stenosis not treated

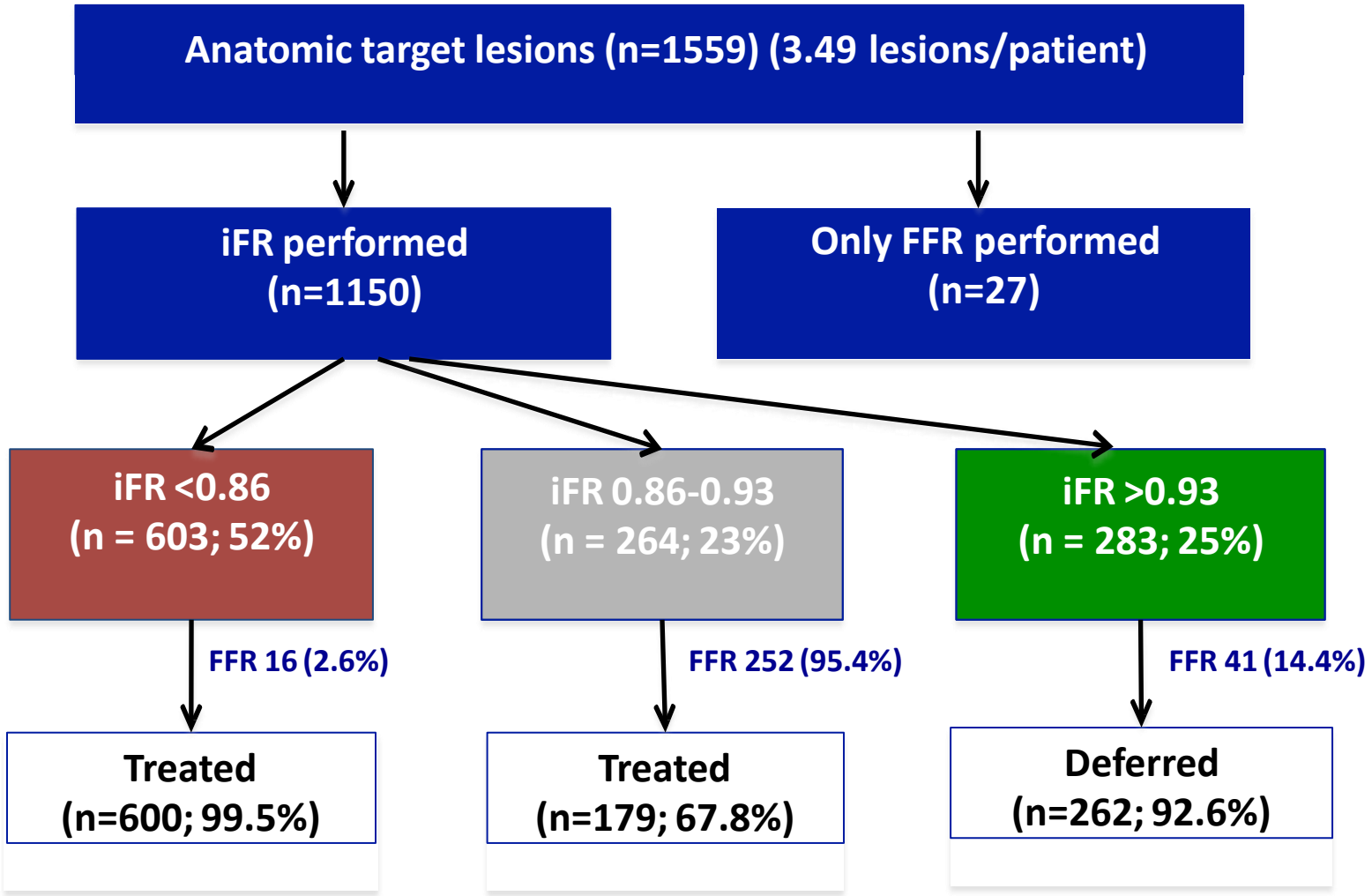
Optimal medical therapy with strict LDL control (≤ 1.8mmol/L)

# SYNTAX Score II

| | | SYNTAX II | | SYNTAX I PCI arm | | P value |
|---|---|---|---|---|---|---|
| **Components of the SYNTAX Score II** | | | | | | |
| 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 |

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

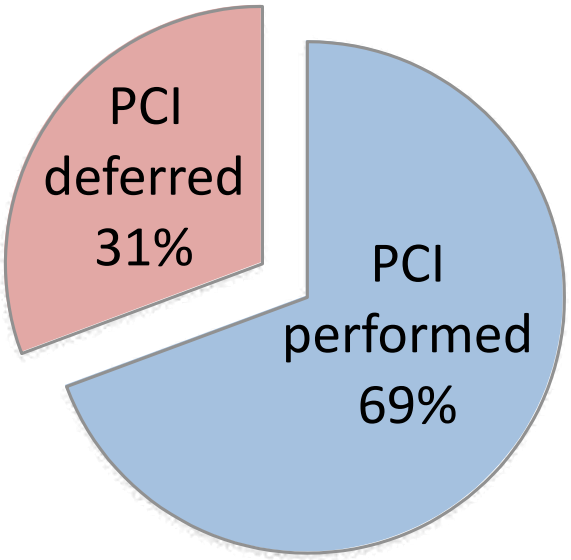
# Physiological stenosis interrogation




Escaned J, Serruys PW. Eur Heart J. 2017 Nov 7;38(42):3124-3134.

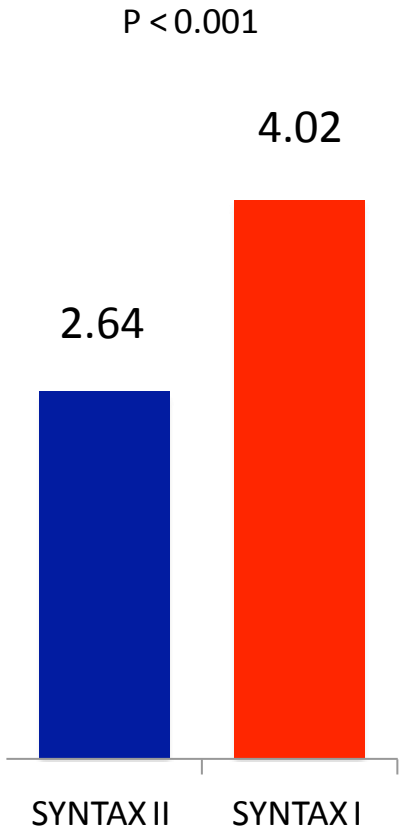
# Impact of intracoronary physiology on PCI

**Lesion treatment after iFR/FFR interrogation (n=1177)**

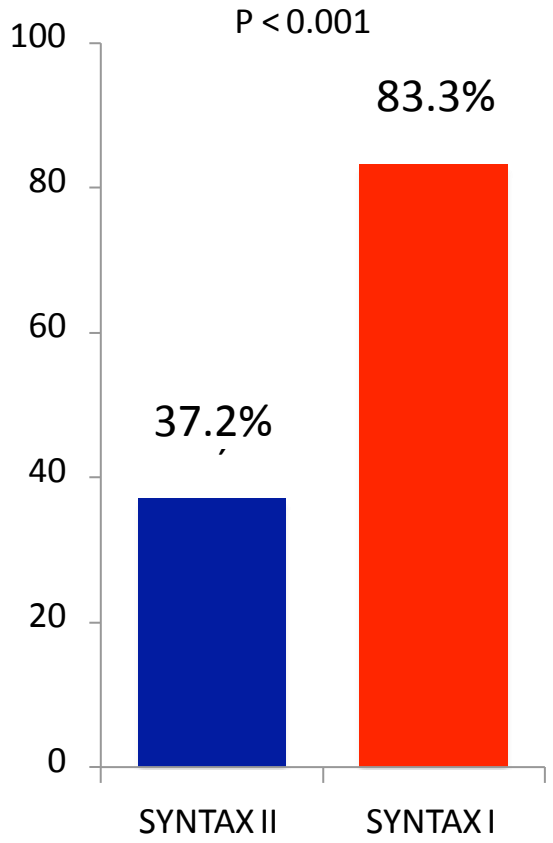



**SYNTAX II**

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

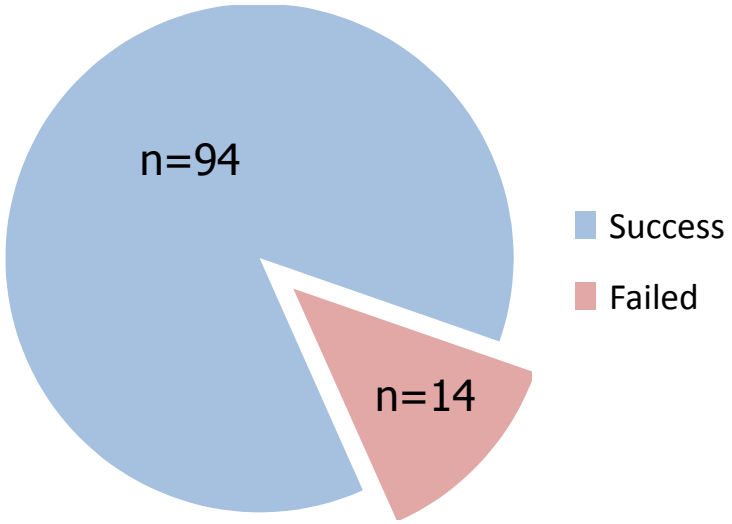



**Cases of three-vessel PCI (%) in SYNTAX II and SYNTAX I**



# Treatment of chronic total occlusions (CTO)

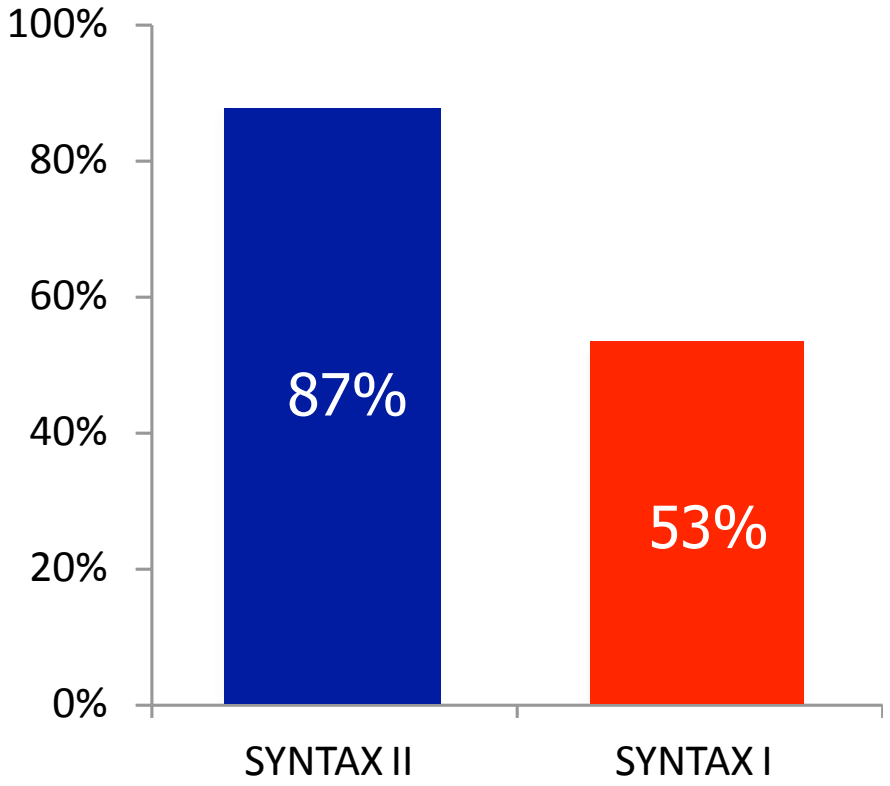
**CTO PCI procedural success rate in SYNTAX II: 87%**



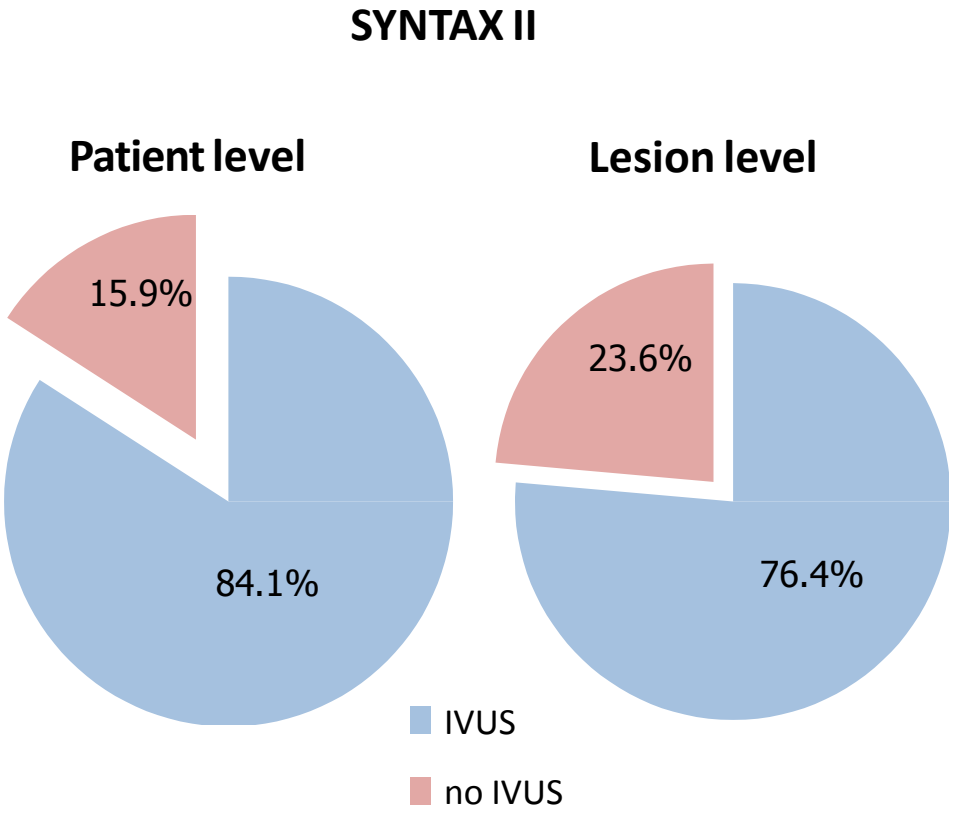

SYNTAX II CTO PCI

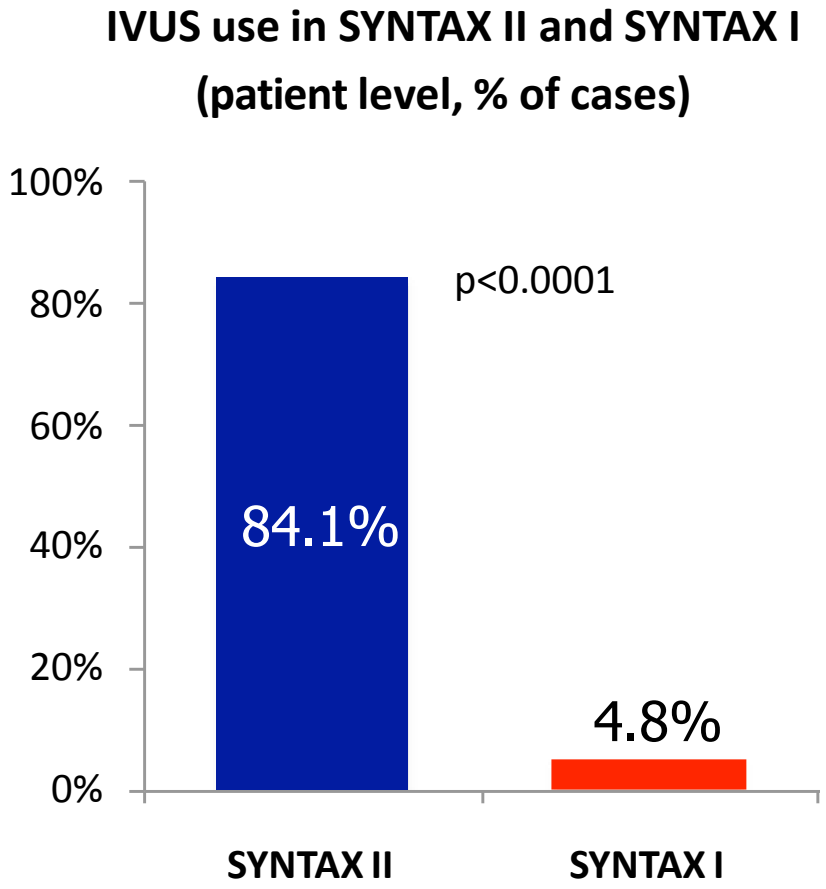
**CTO revascularisation in SYNTAX II and SYNTAX I**

p<0.0001



# Use of intravascular ultrasound (IVUS)



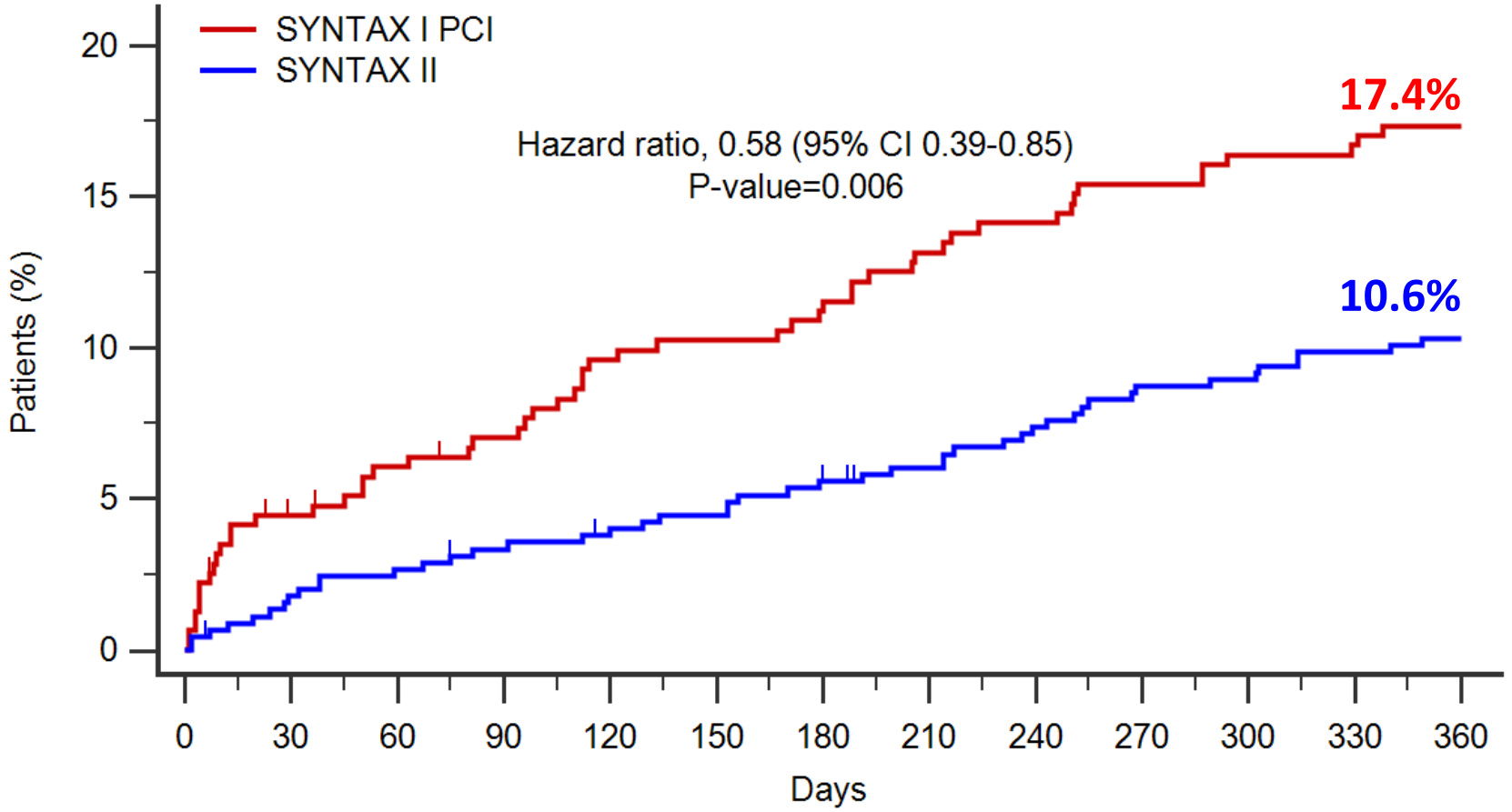




Post-implantation IVUS led to further optimisation of the stented lesion in 30.2%.

# One year follow up results

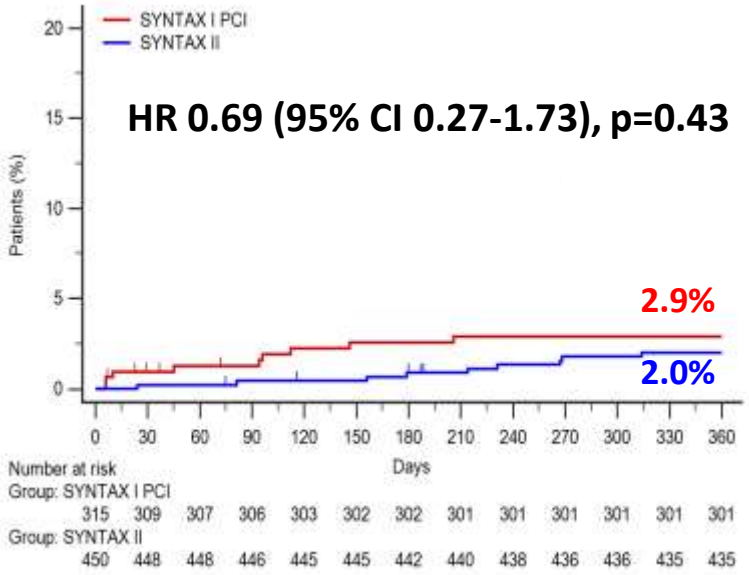
# Comparison with PCI

# Primary endpoint: MACCE

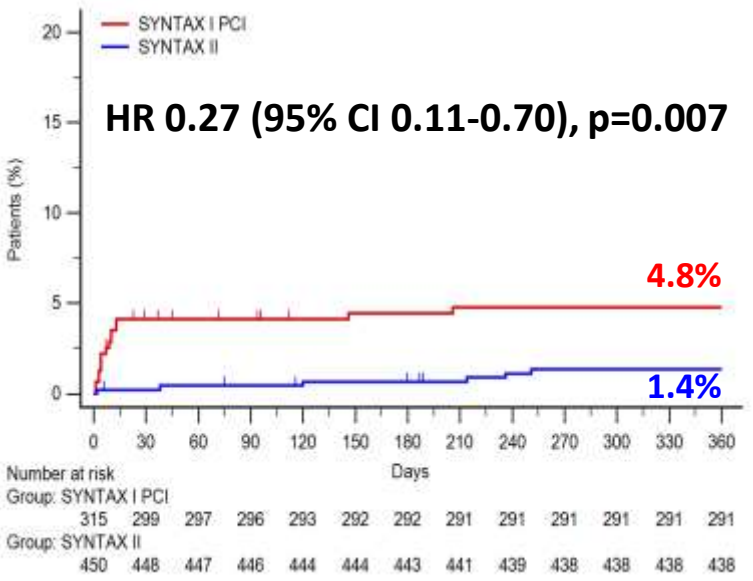



| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SYNTAX I PCI | 315 | 298 | 292 | 288 | 280 | 278 | 274 | 269 | 266 | 262 | 259 | 258 | 256 |
| SYNTAX II | 450 | 441 | 437 | 433 | 429 | 427 | 421 | 417 | 411 | 405 | 404 | 400 | 398 |

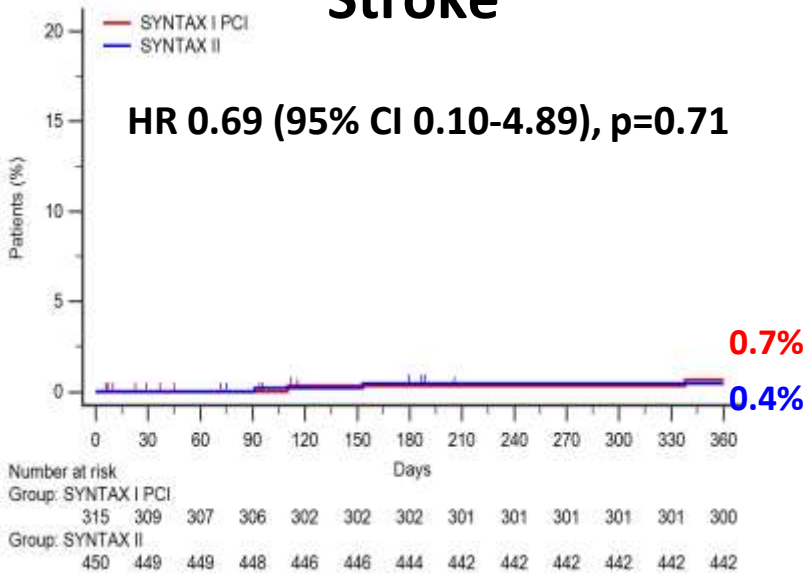
## All-cause death



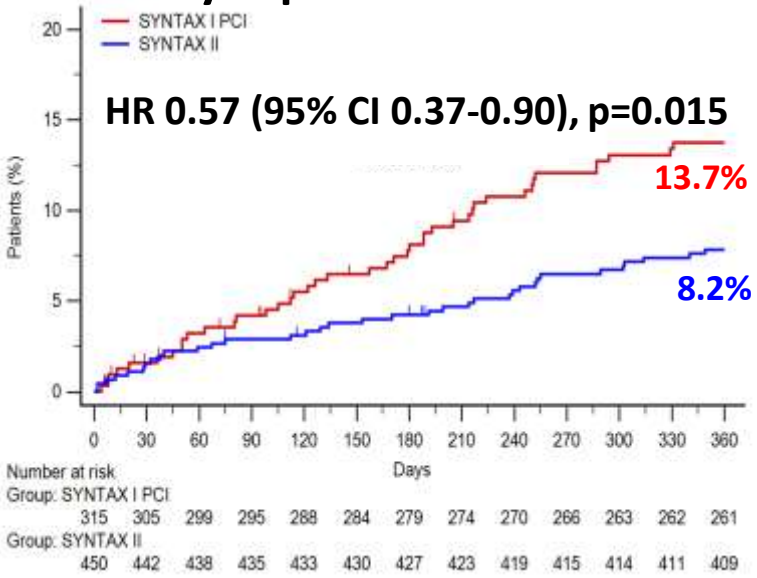

## Myocardial infarction



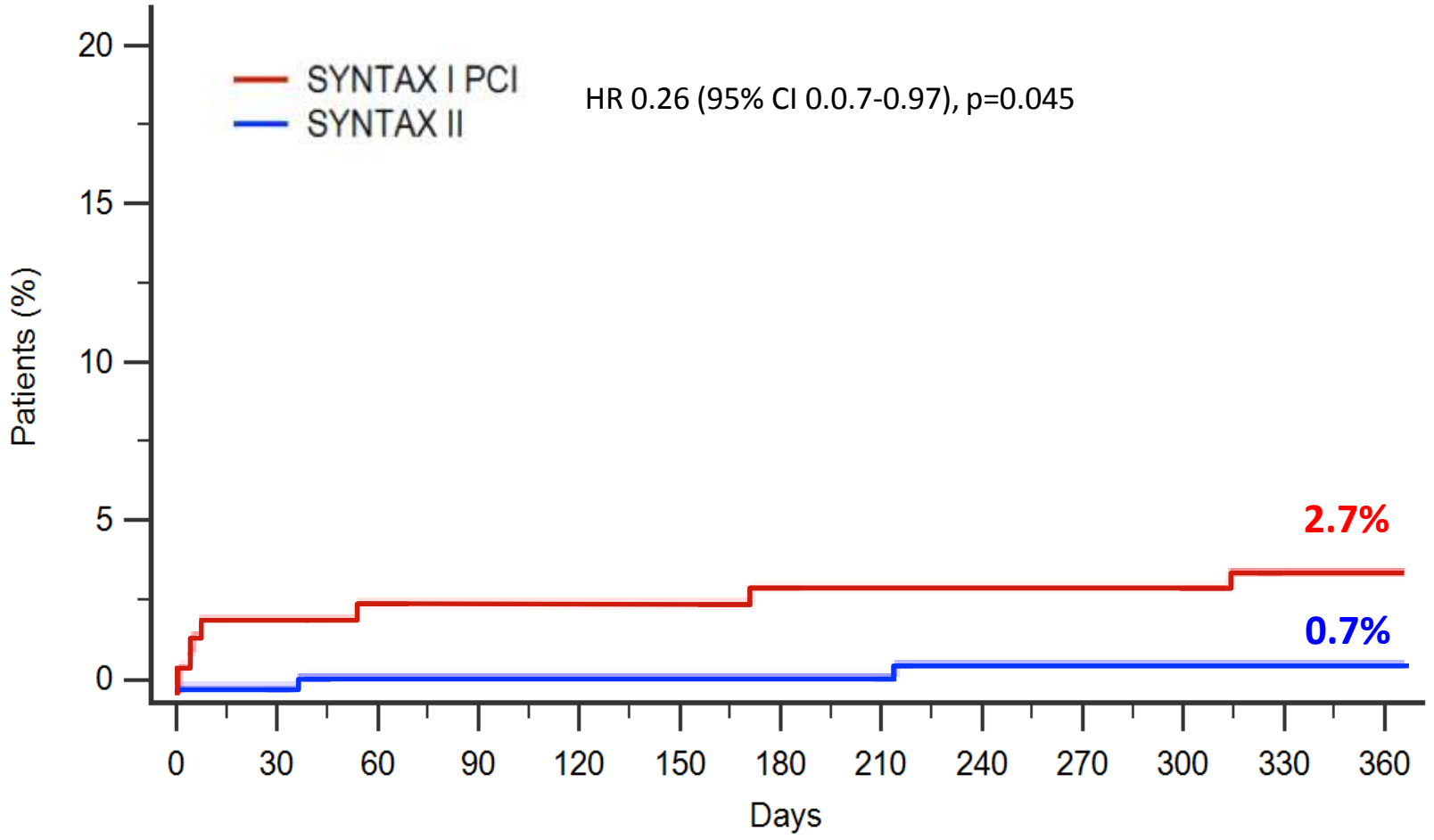

## Stroke




## Any repeat revascularization



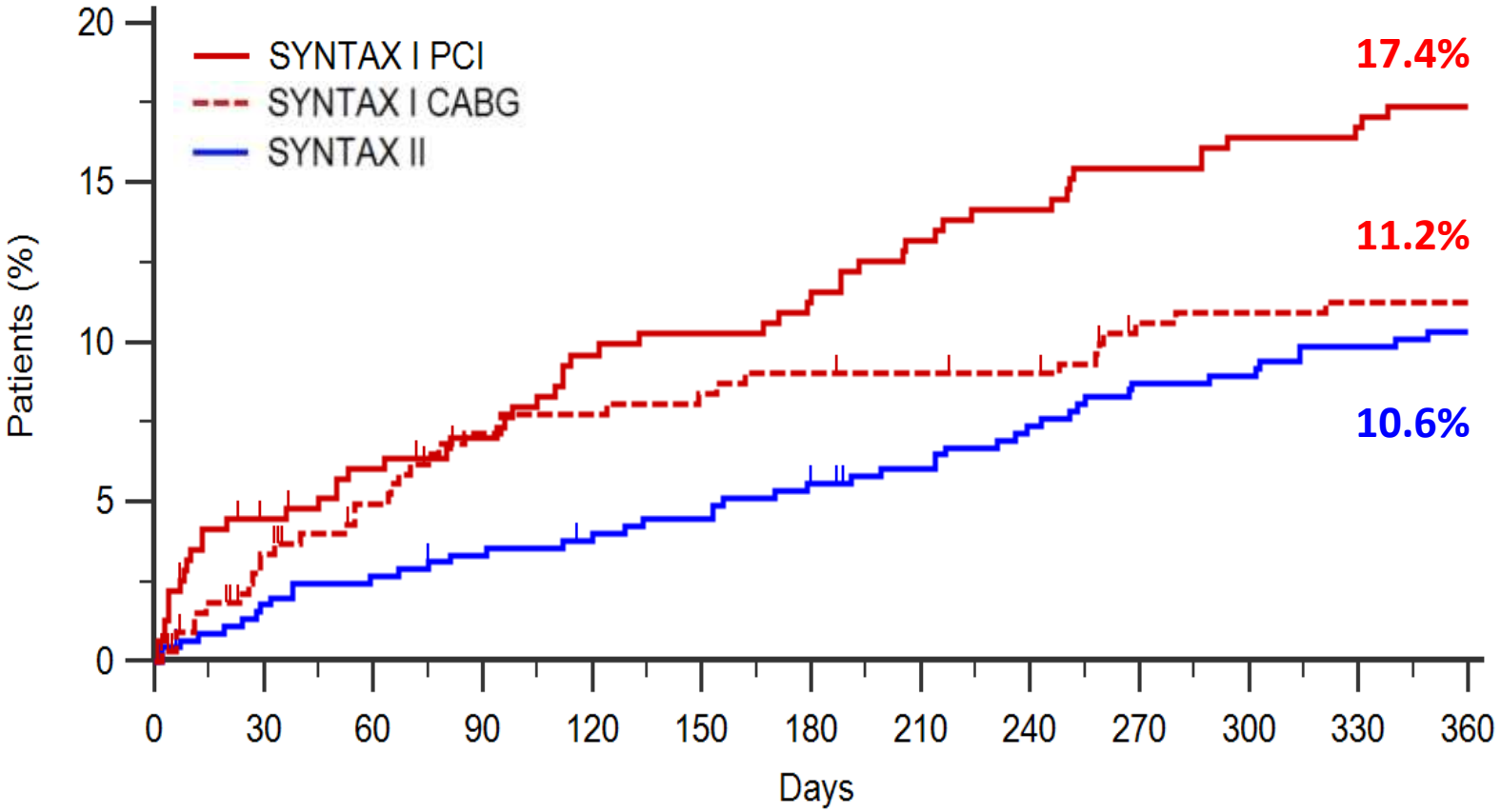
# Definite stent thrombosis




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SYNTAX I PCI | 315 | 299 | 297 | 296 | 292 | 292 | 292 | 291 | 291 | 291 | 291 | 291 | 290 |
| SYNTAX II | 450 | 447 | 446 | 444 | 441 | 441 | 437 | 435 | 431 | 428 | 428 | 427 | 427 |

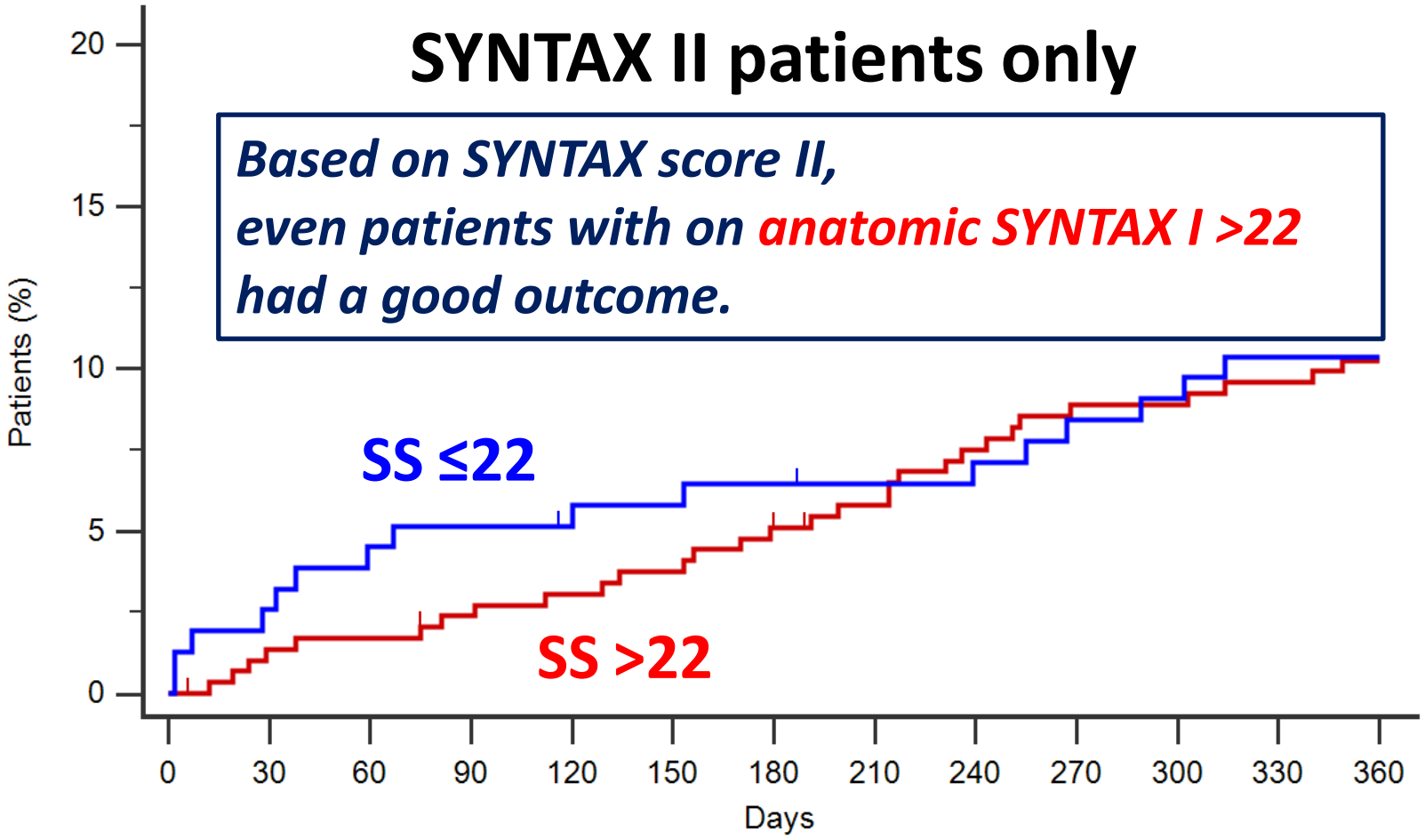
# One year follow up results
# Comparison with CABG

# MACCE SYNTAX II and SYNTAX I PCI / CABG




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SYNTAX I PCI | 315 | 298 | 292 | 288 | 280 | 278 | 274 | 269 | 266 | 262 | 259 | 258 | 256 |
| SYNTAX II | 450 | 441 | 437 | 433 | 429 | 427 | 421 | 417 | 411 | 405 | 404 | 400 | 398 |
| SYNTAX I CABG | 334 | 313 | 304 | 295 | 293 | 291 | 289 | 288 | 287 | 279 | 278 | 277 | 277 |

# SYNTAX II MACCE in SS I ≤22 and >22



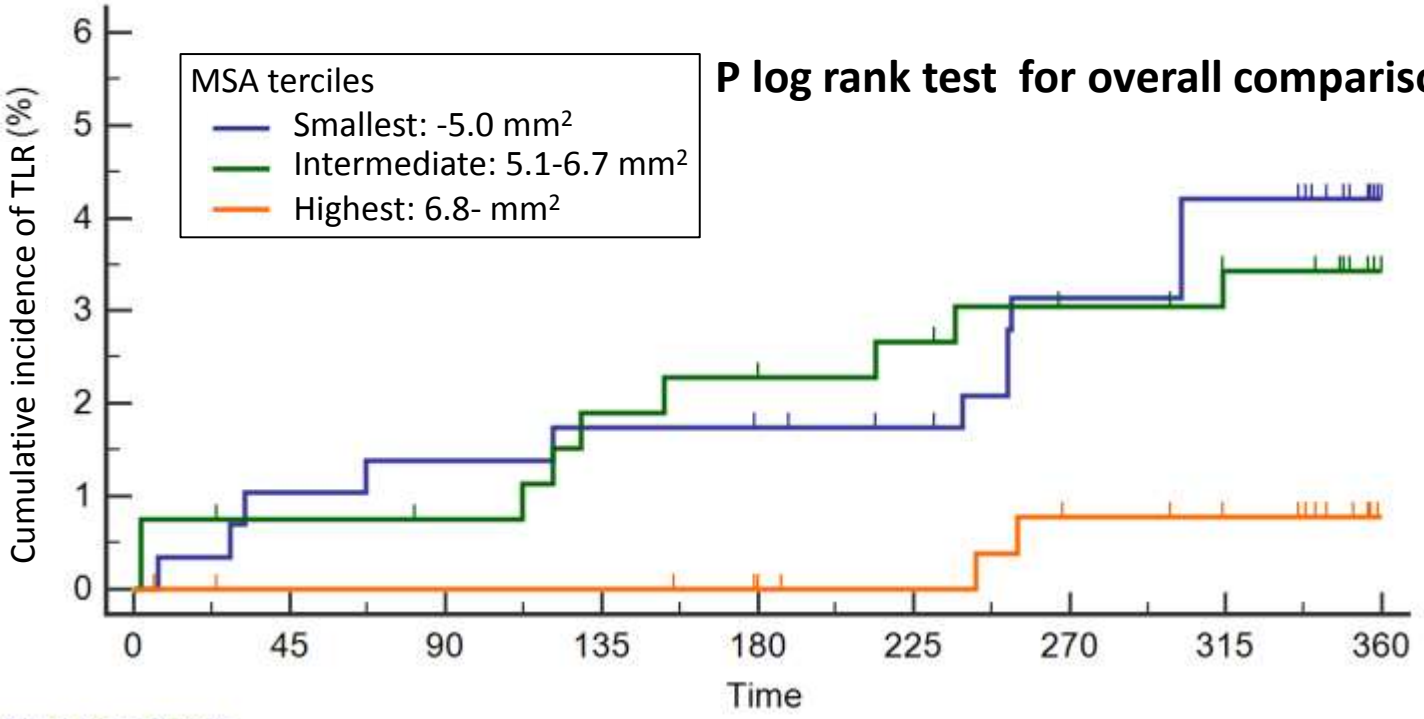

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SYNTAX SCORE >22 | 295 | 290 | 289 | 286 | 284 | 282 | 277 | 274 | 269 | 265 | 265 | 263 | 261 |
| SYNTAX SCORE ≤22 | 155 | 151 | 148 | 147 | 145 | 145 | 144 | 143 | 142 | 140 | 139 | 137 | 137 |

# One year follow up results
# Influence of post procedural MSA measured by IVUS on TLR

## - Lesion based analysis -

# TLR in post procedural MSA terciles

## SYNTAX II patients only
## Lesion based analysis




**P log rank test for overall comparison= 0.043**

Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Smallest MSA tercile: -5.0 mm² | 288 | 285 | 284 | 283 | 282 | 280 | 275 | 272 | 254 |
| Intermediate MSA tercile: 5.1-6.7 mm² | 265 | 262 | 261 | 258 | 256 | 255 | 251 | 248 | 240 |
| Highest MSA tercile: 6.8- mm² | 267 | 264 | 264 | 264 | 260 | 259 | 255 | 251 | 239 |

# Conclusions

- In patients with 3VD the use of the SYNTAX-II strategy was associated with improved clinical outcomes at one year, compared to matched patients treated percutaneously in the original SYNTAX-I trial.

- The one-year exploratory comparison between SYNTAX II and matched CABG patients from the original SYNTAX-I trial suggests non-inferiority of PCI when the SYNTAX-II strategy is followed.

- Compared to SYNTAX I, contemporary state-of-art PCI in SYNTAX II led to significantly fewer lesions treated with PCI, and significantly higher success rates in CTO revascularisation.

- One-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).