# Imaging or Not During Left Main Stenting
# Do we need a randomized trial?

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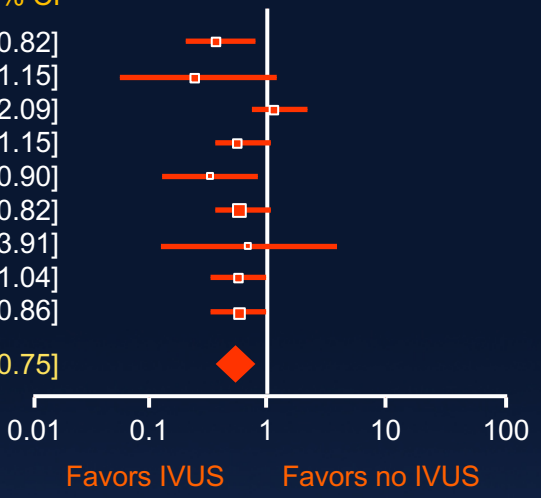
*Cardiovascular Research Foundation*

# Meta-Analysis of 10 LMCA DES Studies

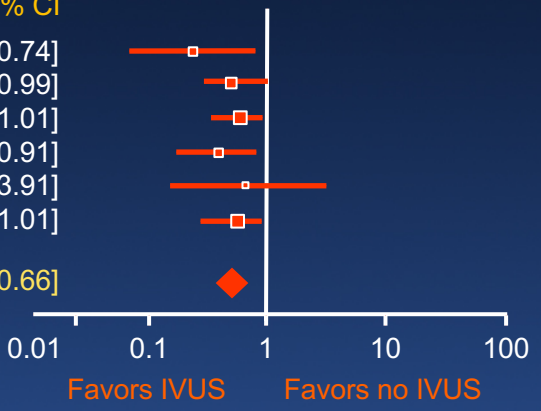
## All cause mortality

| Study or Subgroup | IVUS guided Events | IVUS guided Total | Angiography guided Events | Angiography guided Total | Risk Ratio Random 95% CI |
|---|---|---|---|---|---|
| Park et al. 2009 | 9 | 145 | 23 | 145 | 0.39 [0.19, 0.82] |
| Kinoshita et al. 2010 | 2 | 228 | 8 | 226 | 0.25 [0.05, 1.15] |
| Jama et al. 2011 | 18 | 111 | 25 | 184 | 1.19 [0.68, 2.09] |
| Narbute et al. 2012 | 13 | 294 | 47 | 671 | 0.63 [0.35, 1.15] |
| Park et al. 2012 | 5 | 90 | 15 | 92 | 0.34 [0.13, 0.90] |
| De La Torre Hernandez et al. 2014 | 37 | 505 | 66 | 505 | 0.56 [0.38, 0.82] |
| Tan et al. 2015 | 2 | 61 | 3 | 62 | 0.68 [0.12, 3.91] |
| Tang et al. 2016 | 16 | 713 | 45 | 1186 | 0.59 [0.34, 1.04] |
| Andell et al. 2017 | 37 | 340 | 63 | 340 | 0.59 [0.40, 0.86] |
| Total (95% CI) | 139 | 2487 | 295 | 3411 | 0.60 [0.47, 0.75] |




## Cardiac mortality

| Study or Subgroup | IVUS guided Events | IVUS guided Total | Angiography guided Events | Angiography guided Total | Risk Ratio Random 95% CI |
|---|---|---|---|---|---|
| Park et al. 2009 | 2 | 90 | 12 | 92 | 0.17 [0.04, 0.74] |
| Narbute et al. 2012 | 9 | 294 | 42 | 671 | 0.49 [0.24, 0.99] |
| De La Torre Hernandez et al. 2014 | 17 | 505 | 30 | 505 | 0.57 [0.32, 1.01] |
| Gao et al. 2014 | 5 | 291 | 15 | 291 | 0.33 [0.12, 0.91] |
| Tan et al. 2015 | 2 | 61 | 3 | 62 | 0.68 [0.12, 3.91] |
| Tang et al. 2016 | 9 | 713 | 31 | 1186 | 0.48 [0.23, 1.01] |
| Total (95% CI) | 44 | 1954 | 133 | 2807 | 0.47 [0.33, 0.66] |




| 2° Outcome | # Studies | IVUS | Angio | RR | 95% CI | P-value |
|---|---|---|---|---|---|---|
| MI | 7 | 114/1916 | 181/2465 | 0.80 | 0.61– 1.06 | 0.12 |
| TVR | 6 | 147/1972 | 191/2445 | 0.89 | 0.66– 1.20 | 0.44 |
| TLR | 3 | 18/442 | 43/445 | 0.43 | 0.25– 0.73 | 0.002 |
| ST | 4 | 7/1197 | 37/1198 | 0.28 | 0.12– 0.67 | 0.004 |



*Ye et al. PLoS ONE 2017;12: e0179756*

# Single-center analysis of a 1,016 pt cohort

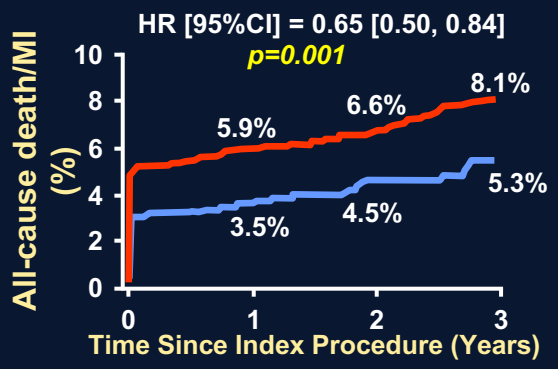
| | IVUS | No IVUS | P |
|---|---|---|---|
| **Overall** | **337** | **679** | |
| Cardiac death | 1.8% | 6.2% | 0.002 |
| STEMI | 1.2% | 3.4% | 0.004 |
| TLR | 2.4% | 9.4% | <0.001 |
| Stent thrombosis | 0.6% | 2.7% | 0.026 |
| MACE | 14.8% | 27.2% | <0.001 |
| **Propensity Score Matched** | **291** | **291** | |
| Cardiac death | 12.4% | 15.1% | 0.023 |
| STEMI | 1.0% | 3.4% | 0.05 |
| TLR | 2.7% | 8.2% | 0.004 |
| Stent thrombosis | 0.3% | 2.4% | 0.075 |
| MACE | 16.2% | 24.4% | 0.014 |

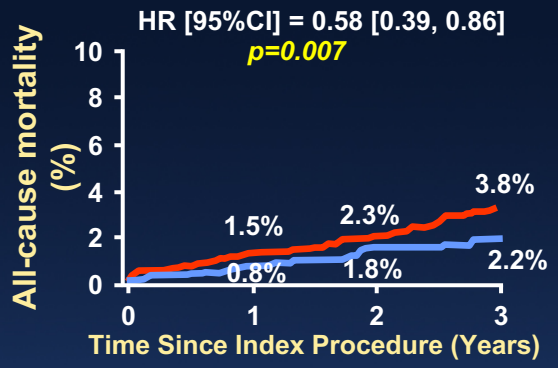
***9% ostial disease, 4.5% body disease, 20% whole trunk disease, 54% isolated distal bifurcation disease; multivessel disease in 55%; CTO in 27% (>1 CTO in 5%)***

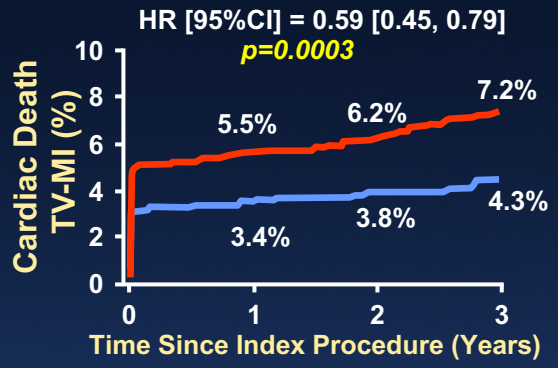


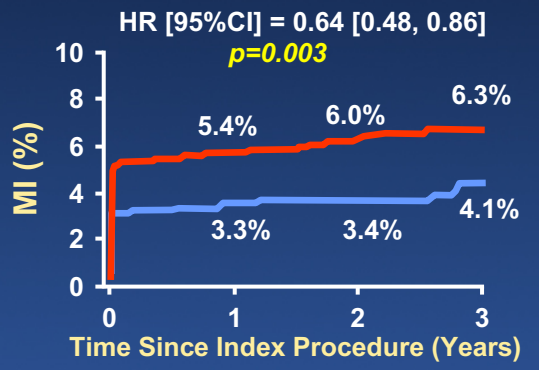
*Gao et al. Patient Pref Adherence 2014;8:1-11*

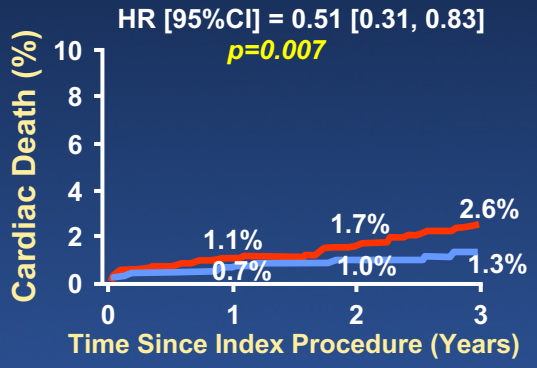
# IVUS vs angiography-guided 1899 LMCA PCI at FuWai Hospital (12% ostial, 7% shaft, 81% distal bifurcation; 7% isolated LMCA disease)




***After adjustment of baseline covariates, the trimmed-IPW model indicated good predictive value (C-statistic 0.78); and 99% of all pts (n=1880) could be entered into the final analysis.***

IVUS Guidance  Angiography Guidance

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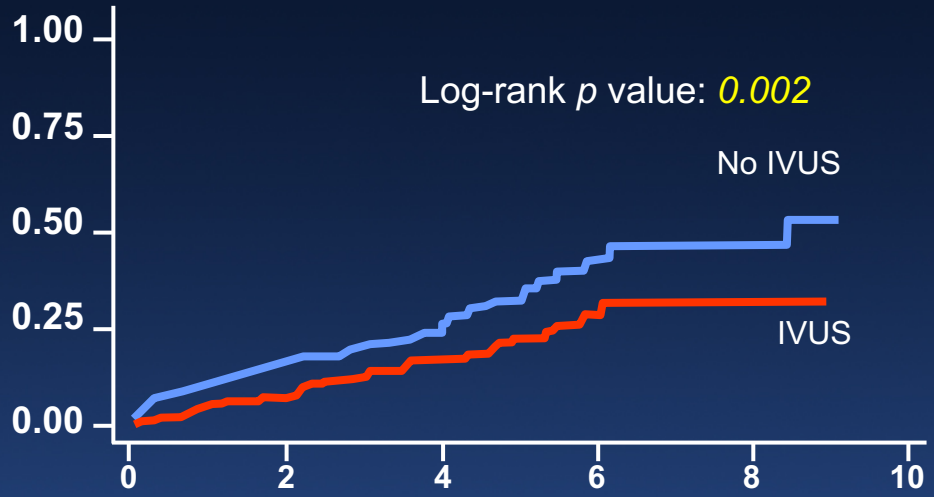
*Tian et al. Sci Rep. 2017;7:2377. doi: 10.1038/s41598-017-02649-5*

# Long-term clinical outcomes comparing IVUS-guided vs angiography-guided stent implantation for LMCA lesions: SCAAR Registry 2005-2014

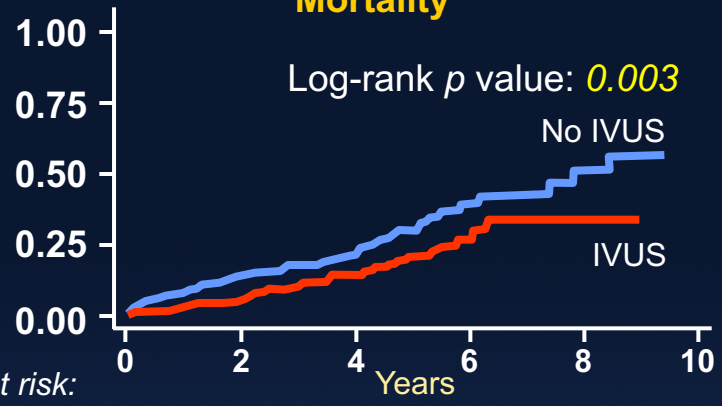
## Primary Composite Endpoint (Mortality, Restenosis, Definite ST)




*No. at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| No IVUS | 340 | 143 | 68 | 18 | 9 | 0 |
| IVUS | 340 | 167 | 70 | 24 | 7 | 0 |

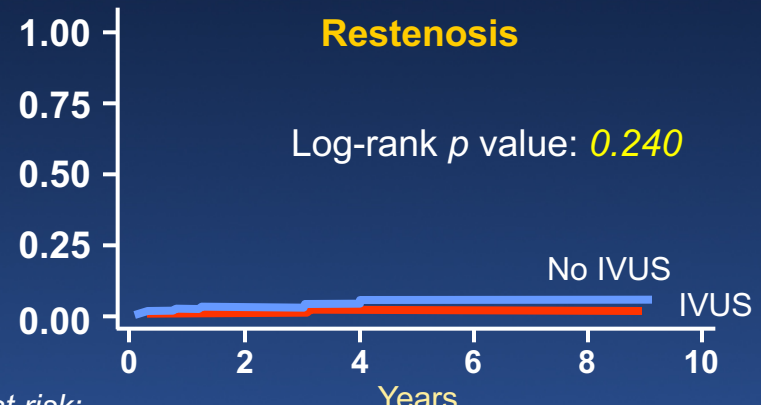
## Mortality




*No. at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| No IVUS | 340 | 148 | 73 | 22 | 10 | 0 |
| IVUS | 340 | 171 | 75 | 26 | 7 | 0 |

## Restenosis




*No. at risk:*

| | | | | | | |
|---|---|---|---|---|---|---|
| No IVUS | 340 | 143 | 68 | 18 | 9 | 0 |
| IVUS | 340 | 167 | 70 | 24 | 7 | 0 |

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*Andell et al. Circ Cardiovasc Interv* 2017;10:e004813

# IVUS-guided LM PCI with DES vs a propensity score-matched group of pts treated without IVUS guidance from 4 Spanish registries

| | IVUS | No IVUS | P |
|---|---|---|---|
| **Overall** | **505** | **505** | |
| Death | 7.4% | 13.0# | 0.01 |
| Cardiac death | 3.3% | 6.0% | 0.07 |
| MI | 4.5% | 6.5% | 0.4 |
| TLR | 7.7% | 6.3% | 0.7 |
| Death+MI+TLR | 14.4% | 22.2% | 0.006 |
| Cardiac death+MI+TLR | 11.7% | 16.0% | 0.04 |
| Definite/probable ST | 0.6% | 2.2% | 0.04 |
| **Distal lesions** | **221** | **226** | |
| Cardiac death+MI+TLR | 11.0% | 19.0% | 0.03 |
| **Distal lesions - 2 stents** | **63** | **62** | |
| Cardiac death+MI+TLR | 16.7% | 41.0% | 0.02 |



*De la Torre Hernandez et al. J Am Coll Cardiol 2014:244-54*

# Independent predictors of adverse events

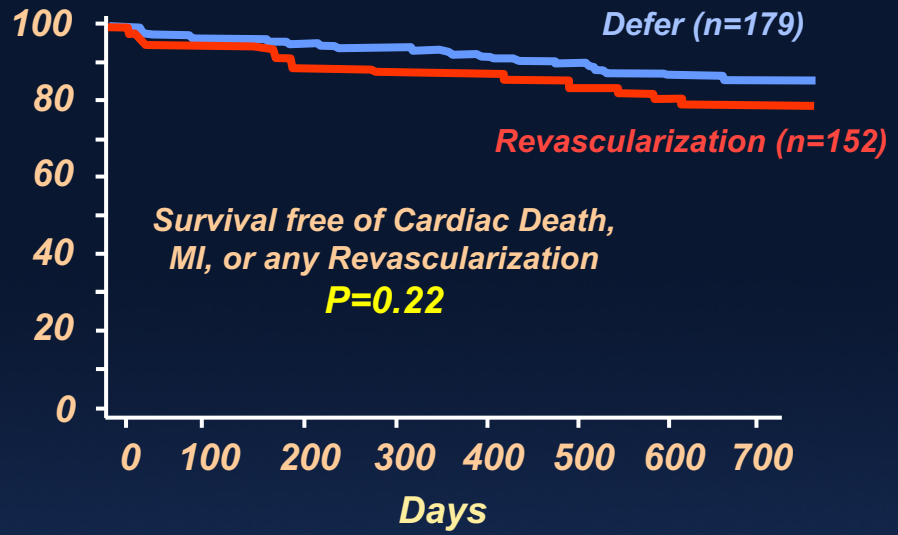
| | HR | 95% CI | P |
|---|---|---|---|
| Overall | | | |
| IVUS | 0.7 | 0.52-0.99 | 0.04 |
| Age | 1.03 | 1.01-1.05 | 0.0001 |
| LVEF | 0.98 | 0.97-0.99 | 0.01 |
| Diabetes mellitus | 1.81 | 1.32-2.47 | 0.0002 |
| Distal LM – 2 stents | 2.23 | 1.44-3.48 | 0.0004 |
| ACS | 1.84 | 1.30-2.60 | 0.0006 |
| Distal LM disease | | | |
| IVUS | 0.54 | 0.34-0.90 | 0.02 |
| Age | 1.02 | 1.00-1.05 | 0.02 |
| Diabetes mellitus | 1.62 | 1.02-2.59 | 0.04 |
| Distal LM – 2 stents | 2.86 | 1.71-4.77 | 0.0001 |
| ACS | 1.95 | 1.14-3.31 | 0.01 |

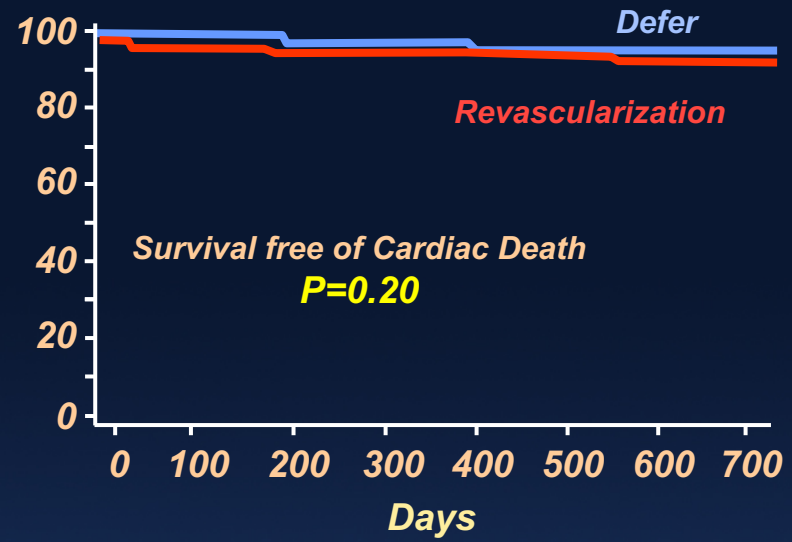


*De la Torre Hernandez et al. J Am Coll Cardiol 2014:244-54*

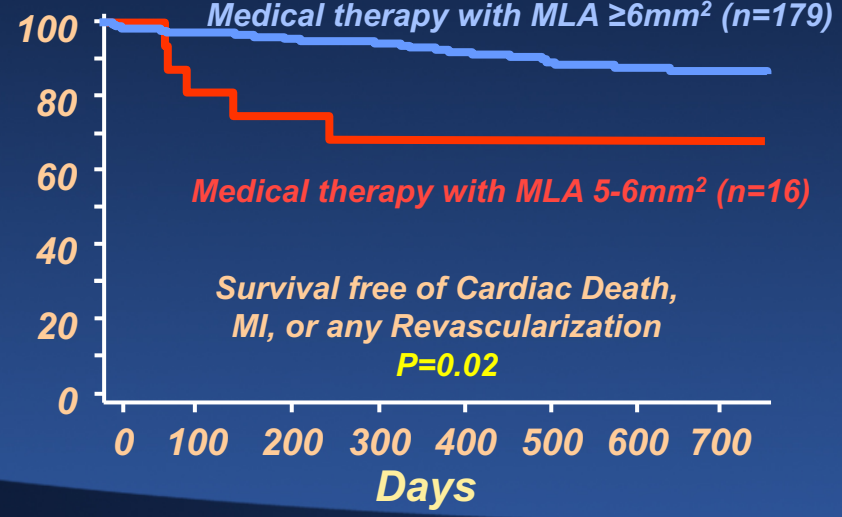
# Comprehensive use of imaging in LMCA PCI

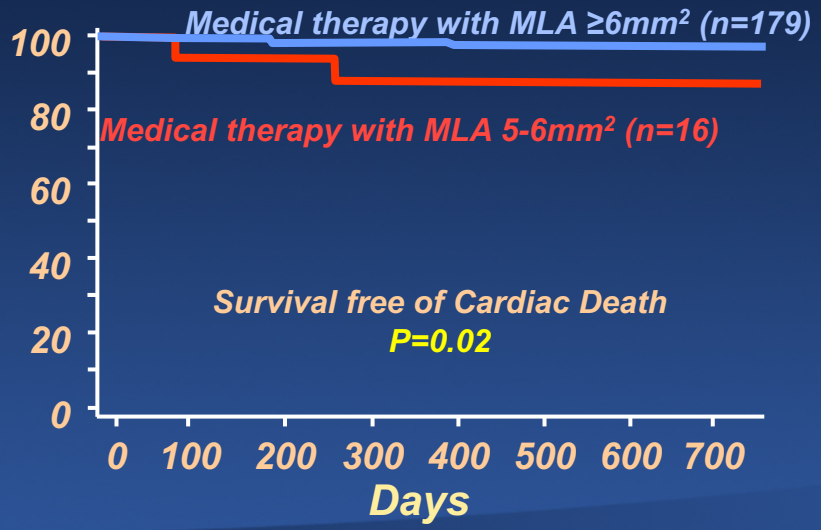
# Outcomes in 179 pts with an IVUS MLA >6mm² managed medically vs 152 pts with an IVUS MLA <6mm² managed with CABG or PCI




## Clinical Outcome of Pts Treated Medically According to MLA

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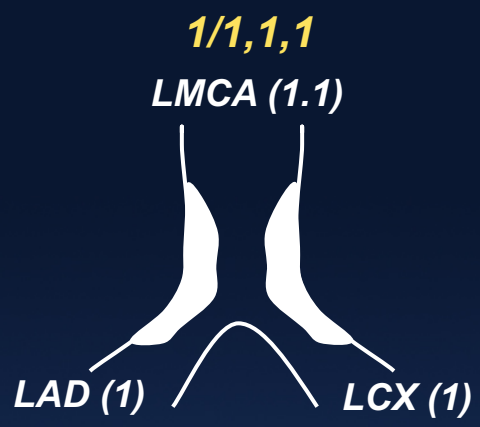
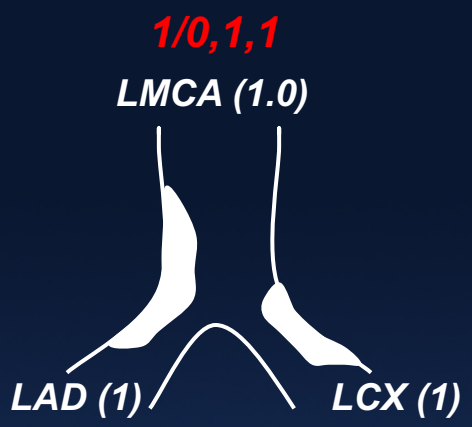
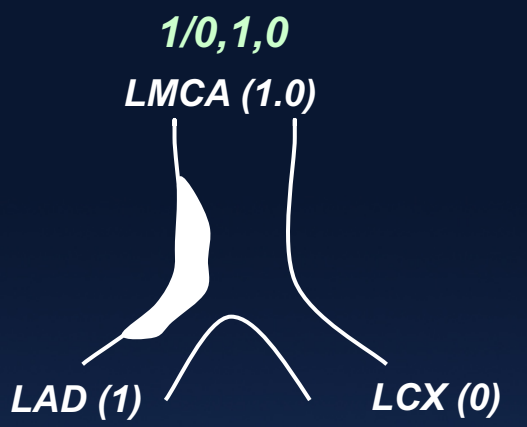
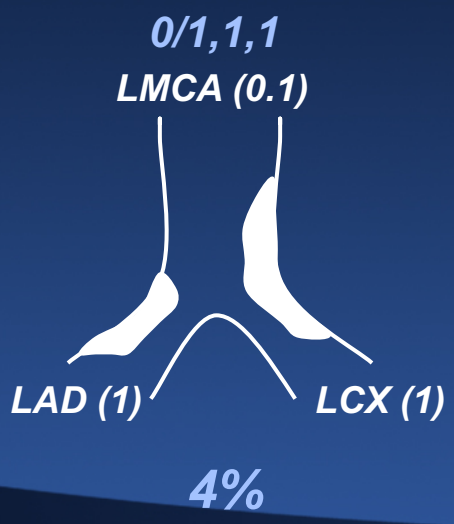
De La Torre Hernandez et al. J Am Coll Cardiol 2011;58:351-8

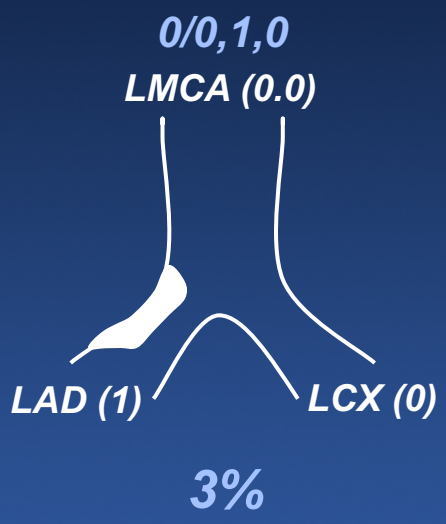
# IVUS plaque distribution in 140 distal LMCA bifurcation lesions – same patterns seen regardless of the Medina classification

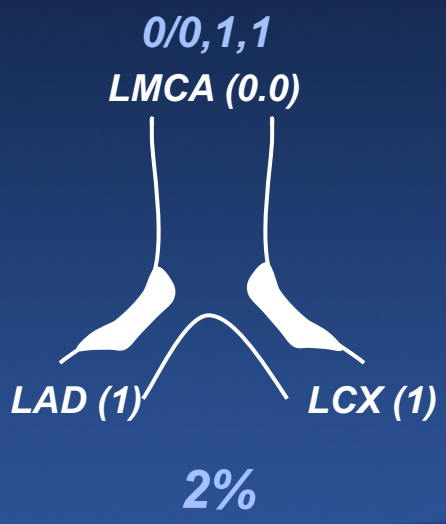


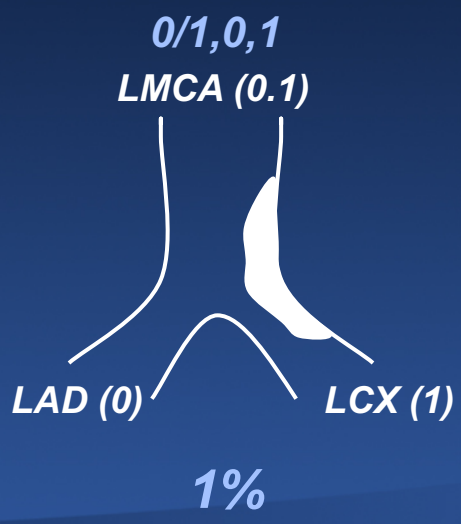

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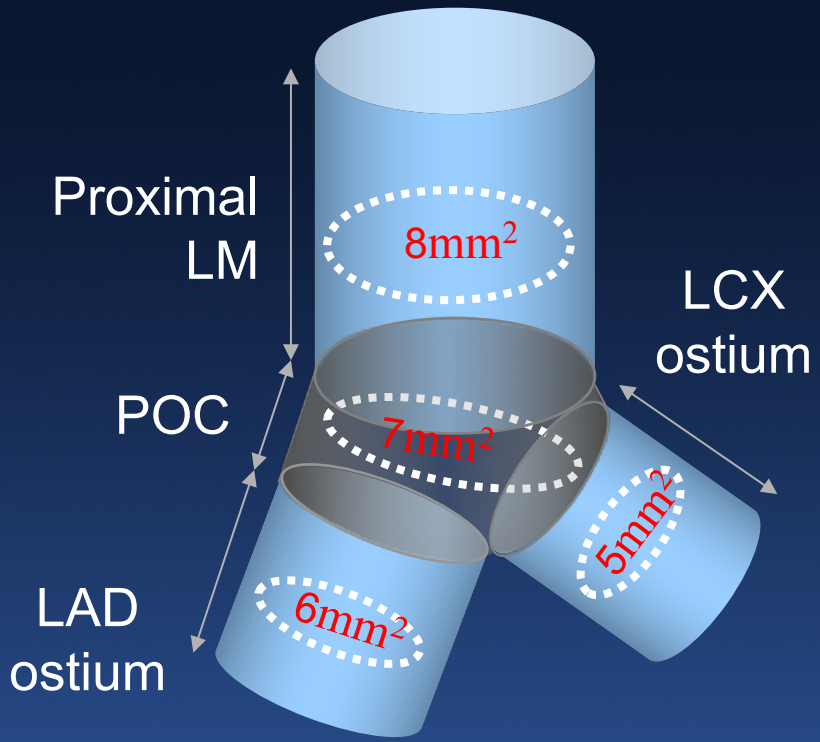
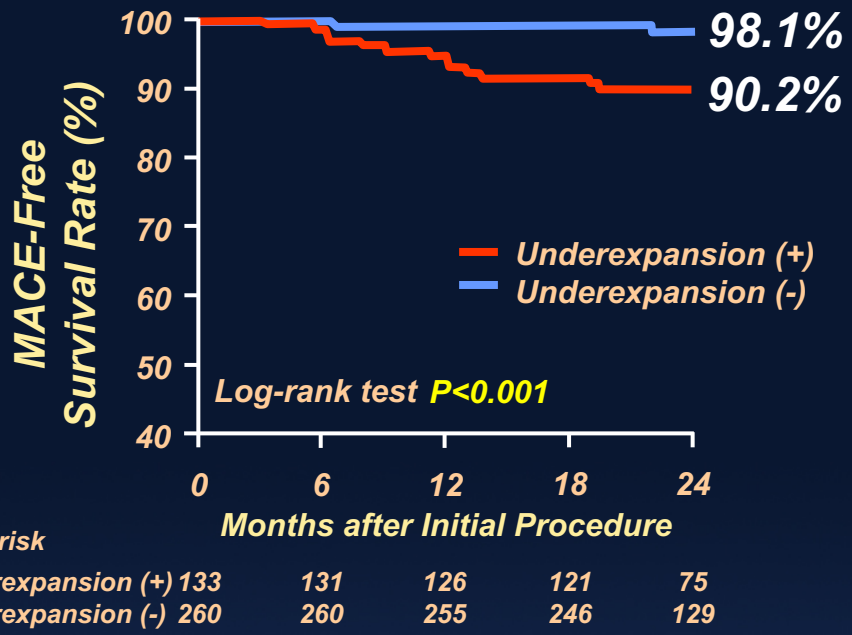
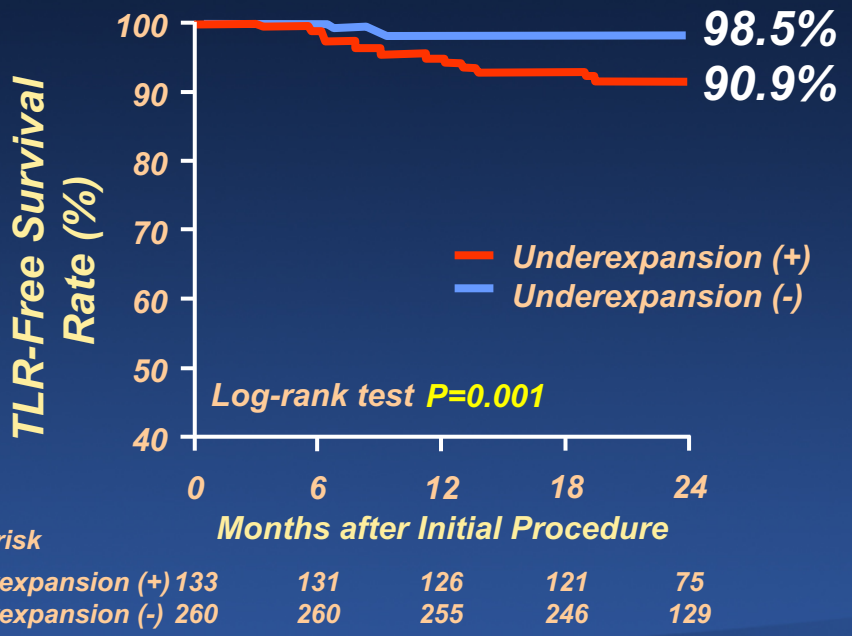
Oviedo et al. Circ Cardiovasc Interv. 2010;3:105-12

# Criteria for LMCA stent underexpansion (n=403)

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Kang et al. Circulation Cardiovasc Interv. 2011;4:562-9

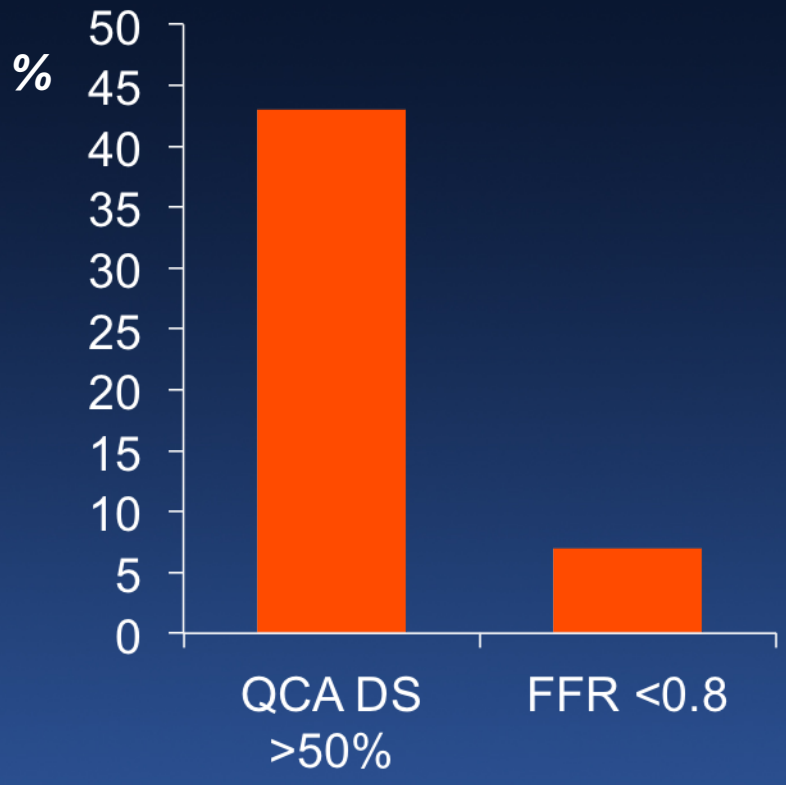
# Stent Coverage of the Ostium in 199 LMCA treated with DES

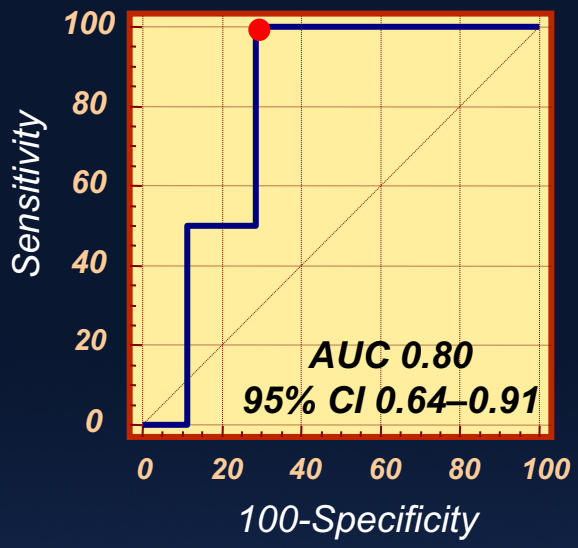
- Strut protrusion into the aorta was seen in 68%, with a protrusion length of 3.4±1.7mm
- Incomplete stent coverage of the ostium was seen in 23%, with a length of uncovered ostial segment of 2.3±1.3mm and a residual plaque burden of 38±12%
- Acute malapposition was seen in 18.8%
- Only 1.2% of LMCA developed ostial restenosis; this was not related to strut protrusion or ostial coverage or acute malapposition



*Kang et al. Am J Cardiol 2013;111:1401-7*

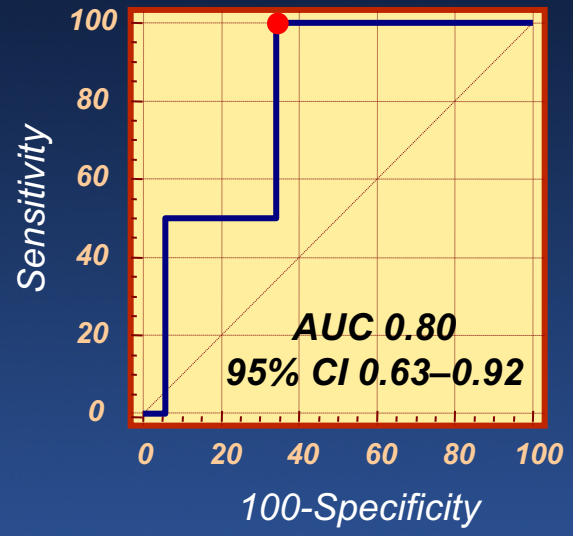
# 43 LMCA bifurcation lesions with a pre-PCI LCX ostial DS<50% were treated by single-stent cross-over




***MLA <3.7mm²***

- ***Sensitivity 100%***
- ***Specificity 71%***
- ***PPV 16%***
- ***NPV 100%***



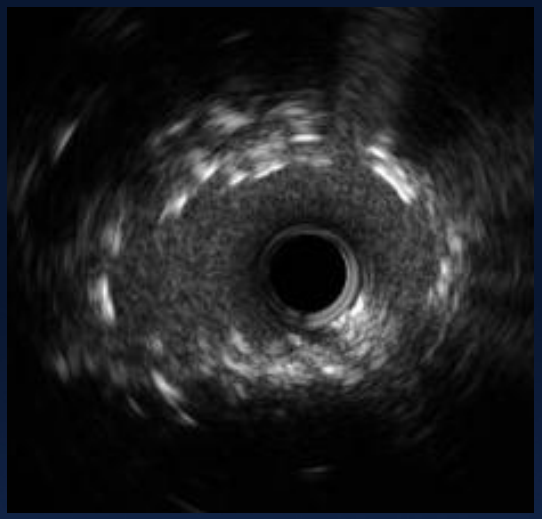

***Plaque Burden >56%***

- ***Sensitivity 100%***
- ***Specificity 65%***
- ***PPV 14%***
- ***NPV 100%***

***Kang et al. Catheter Cardiovasc Interv 2014;83:545-52***

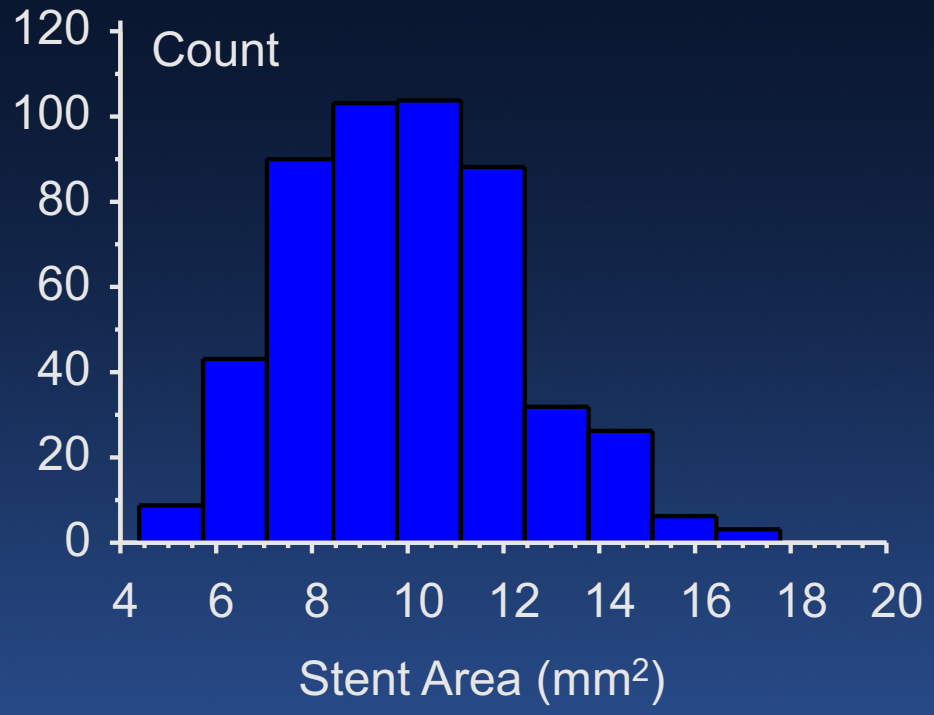
# Stent Deformation in EXCEL

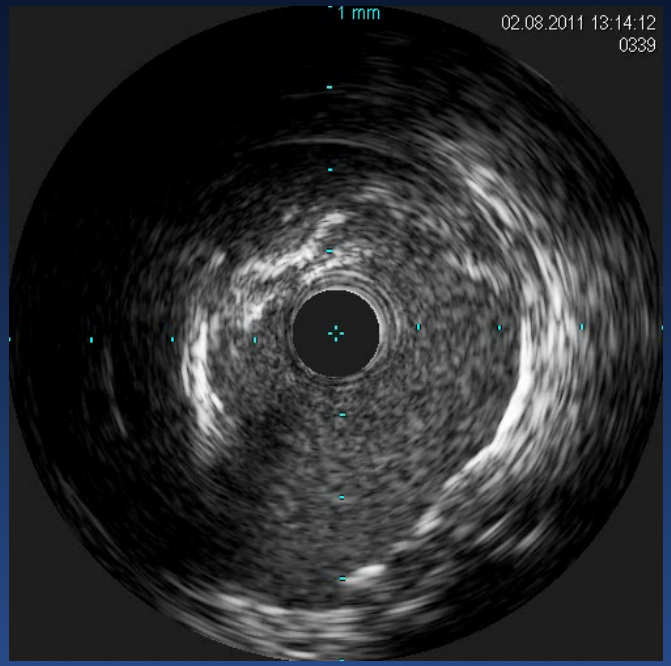
- Multiple overlapping strut layers within a single stent accompanied by stent shortening.
- Observed in 33 pts (6.6%) and was most commonly located at the LMCA ostium (27/33 [81.8%])



| | Deformation | No Deformation | P value |
|---|---|---|---|
| **3-yr LMCA-related events** | **HR [95%CI] = 2.15 [1.05, 4.40], p=0.04** | | |
| Cardiac death/MI/IDR | 28.3% | 13.9% | 0.02 |
| - Cardiac death | 9.4% | 3.6% | 0.08 |
| - MI | 18.9% | 4.7% | 0.0005 |
| - Ischemia-driven TLR | 19.9% | 8.0% | 0.02 |
| Definite/probable ST | 3.1% | 1.1% | 0.29 |

# Despite prescribing the “Kang criteria” for optimal stent expansion, this was frequently not achieved



# Lessons from Non-LMCA studies

# STARS



## A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*

**ABSTRACT**

***Background*** Antithrombotic drugs are used after coronary-artery stenting to prevent stent thrombosis. We compared the efficacy and safety of three antithrombotic-drug regimens — aspirin alone, aspirin and warfarin, and aspirin and ticlopidine — after coronary stenting.

***Methods*** Of 1965 patients who underwent coronary stenting at 50 centers, 1653 (84.1 percent) met angiographic criteria for successful placement of the stent and were randomly assigned to one of three regimens: aspirin alone (557 patients), aspirin and warfarin (550 patients), or aspirin and ticlopidine (546 patients). All clinical events reflecting stent thrombosis were included in the prespecified primary end point: death, revascularization of the target lesion, angiographically evident thrombosis, or myocardial infarction within 30 days.

***Results*** The primary end point was observed in 38 patients: 20 (3.6 percent) assigned to receive aspirin alone, 15 (2.7 percent) assigned to receive aspirin and warfarin, and 3 (0.5 percent) assigned to receive aspirin and ticlopidine ($P=0.001$ for the comparison of all three groups). Hemorrhagic complications occurred in 10 patients (1.8 percent) who received aspirin alone, 34 (6.2 percent) who received aspirin and warfarin, and 30 (5.5 percent) who received aspirin and ticlopidine ($P<0.001$ for the comparison of all three groups); the incidence of vascular surgical complications was 0.4 percent (2 patients), 2.0 percent (11 patients), and 2.0 percent (11 patients), respectively ($P=0.02$). There were no significant differences in the incidence of neutropenia or thrombocytopenia (overall incidence, 0.3 percent) among the three treatment groups.

***Conclusions*** As compared with aspirin alone and a combination of aspirin and warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis, although there were more hemorrhagic complications than with aspirin alone. After coronary stenting, aspirin and ticlopidine should be considered for the prevention of the serious complication of stent thrombosis. (N Engl J Med 1998;339:1665-71.)



THE implantation of coronary stents has become a major form of revascularization therapy for coronary artery disease. In early clinical trials,[1] there were high rates of stent thrombosis (approaching 20 percent), leading to the adoption of an antiplatelet and anticoagulant regimen that included intravenous low-molecular-weight dextran, oral aspirin and dipyridamole, and intravenous heparin followed by oral warfarin. The incorporation of this aggressive antithrombotic treatment strategy in subsequent randomized clinical trials[2-4] reduced the risk of acute and subacute stent thrombosis to approximately 3.5 percent. However, as compared with conventional balloon angioplasty, stenting with aggressive antithrombotic-drug therapy doubled the length of hospitalization (from three to six days) and increased the rate of hemorrhagic and vascular complications from 3 to 4 percent to 7 to 13 percent.[2,3,5]

More recently, registry data have demonstrated that the risk of stent thrombosis can be further reduced by the use of a combination of high-pressure, balloon-expandable stents and antithrombotic therapy with aspirin and ticlopidine.[6-8] A single-center, randomized trial also demonstrated the superiority of aspirin and ticlopidine over aspirin and warfarin for the prevention of stent thrombosis in high-risk patients.[9] Moreover, a single-center registry and one small, randomized trial suggested that aspirin alone might be adequate for the prevention of stent thrombosis.[10,11] There has also been concern about the possibility of neutropenia and thrombocytopenia in association with ticlopidine therapy.[12] We compared the 30-day clinical outcomes for three antithrombotic-drug regimens — aspirin alone, aspirin and warfarin, and aspirin and ticlopidine — after elective coronary-artery stenting.

### METHODS

#### Objectives and Design of the Study and Selection of Patients

The primary objective was to compare the incidence of stent thrombosis in patients with single-vessel or multivessel disease of native coronary arteries who were successfully treated with a high-pressure, balloon-expandable stent at 1 of 50 centers in the United States and who were then randomly assigned to receive one of three antithrombotic-drug regimens. The implantation of a Palmaz–Schatz stent (Cordis, Warren, N.J.) was considered to

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*Other members of the Stent Anticoagulation Restenosis Study are listed in the Appendix.





# CRUISE

## Final Results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) Study

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***Background***—Intravascular ultrasound (IVUS) can assess stent geometry more accurately than angiography. Several studies have demonstrated that the degree of stent expansion as measured by IVUS directly correlated to clinical outcome. However, it is unclear if routine ultrasound guidance of stent implantation improves clinical outcome as compared with angiographic guidance alone.

***Methods and Results***—The CRUISE (Can Routine Ultrasound Influence Stent Expansion) study, a multicenter study IVUS substudy of the Stent Anti-thrombotic Regimen Study, was designed to assess the impact of IVUS on stent deployment in the high-pressure era. Nine centers were prospectively assigned to stent deployment with the use of ultrasound guidance and 7 centers to angiographic guidance alone with documentary (blinded) IVUS at the conclusion of the procedure. A total of 525 patients were enrolled with completed quantitative coronary angiography, quantitative coronary ultrasound, and clinical events adjudicated at 9 months for 499 patients. The IVUS-guided group had a larger minimal lumen diameter ($2.9\pm0.4$ versus $2.7\pm0.5$ mm, $P<0.001$) by quantitative coronary angiography and a larger minimal stent area ($7.78\pm1.72$ versus $7.06\pm2.13$ mm$^2$, $P<0.001$) by quantitative coronary ultrasound. Target vessel revascularization, defined as clinically driven repeat interventional or surgical therapy of the index vessel at 9 month-follow-up, occurred significantly less frequently in the IVUS-guided group (8.5% versus 15.3%, $P<0.05$; relative reduction of 44%).

***Conclusions***—These data suggest that ultrasound guidance of stent implantation may result in more effective stent expansion compared with angiographic guidance alone. (***Circulation*. 2000;102:523-530.**)

**Key Words:** stents ■ coronary disease ■ ultrasonics ■ angiography ■ restenosis

Coronary stenting has evolved into the most common catheter-based treatment of coronary artery disease.[1–3] Early in the clinical experience with stenting, intravascular ultrasound (IVUS) played a key role in refining appropriate stent deployment strategies. IVUS studies demonstrated that incomplete deployment of stents occurred in up to 80% of patients at nominal pressures (8 to 12 atm). This insight helped usher in the use of high pressure (>12 atm) techniques and emphasized the need for careful attention to maximizing target segment expansion.

The role of IVUS in the current, high-pressure era of stenting has not been clearly defined. Several studies have shown that IVUS is more accurate than angiography in determining in-stent dimensions and is better able to detect subtle findings such as incomplete apposition of the stent to the vessel wall and dissections at the stent margins.[4–9] Recently, several single-center studies have demonstrated that the IVUS measurement of minimal stent area (MSA) is the single most powerful predictor of long-term patency and clinical outcome.[10–13] No previous study, however, has directly addressed whether IVUS-guided stenting leads to improved results than stenting with angiographic guidance alone.

The CRUISE study (Can Routine Ultrasound Influence Stent Expansion) was designed to compare IVUS-guided

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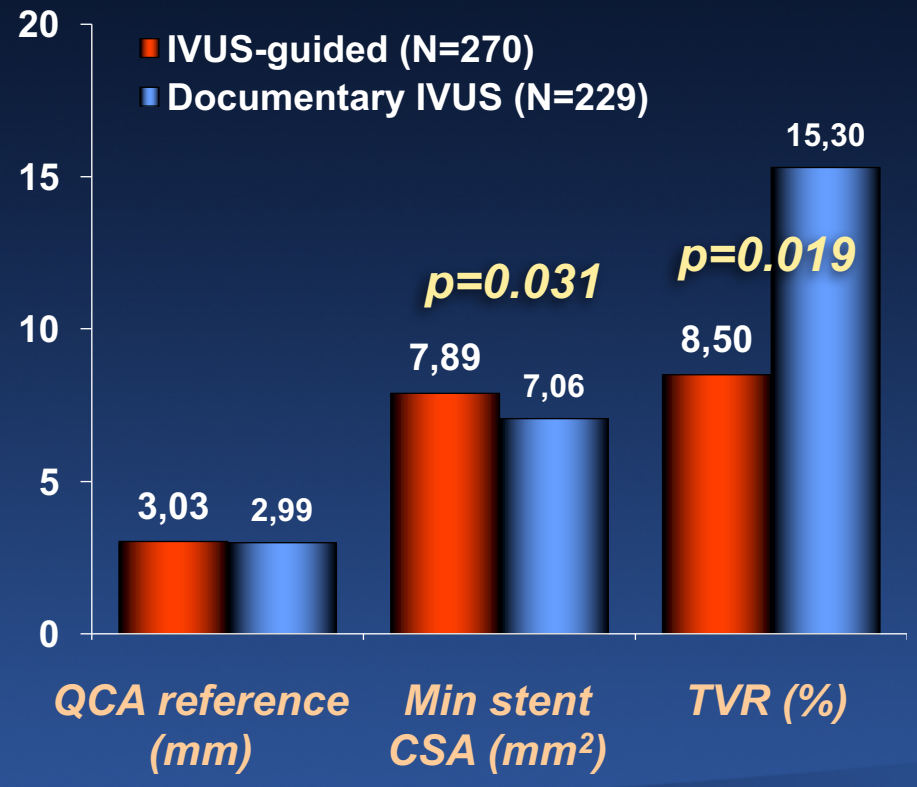
# CRUISE

## (Can Routine Ultrasound Impact Stent Expansion)

***Study was designed to deal with the conundrum of a RCT in which experienced IVUS users approach angio-guided PCI with a different mindset and "eye" vs inexperienced IVUS users who (1) do not know how to use the IVUS information and/or (2) might improve their angio-guided PCI results based on the IVUS experience acquired during the trial***

***By choice, STARS sites opted for:***

- ***IVUS-guided stenting (N=270)***
- ***Angiographically-guided stenting with documentary (binded) IVUS (N=229)***
- ***Angiographically-guided stenting without IVUS***

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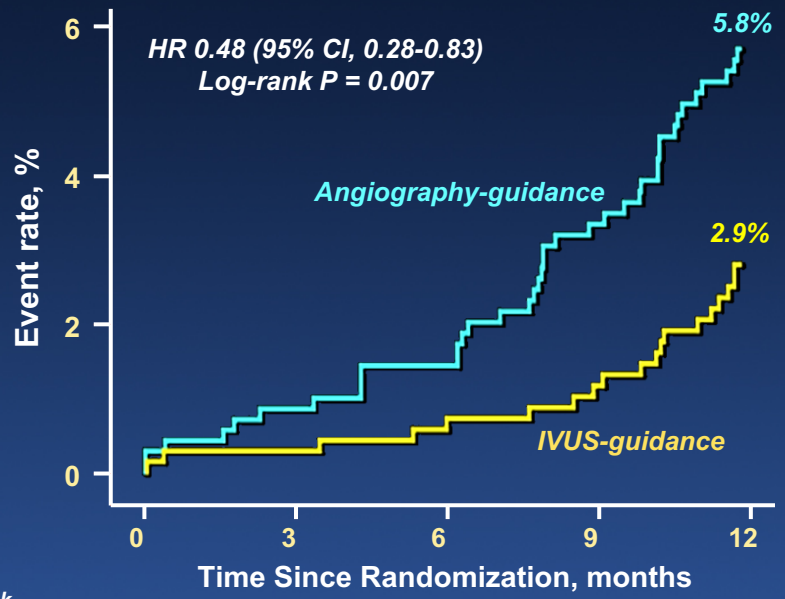
***Fitzgerald et al. Circulation 2000;102:523-530***

# Effect of IVUS- vs. Angiography-Guided Everolimus-Eluting Stent Implantation:

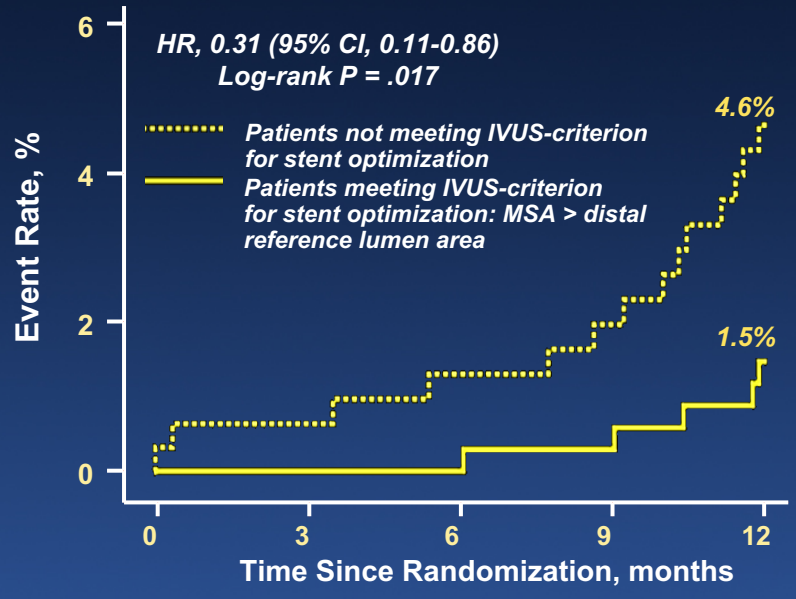
## The 1400 pt IVUS-XPL Randomized Clinical Trial in which (1) the same >28mm EES stent was used in all pts and (2) there was minimal cross-over between groups

### Primary End Point – Intention-to-Treat Analysis




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Angiography arm | 700 | 673 | 660 | 643 | 624 |
| IVUS arm | 700 | 671 | 665 | 654 | 641 |

### IVUS-guided acute optimization was reached in *only half*




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Not meeting criteria | 315 | 299 | 297 | 394 | 285 |
| Meeting criteria | 363 | 362 | 345 | 338 | 334 |

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*Hong et al. JAMA 2015;314:2155-63*

# Issues to consider in a randomized trial of imaging vs angiography guided LMCA PCI

- Extent of disease
  - Isolated LMCA
  - Multivessel disease
  - Concomitant CTO(s)
- IVUS or OCT or “either (operator preference)”
- Pre-intervention imaging? If so, just the main branch or both main and side branches?
- PCI Stratergy and Optimization
  - Definition
  - Need to “control” imaging arm to ensure optimization
- Site selection
  - Experienced vs novice imagers
  - Need to “control” image interpretation competency in the cath lab – measurements, stent deformation, etc
- Study endpoints

We are in the “business” of collecting data, doing trials, and writing papers. Therefore, the automatic response to any question is “we need more data” or “we need a randomized trial.”

But first, we should stop to ask ourselves. . .

What is the question that we want to answer?
Do we already know the answer?
Will a randomized trial make a difference – especially, in terms of clinical practice?

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