

# Approaches to Stable CAD In Favor of Revascularization: **Ischemia Makes the Difference!**

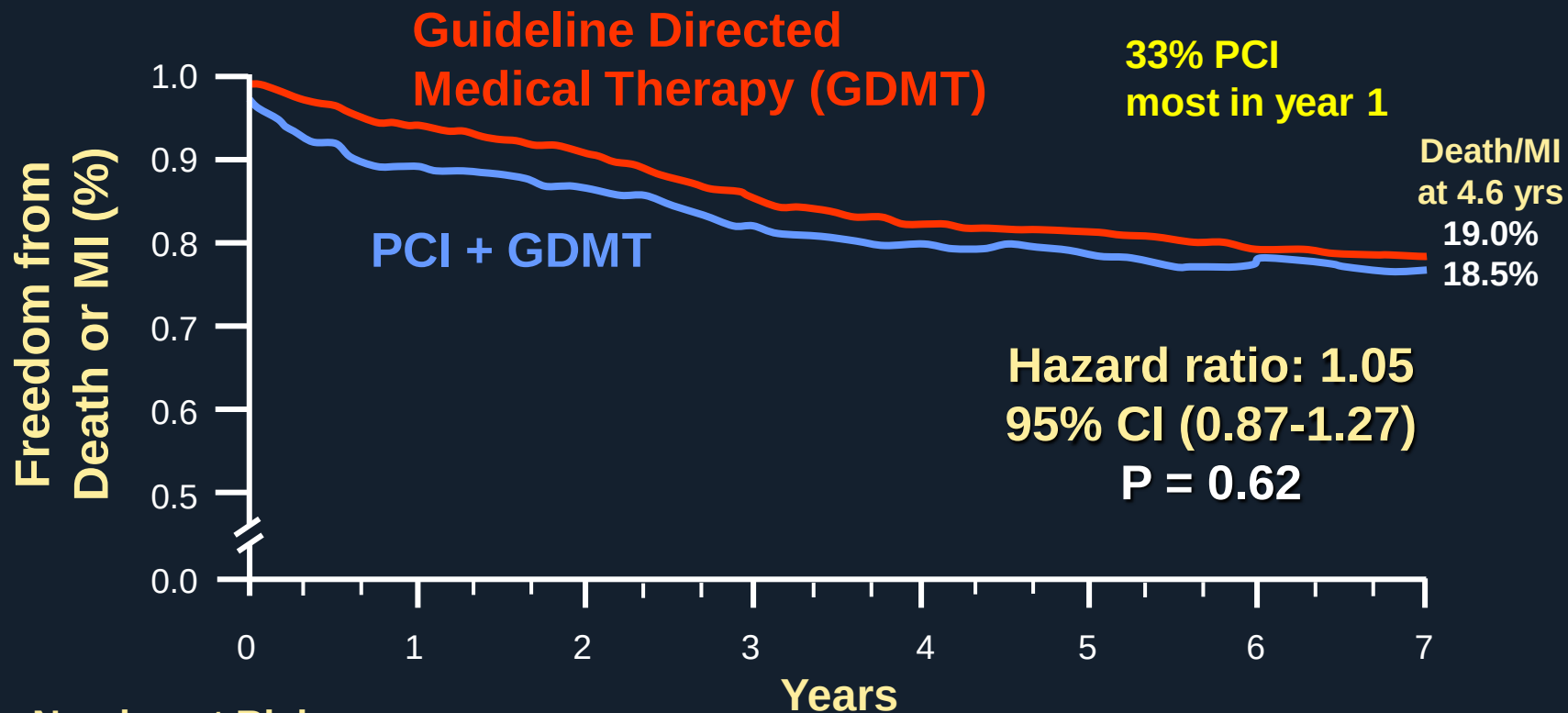
Gregg W. Stone, MD

Professor of Medicine  
Columbia University Medical Center  
NewYork-Presbyterian Hospital  
Cardiovascular Research Foundation



# PCI in Stable CAD: **COURAGE**

Median FU 4.6 years (n=2,287)



## Number at Risk

|     |      |      |     |     |     |     |     |    |
|-----|------|------|-----|-----|-----|-----|-----|----|
| OMT | 1138 | 1017 | 959 | 834 | 638 | 408 | 192 | 30 |
| PCI | 1149 | 1013 | 952 | 833 | 637 | 417 | 200 | 35 |



# Reduction in Angina According to Baseline Anginal Severity (SAQ)

Baseline  
angina  
frequency

~2-3x/  
week

~1x/  
month

Almost  
never

| P <sub>int</sub> = 0.008 | Score               |       | Change from Baseline |            |      |
|--------------------------|---------------------|-------|----------------------|------------|------|
|                          | PCI + GDMT          | GDMT  | P Value              | PCI + GDMT | GDMT |
|                          | No. of scale points |       |                      |            |      |
| First tertile            |                     |       |                      |            |      |
| Baseline                 | 35±14               | 35±14 | 0.75                 |            |      |
| 1 mo                     | 68±27               | 58±25 | <0.001               | 33         | 23   |
| 3 mo                     | 74±27               | 65±26 | <0.001               | 39         | 30   |
| 6 mo                     | 78±25               | 72±25 | 0.02                 | 43         | 38   |
| 12 mo                    | 78±25               | 75±23 | 0.09                 | 44         | 40   |
| 24 mo                    | 79±25               | 79±23 | 0.03                 | 49         | 45   |
| 36 mo                    | 83±21               | 82±22 | 0.94                 | 48         | 48   |
| Second tertile           |                     |       |                      |            |      |
| Baseline                 | 71±8                | 71±8  | 0.18                 |            |      |
| 1 mo                     | 81±19               | 76±20 | 0.002                | 9.5        | 5.3  |
| 3 mo                     | 86±18               | 79±22 | <0.001               | 15         | 8.8  |
| 6 mo                     | 87±18               | 82±21 | 0.002                | 16         | 12   |
| 12 mo                    | 88±17               | 85±20 | 0.02                 | 17         | 14   |
| 24 mo                    | 90±16               | 85±19 | 0.001                | 18         | 14   |
| 36 mo                    | 89±18               | 87±17 | 0.28                 | 17         | 16   |
| Third tertile            |                     |       |                      |            |      |
| Baseline                 | 97±5                | 97±5  | 0.61                 |            |      |
| 1 mo                     | 93±14               | 88±19 | 0.002                | -4.4       | -8.7 |
| 3 mo                     | 91±18               | 90±16 | 0.67                 | -6.0       | -6.7 |
| 6 mo                     | 92±15               | 89±19 | 0.02                 | -4.9       | -8.2 |
| 12 mo                    | 93±14               | 90±18 | 0.02                 | -4.3       | -7.3 |
| 24 mo                    | 92±15               | 91±15 | 0.64                 | -5.0       | -5.8 |
| 36 mo                    | 94±14               | 93±14 | 0.31                 | -2.8       | -4.4 |



# Freedom from Anti-anginal Meds

Despite 32% XO to PCI in the GDMT group

## PCI + GDMT compared to GDMT resulted in:

- Significantly less use of nitrates at:
  - 1 year (53% vs. 67%)
  - 3 years (47% vs. 61%)
  - 5 years (40% vs. 57%)
- Significantly less use of  $\text{Ca}^{+2}$  channel blockers at:
  - 1 year (40% vs. 49%)
  - 3 years (43% vs. 50%)
  - 5 years (42% vs. 52%)

# Meta-analysis of PCI vs GDMT in Stable CAD

## 12 RCTs with 7,182 randomized pts

|                     | <b>PCI<br/>(n=3584)</b> | <b>GDMT<br/>(n=3593)</b> | <b>RR (95%CI)</b> | <b>P value</b> |
|---------------------|-------------------------|--------------------------|-------------------|----------------|
| <b>Mortality</b>    | 7.9%                    | 9.2%                     | 0.85 (0.71, 1.01) | <b>0.07</b>    |
| <b>- Cardiac</b>    | 3.5%                    | 4.6%                     | 0.71 (0.47, 1.06) | <b>0.09</b>    |
| <b>Nonfatal MI</b>  | 9.5%                    | 9.5%                     | 0.93 (0.70, 1.24) | 0.61           |
| <b>Angina, any</b>  | 53.0%                   | 58.0%                    | 0.83 (0.73, 0.94) | <b>0.005</b>   |
| <b>- ≤1 year*</b>   | 45.8%                   | 57.1%                    | 0.76 (0.65, 0.88) | <b>0.0006</b>  |
| <b>- 1-5 years*</b> | 39.2%                   | 59.2%                    | 0.64 (0.43, 0.94) | <b>0.02</b>    |
| <b>- ≥5 years*</b>  | 54.0%                   | 58.0%                    | 0.85 (0.72, 1.00) | <b>0.05</b>    |

\*not all pts represented in each time period

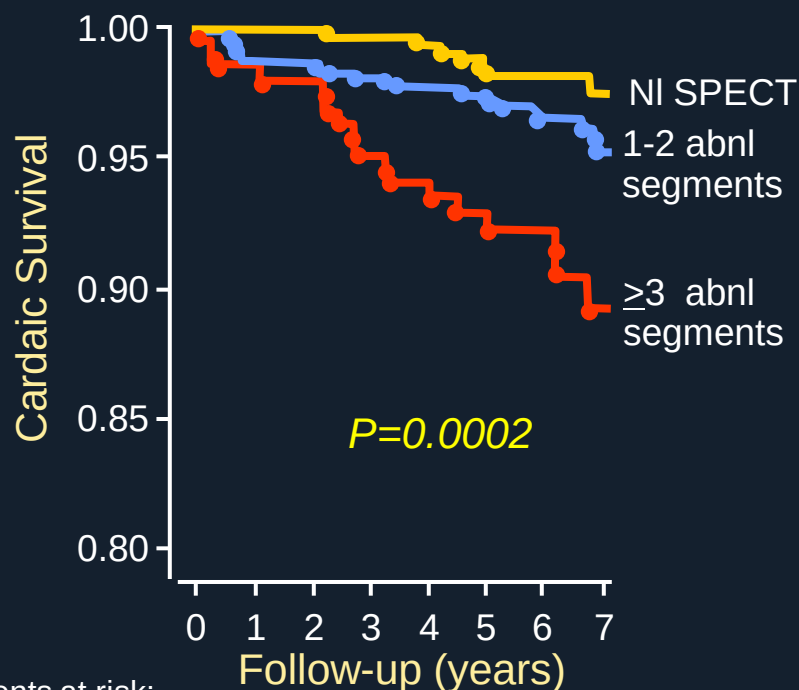
# Limitations of COURAGE

- **Low risk population:** Low levels of ischemia → low mortality rates
- **Enrolled after angiography:** Highly selected
- **PCI approach:** Not ischemia-guided
- **PCI technology:** DES in only 2.7% of pts
- **PCI success:** Only 93%
- **GDMT:** The best ever! Free drugs and visits...

# Multiple Studies have Shown a Powerful Relationship Between Ischemia and Survival

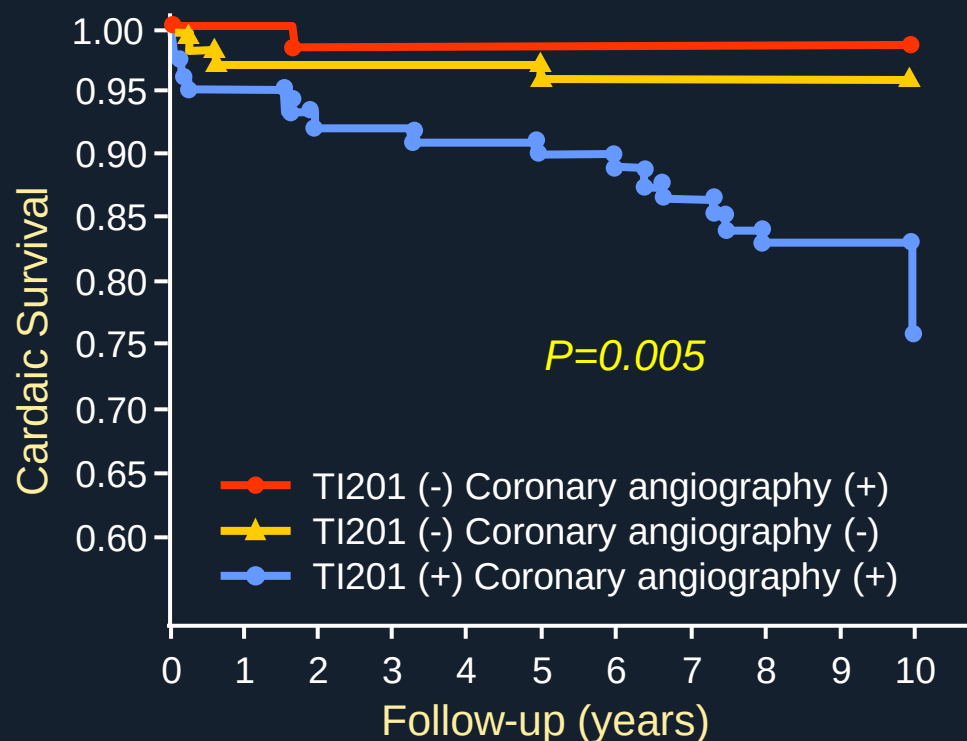
1,137 pts with chest pain or suspected CAD

10 yr survival in 307 pts according to CAD and Thallium-201



Patients at risk:

|                    |     |     |     |     |     |     |     |     |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Normal SPECT:      | 388 | 385 | 369 | 369 | 353 | 342 | 208 | 95  |
| 1-2 abnl segments: | 554 | 544 | 528 | 518 | 498 | 783 | 327 | 168 |
| ≥3 abnl segments:  | 195 | 489 | 183 | 173 | 170 | 159 | 106 | 53  |

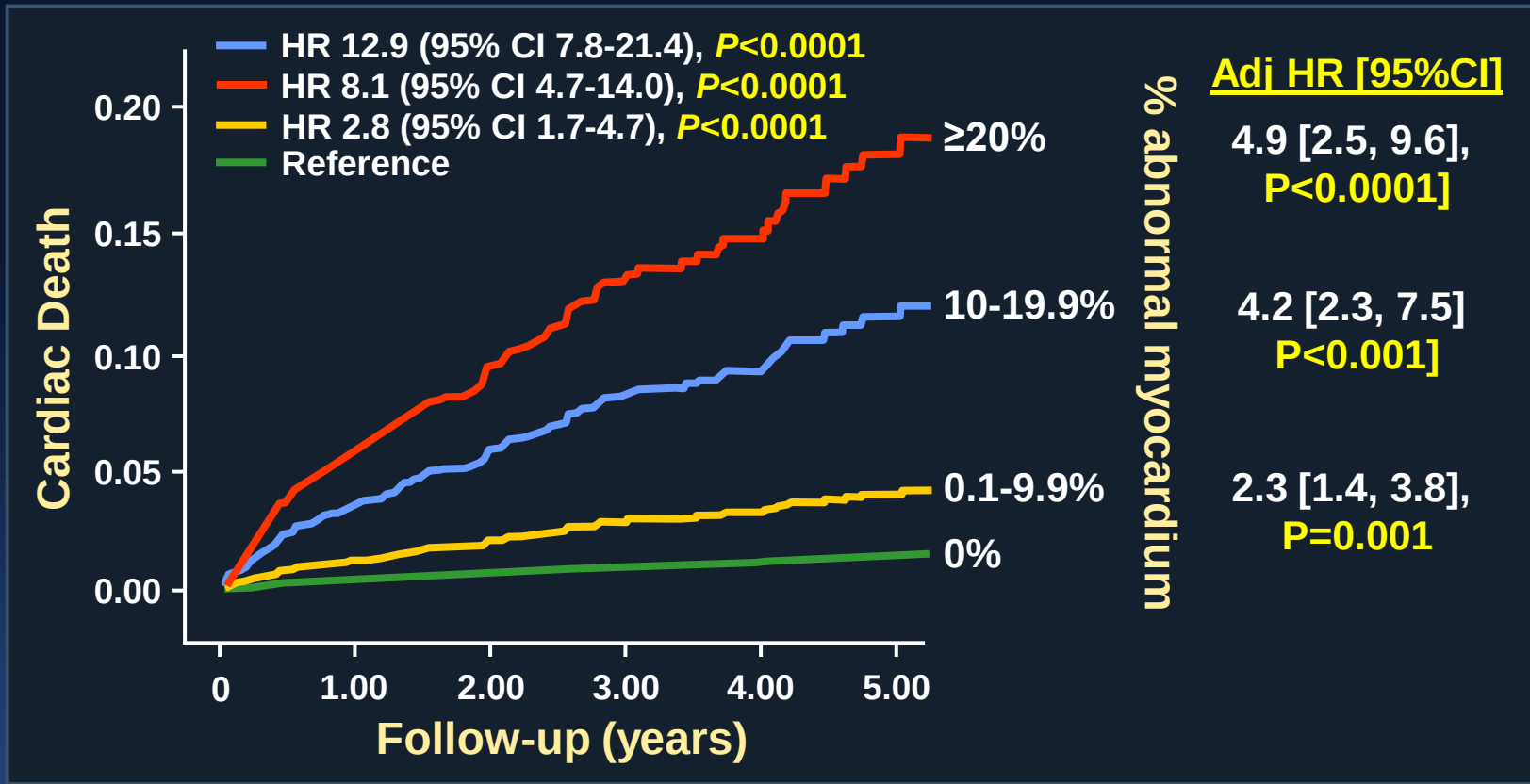


|     |     |     |     |     |     |     |    |    |    |    |
|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| 69  | 67  | 66  | 66  | 63  | 56  | 50  | 40 | 36 | 28 | 27 |
| 136 | 126 | 124 | 120 | 119 | 117 | 111 | 86 | 62 | 40 | 23 |
| 102 | 95  | 95  | 95  | 95  | 94  | 93  | 90 | 68 | 47 | 28 |



# PET Ischemia and Cardiac Death

Rest/stress rubidium-82 PET MPI performed in 7,061 pts at 4 centers;  
Median FU 2.2 years



**MVA:** HR↑ by 34% and 57% for each 10% increase in %myo ischemic and scarred, respectively (each  $P < 0.001$ ). Addition of %abnormal myo improved model performance (C-stat 0.805 to 0.839), NRI (0.116) and IDI (0.018).

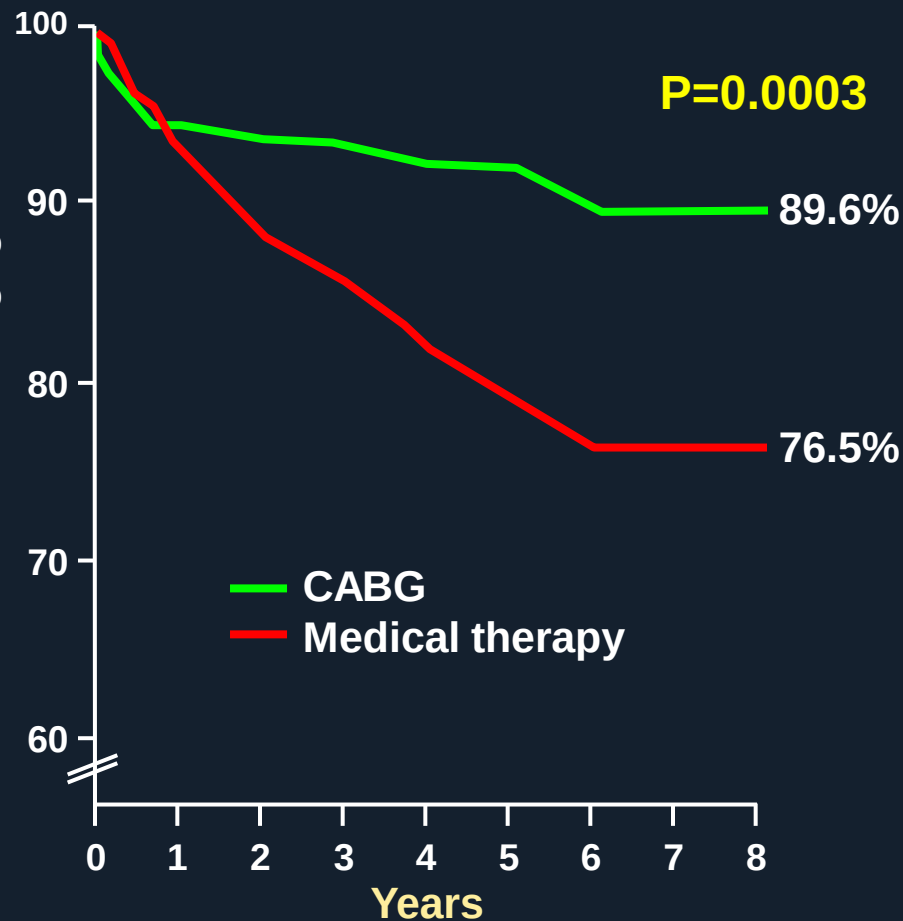
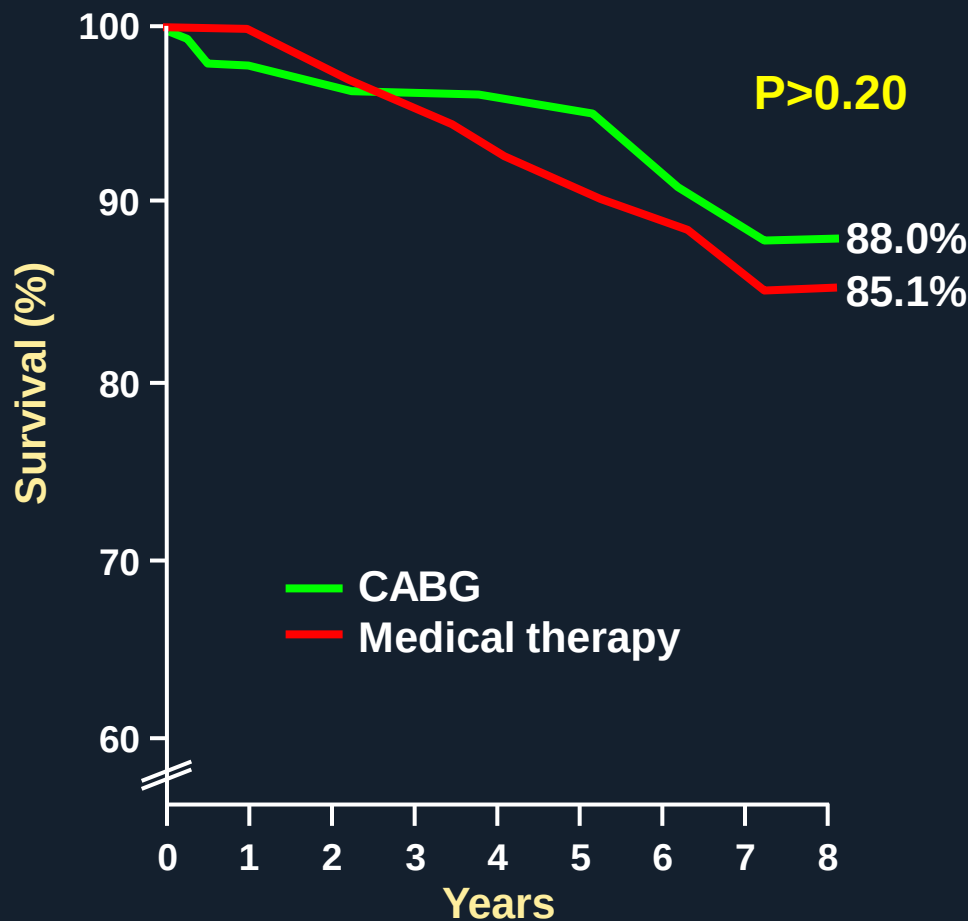


# ECSSG RCT: CABG vs. Med Rx

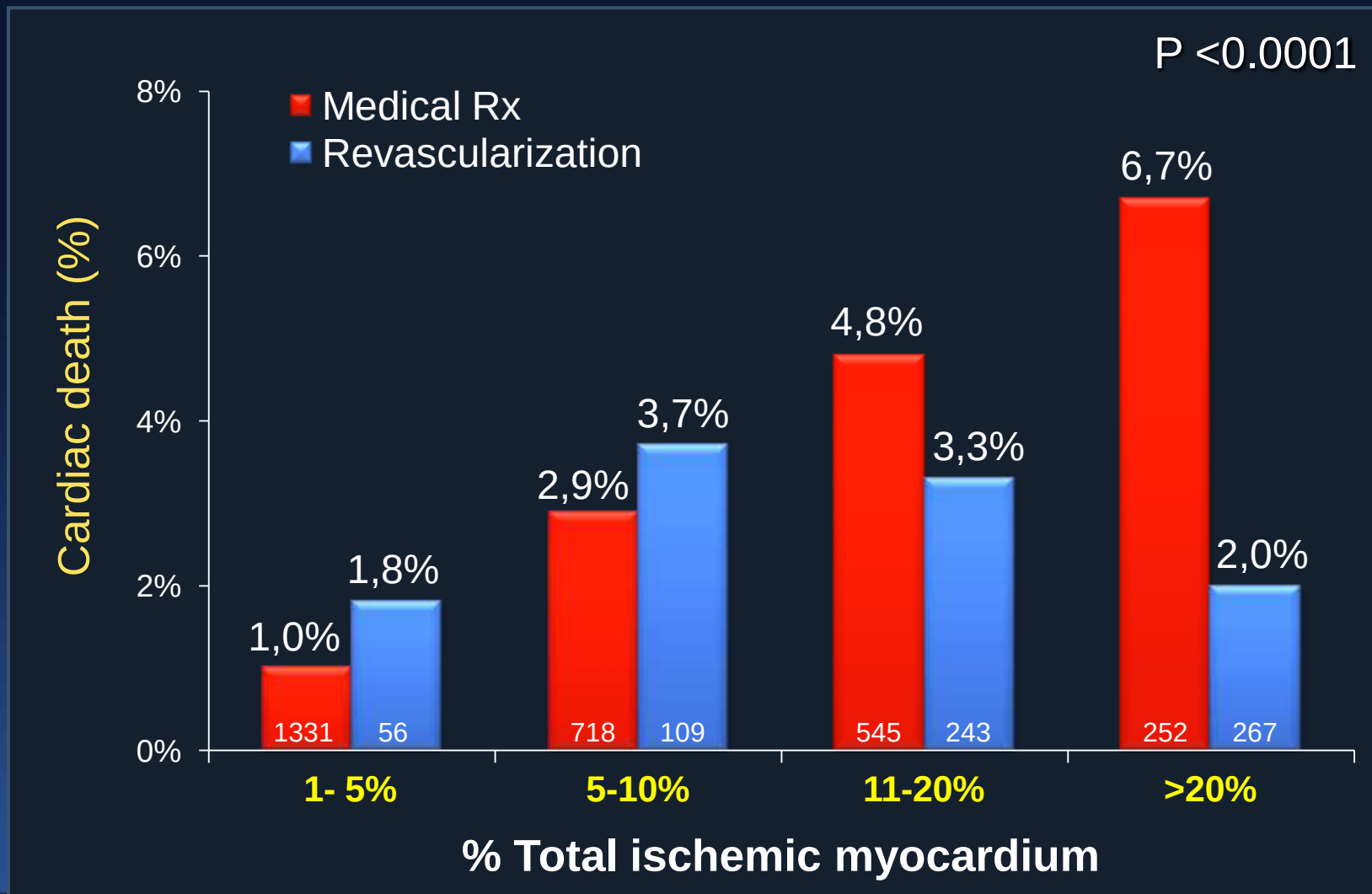
768 men <65 years old with MVD and good LV function

Ex ST depression 0-1 mm

Ex ST depression  $\geq 1.5$  mm

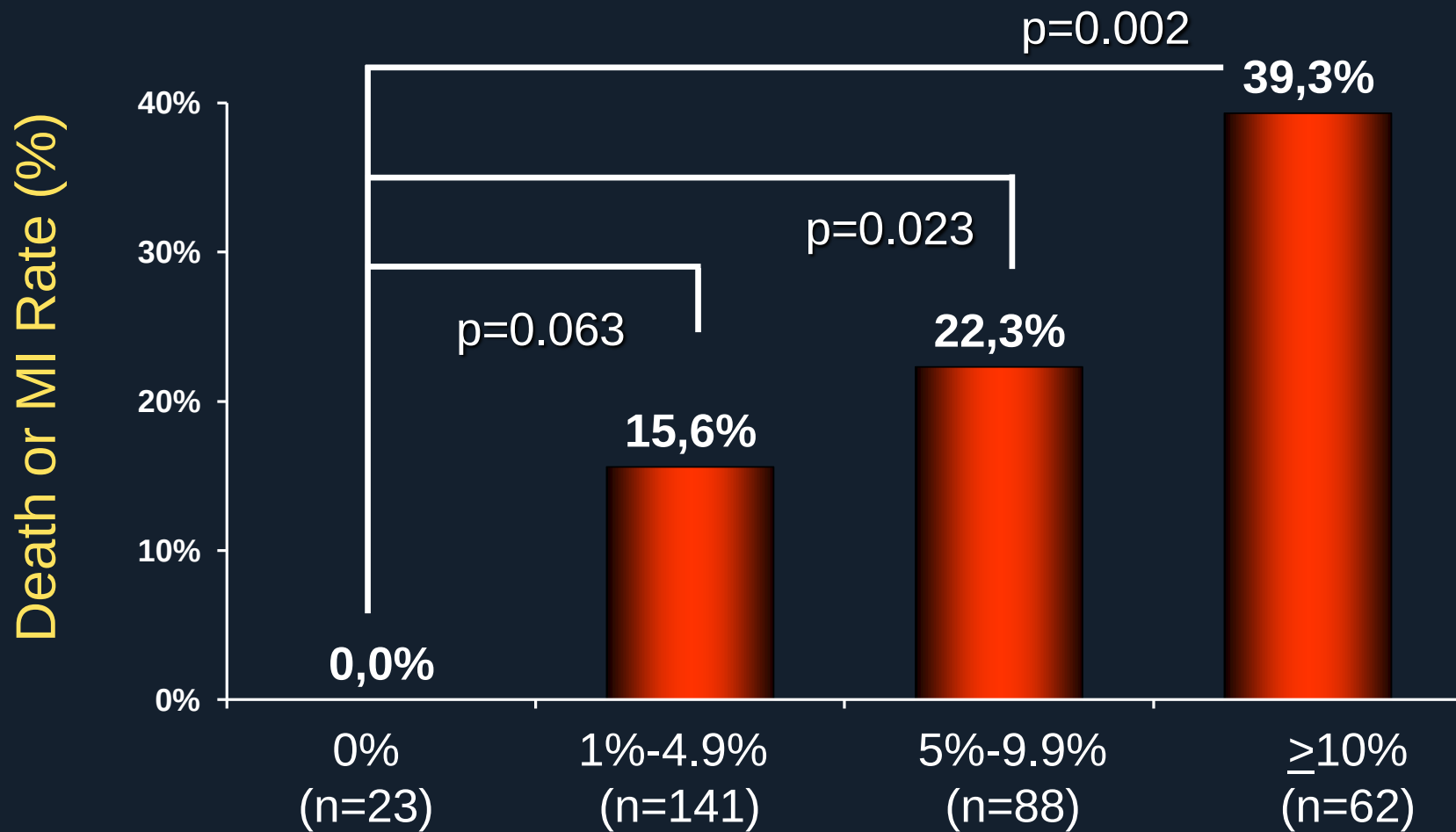


# CSMC: Revascularization vs. Med Rx. According to Ischemic Risk (n=3,251; F/U 1.9 yr)





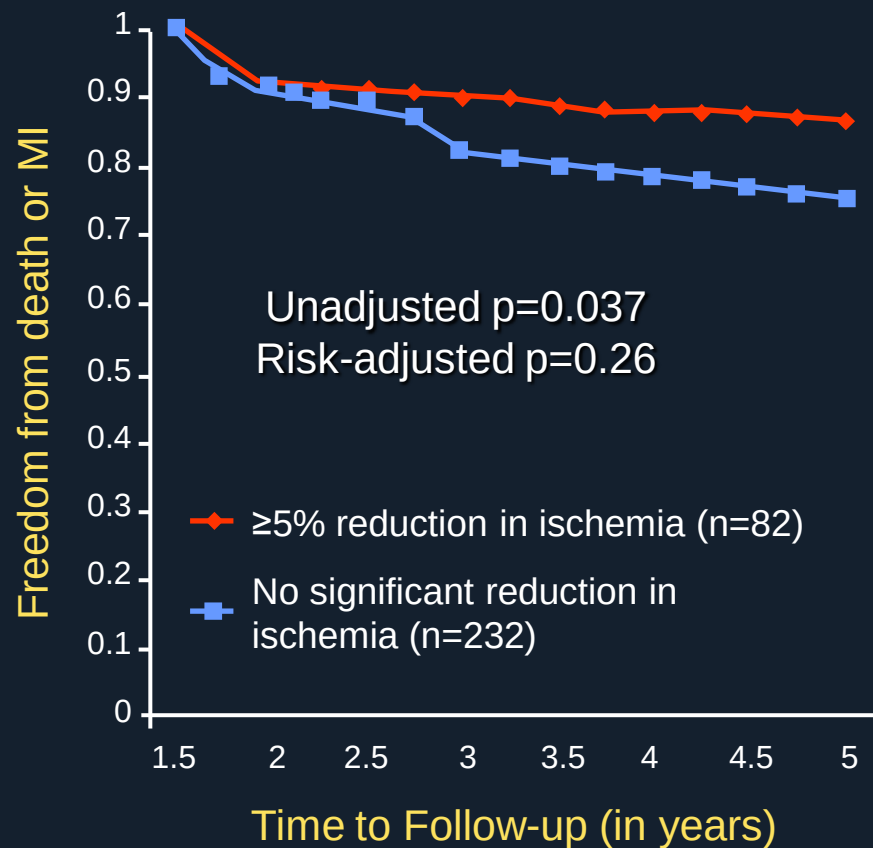
# **COURAGE:** Rates of Death or MI by Residual Ischemia on 6-18m MPS



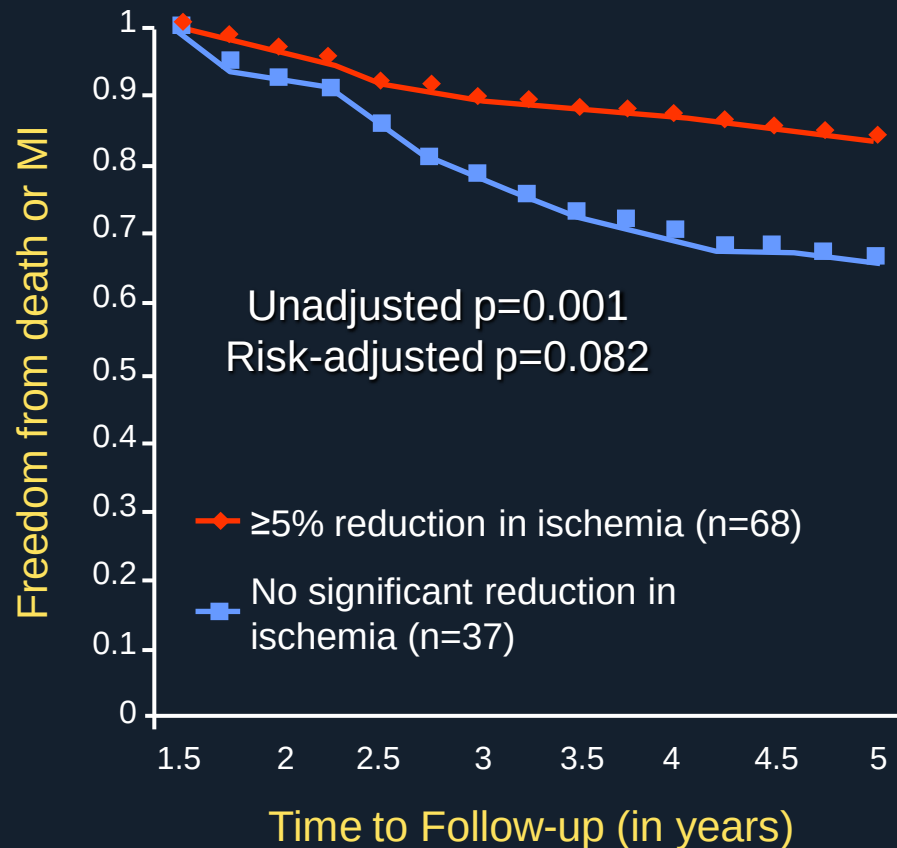


# COURAGE: Reduction in Ischemia Is Associated with Less Death and MI

All patients



Moderate-severe ischemia

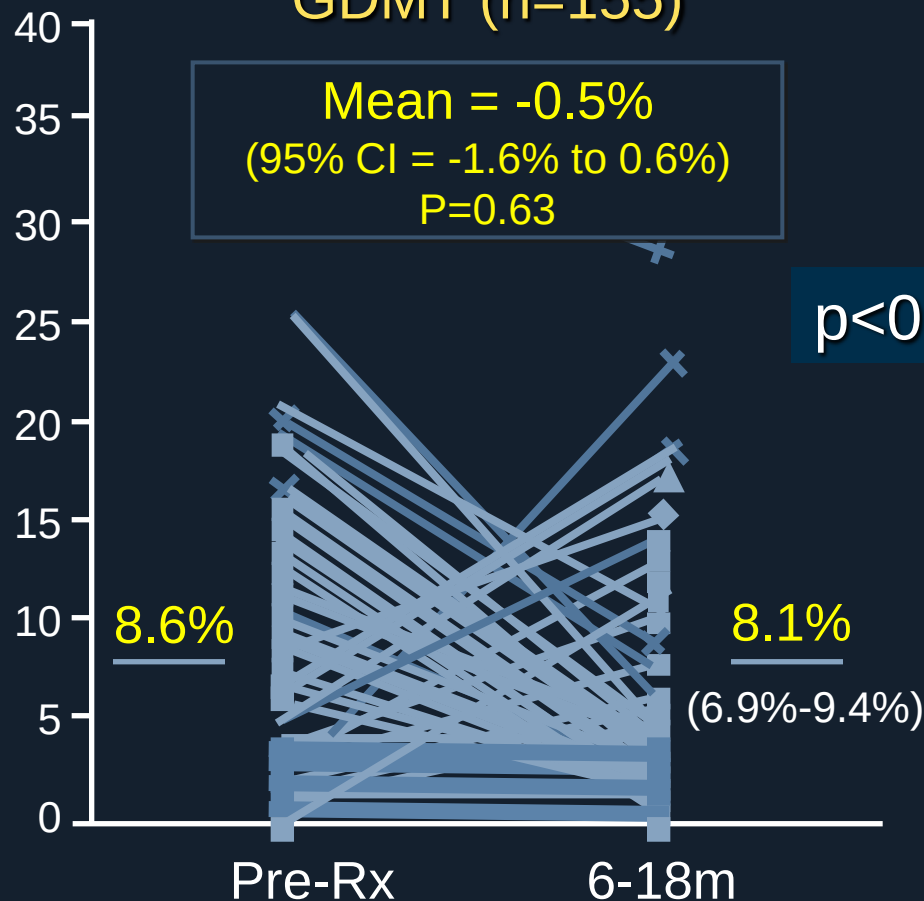




# COURAGE: MPS % Ischemic Myocardium Pre-Rx & 6-18 Months

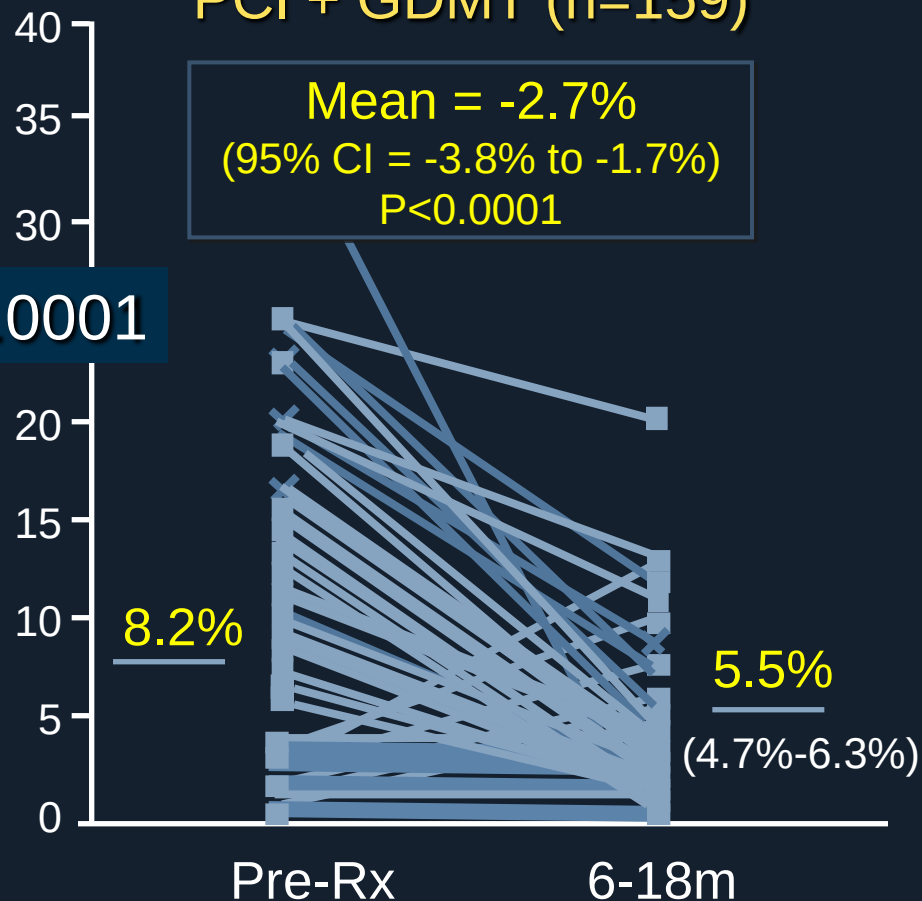
GDMT (n=155)

Mean = -0.5%  
(95% CI = -1.6% to 0.6%)  
P=0.63



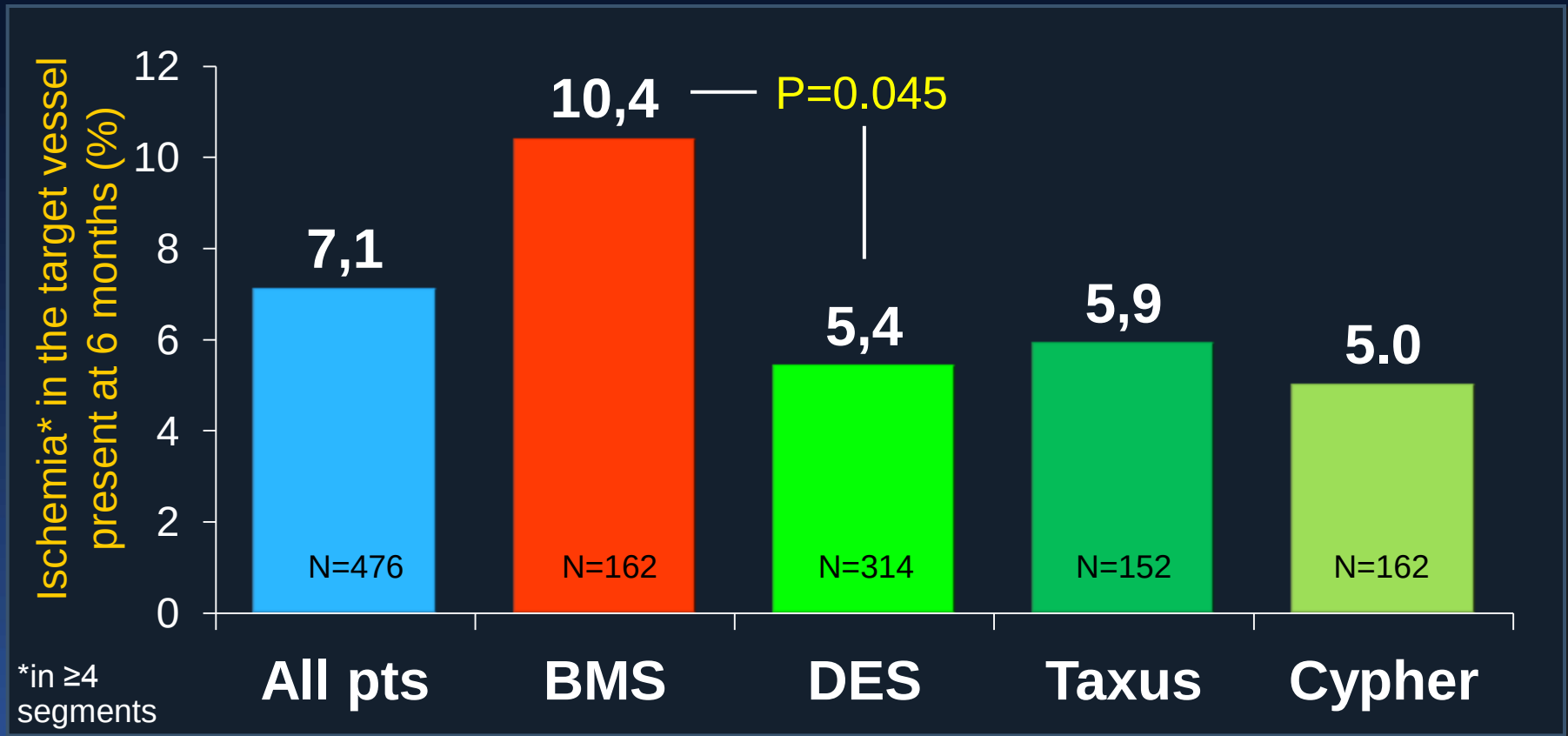
PCI + GDMT (n=159)

Mean = -2.7%  
(95% CI = -3.8% to -1.7%)  
P<0.0001



# Impact of DES in Relieving Ischemia

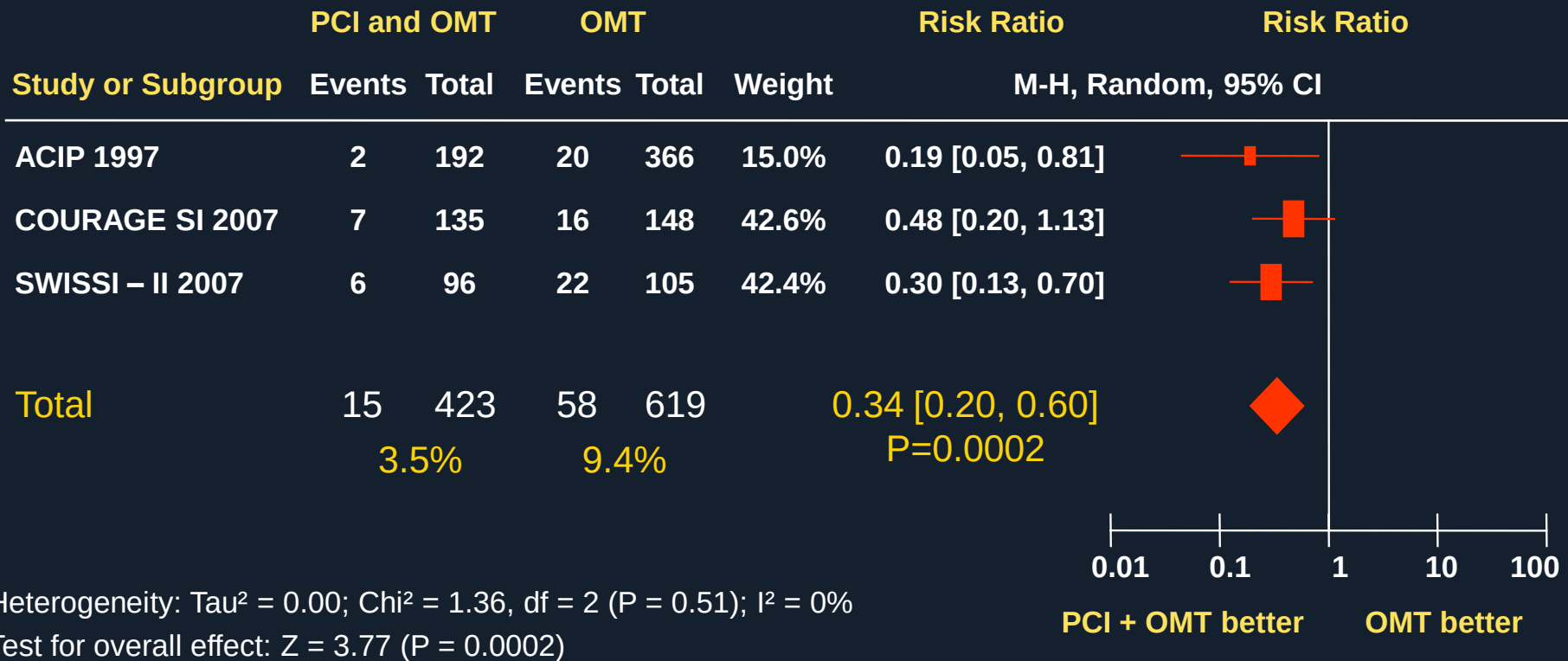
**BASKET Trial:** 826 “real-world” pts rand 2:1 to DES vs. BMS  
**SPECT** (rest–stress dual-isotope ( $^{201}\text{Tl}$  rest/ $^{99\text{m}}\text{Tc}$  sestamibi) was performed in 476 of 747 stable pts w/o MACE at 6 mos



# PCI vs. OMT in Silent Myocardial Ischemia

## Mortality

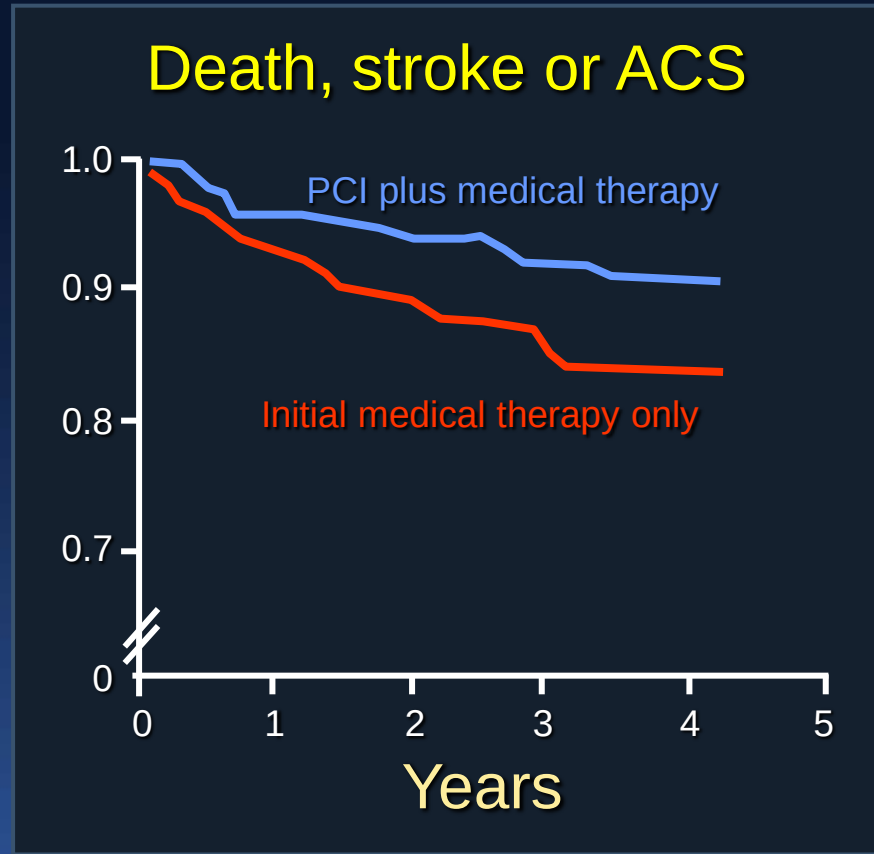
ACIP, SWISSI-II, and COURAGE (n=1,042)





# JSAP: PCI vs OMT in Stable Angina

365 pts with exertional angina and ischemia were randomized PCI vs OMT at 78 centers in Japan



16.4% vs. 8.5%,

HR [95%CI] =  
0.54 [0.29, 0.98]

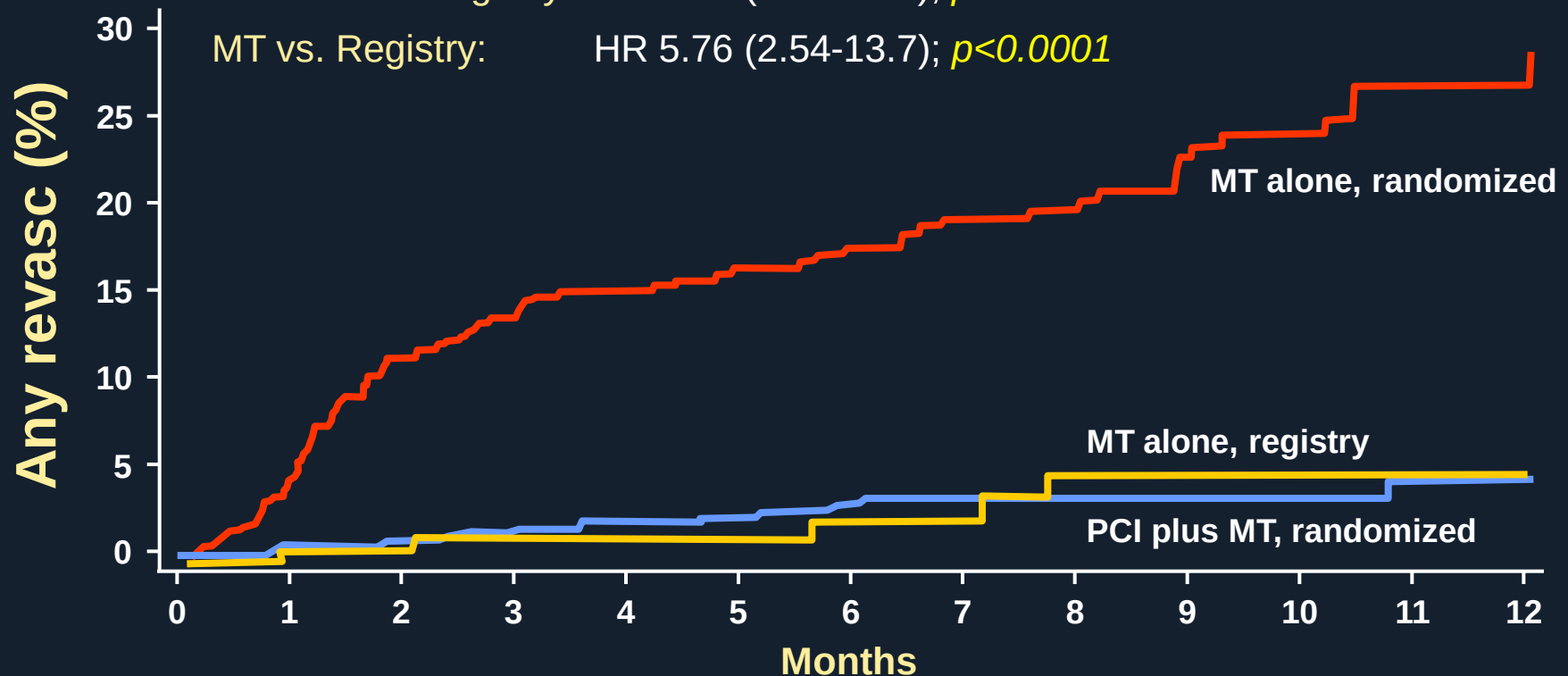
P=0.045

# **FRAME 2:** 888 pts with lesions w/FFR $\leq 0.80$ randomized to PCI vs OMT

PCI+MT vs. MT: HR 0.14 (0.08-0.26);  $p < 0.0001$

PCI+MT vs. Registry: HR 0.84 (0.33-2.14);  $p = 0.72$

MT vs. Registry: HR 5.76 (2.54-13.7);  $p < 0.0001$

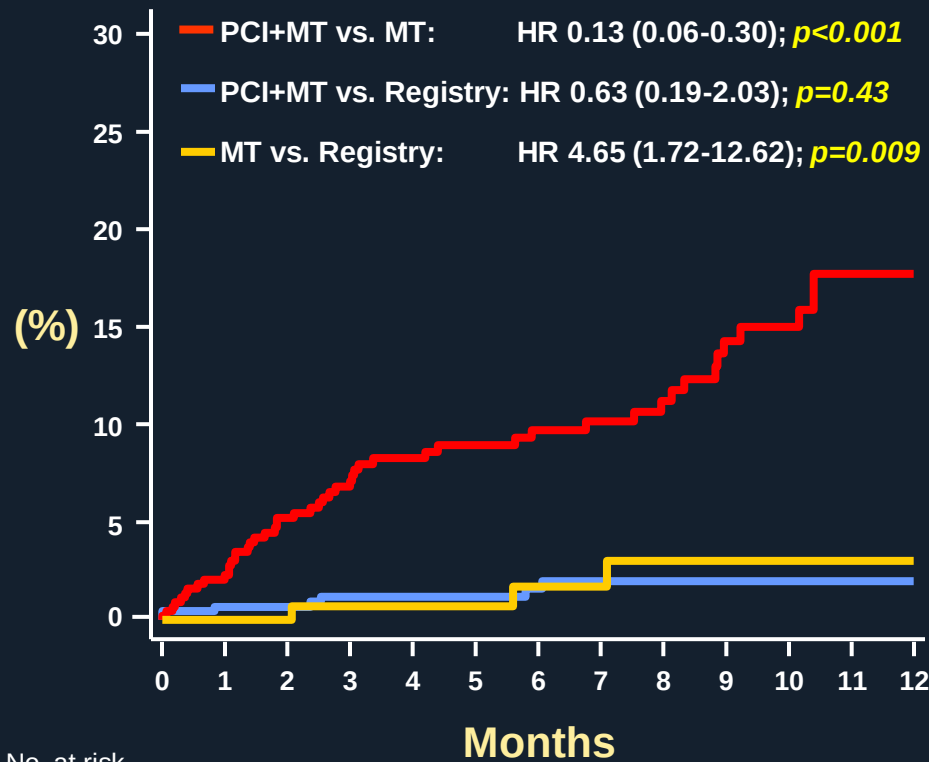


No. at risk

|          |     |     |     |     |     |     |     |     |     |     |     |    |    |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| MT       | 441 | 404 | 348 | 302 | 267 | 236 | 203 | 175 | 150 | 118 | 91  | 63 | 35 |
| PCI+MT   | 447 | 420 | 393 | 353 | 311 | 280 | 243 | 212 | 176 | 156 | 116 | 89 | 52 |
| Registry | 166 | 155 | 144 | 132 | 117 | 106 | 94  | 75  | 64  | 53  | 42  | 26 | 13 |

# FAME 2: Revascularization

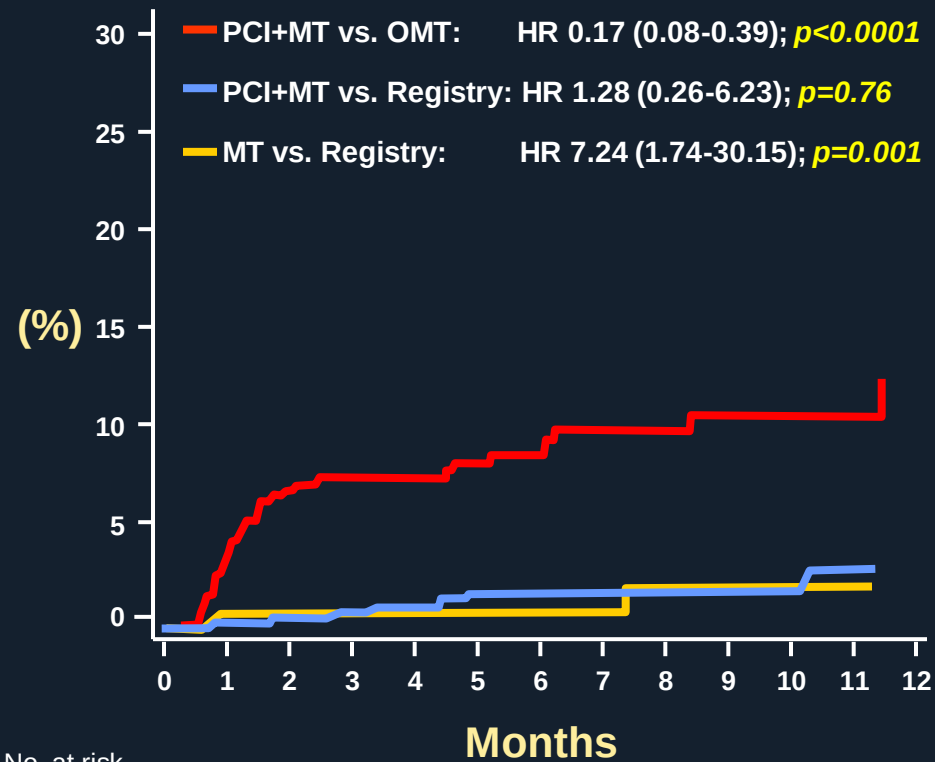
## Urgent



No. at risk

|          |     |     |     |     |     |     |     |     |     |     |     |    |    |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| MT       | 441 | 414 | 371 | 325 | 286 | 256 | 223 | 195 | 164 | 129 | 101 | 71 | 38 |
| PCI+MT   | 447 | 421 | 395 | 356 | 315 | 285 | 248 | 217 | 180 | 160 | 119 | 93 | 53 |
| Registry | 166 | 156 | 145 | 133 | 117 | 106 | 94  | 75  | 65  | 53  | 42  | 26 | 13 |

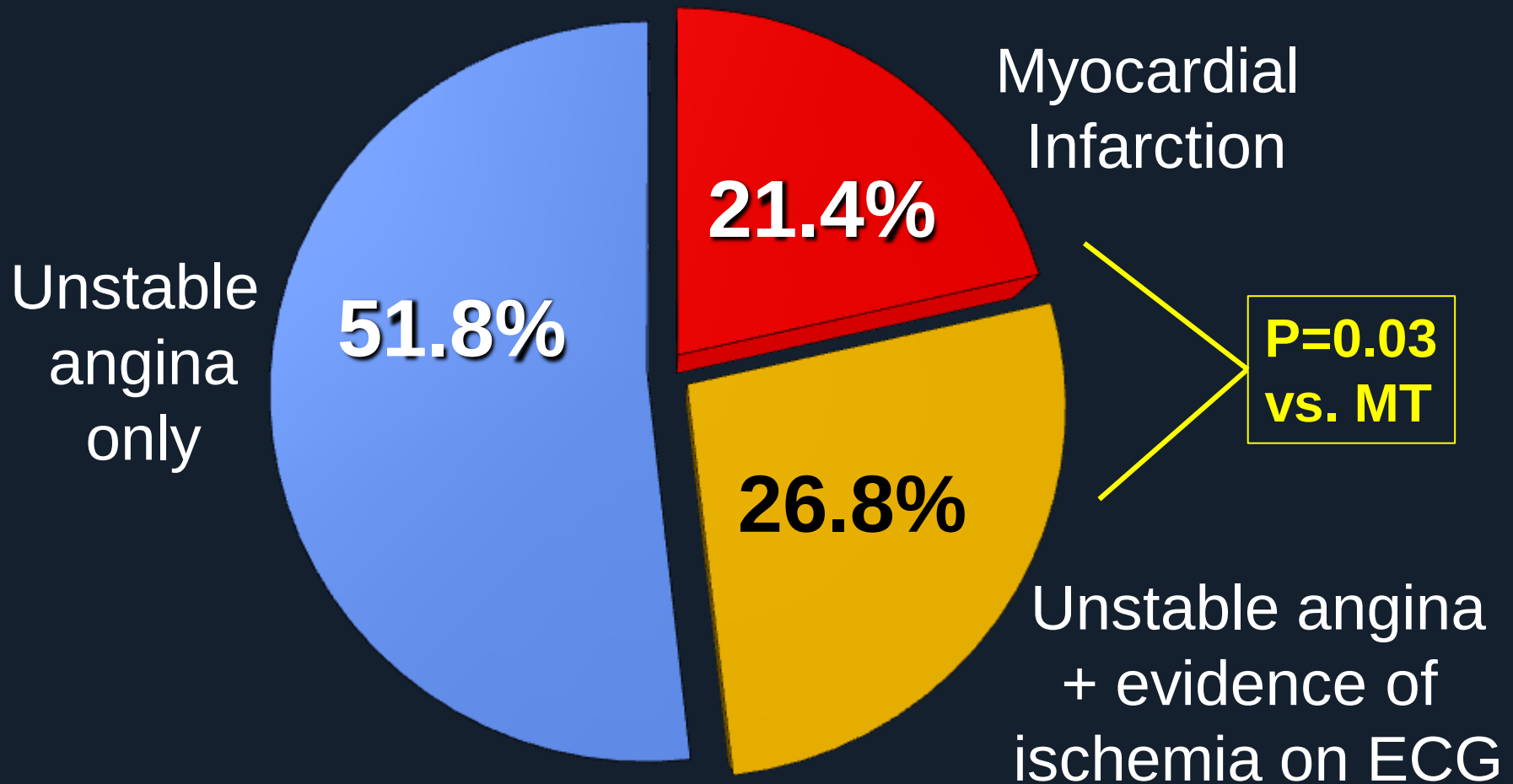
## Non-Urgent



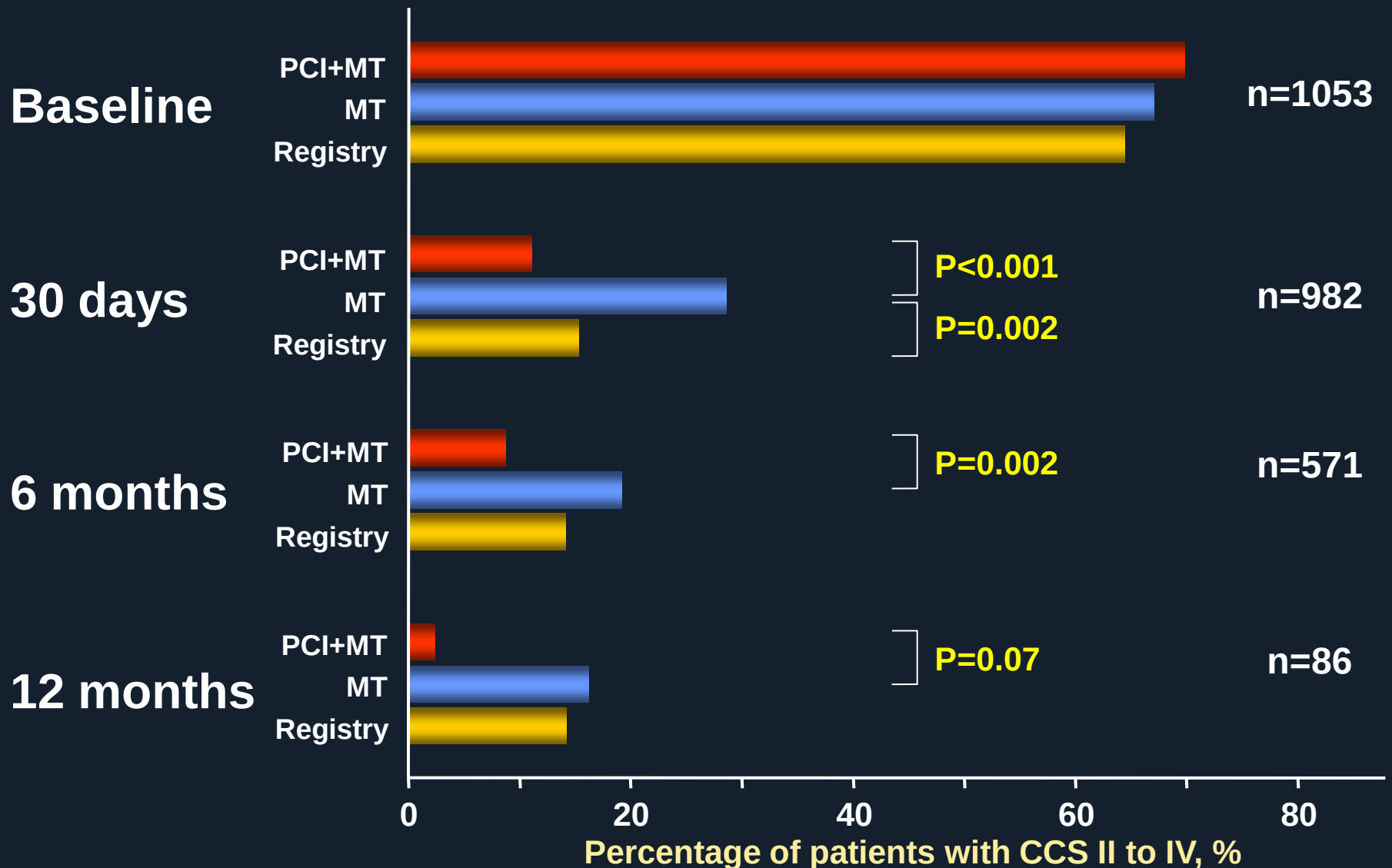
No. at risk

|          |     |     |     |     |     |     |     |     |     |     |     |    |    |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| OMT      | 441 | 413 | 367 | 327 | 293 | 261 | 227 | 199 | 174 | 142 | 111 | 82 | 51 |
| PCI+OMT  | 447 | 422 | 394 | 356 | 314 | 283 | 245 | 215 | 179 | 159 | 119 | 91 | 53 |
| Registry | 166 | 155 | 144 | 133 | 118 | 107 | 96  | 76  | 66  | 55  | 43  | 27 | 13 |

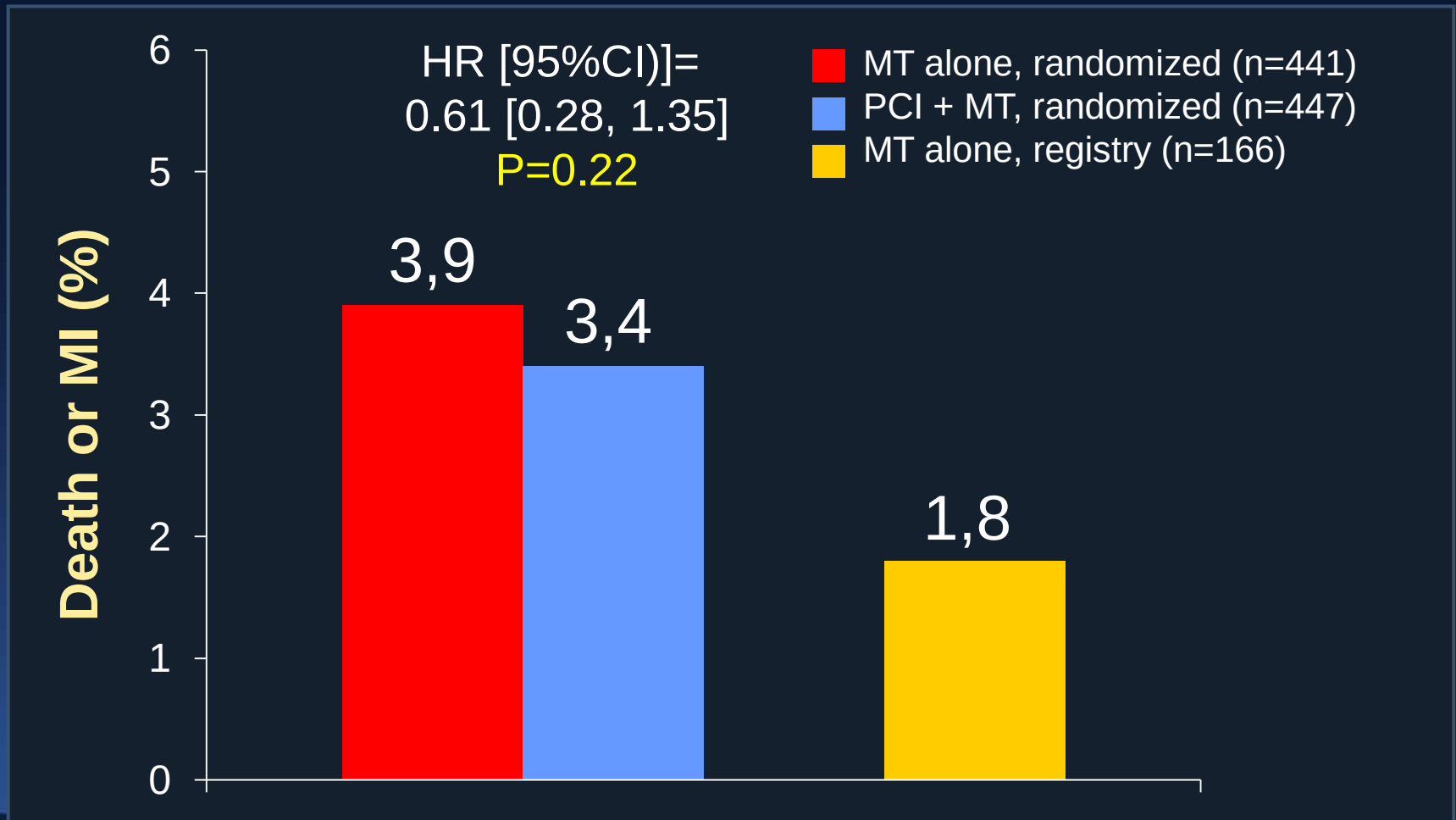
# FAME 2: Patients with Urgent Revascularization



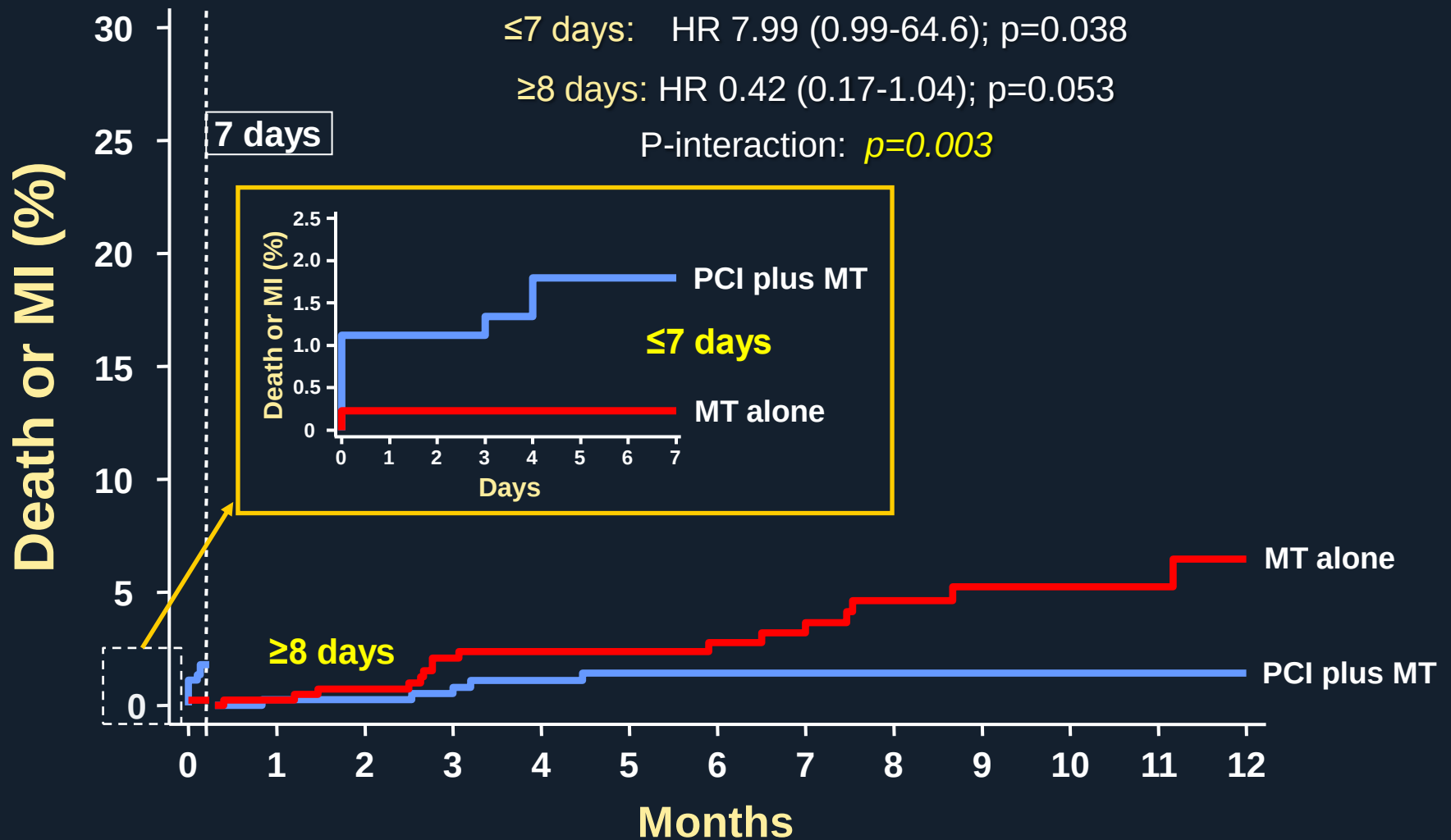
# FAAME 2: Patients with Class II-IV Angina



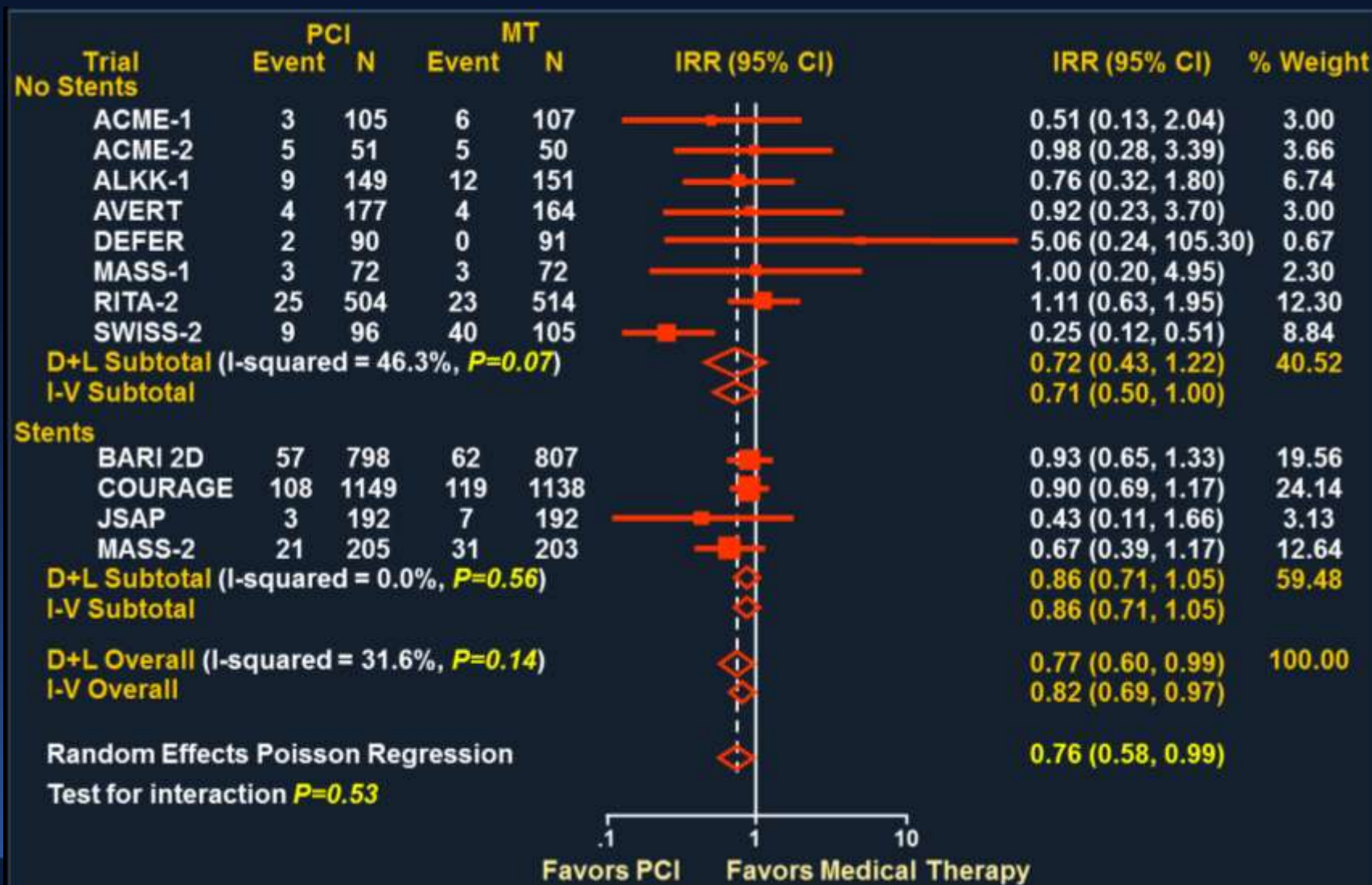
# **FAME 2:** 888 pts with lesions w/FFR $\leq 0.80$ randomized to PCI vs OMT - Mean follow-up duration 7 months -



# FRAME 2: Landmark Analysis of Death or MI



# 12 RCTs of PCI vs OMT with 37,548 pt-years of follow-up: **Effect on spontaneous MI**





# Meta-analysis of RCTs of PCI vs OMT

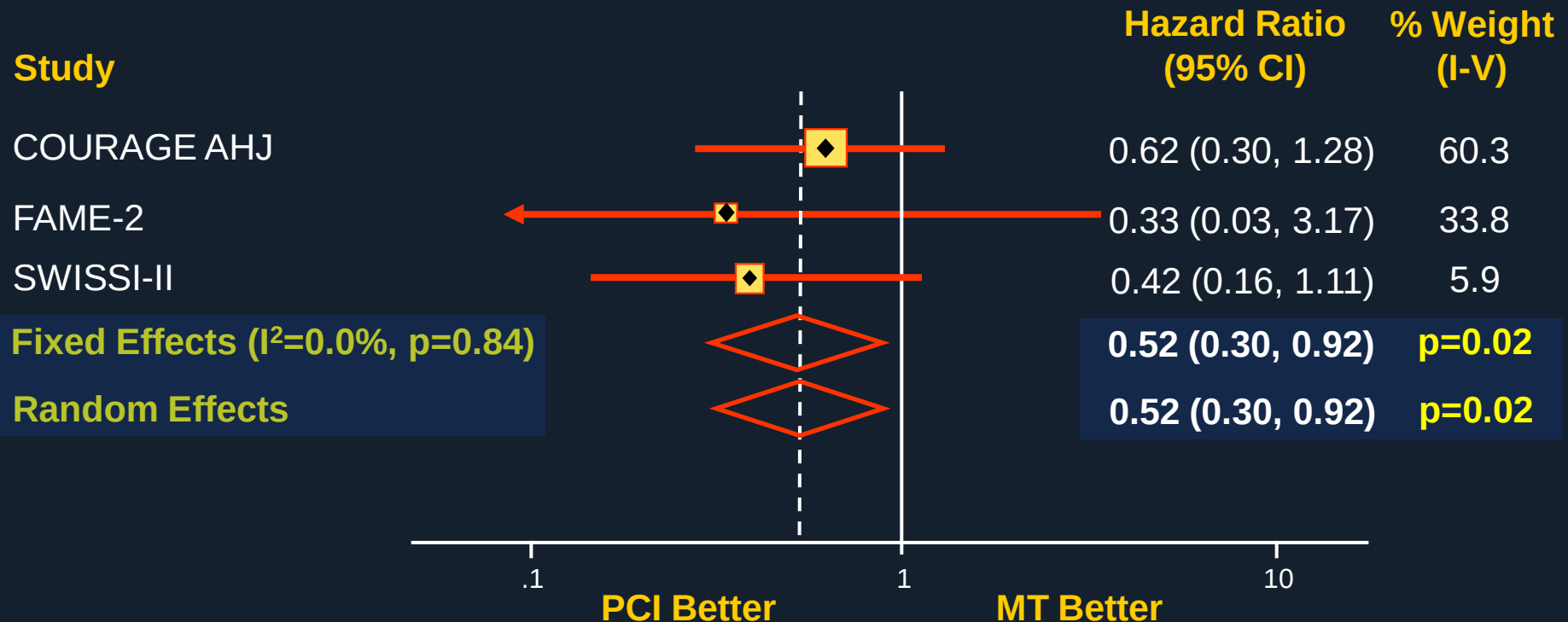
- Pts with ischemia by noninvasive imaging or FFR -

| Trial                                                                                                                        | Inclusion Criteria                                                                                                                                                                                                                                                       | Ischemia Testing                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>COURAGE AHJ</b> <ul style="list-style-type: none"><li>• 468 pts</li><li>• 97% BMS</li><li>• Median f/u: 4.6 yrs</li></ul> | <ul style="list-style-type: none"><li>• Stable angina, or initial unstable angina stabilized medically, stable post-MI</li><li>• <math>\geq 1</math> major epicardial coronary artery with <math>&gt;70\%</math> stenosis</li></ul>                                      | <ul style="list-style-type: none"><li>• SPECT</li><li>• Moderate to severe ischemia defined as <math>\geq 3</math> ischemic segments by core lab</li></ul>                              |
| <b>FAME-2</b> <ul style="list-style-type: none"><li>• 888 pts</li><li>• DES only</li><li>• Median f/u: 7 mo</li></ul>        | <ul style="list-style-type: none"><li>• Stable angina, initial unstable angina stabilized medically, or atypical chest pain with documented silent ischemia</li><li>• <math>\geq 1</math> major epicardial coronary artery with <math>&gt;50\%</math> stenosis</li></ul> | <ul style="list-style-type: none"><li>• Fractional flow reserve <math>\leq 0.80</math></li></ul>                                                                                        |
| <b>SWISSI-II</b> <ul style="list-style-type: none"><li>• 201 pts</li><li>• PTCA only</li><li>• Mean f/u: 10.2 yrs</li></ul>  | <ul style="list-style-type: none"><li>• First MI within preceding 3 months, no chest pain at maximal symptom-limited exercise test</li><li>• 1- or 2-vessel CAD</li></ul>                                                                                                | <ul style="list-style-type: none"><li>• Symptom-limited bicycle ETT with qualifying ST depression <math>\geq 1.0</math> mm in 1 or more leads and confirmatory SPECT or echo)</li></ul> |

**N=1,557 randomized patients**

# Meta-analysis: All-Cause Mortality

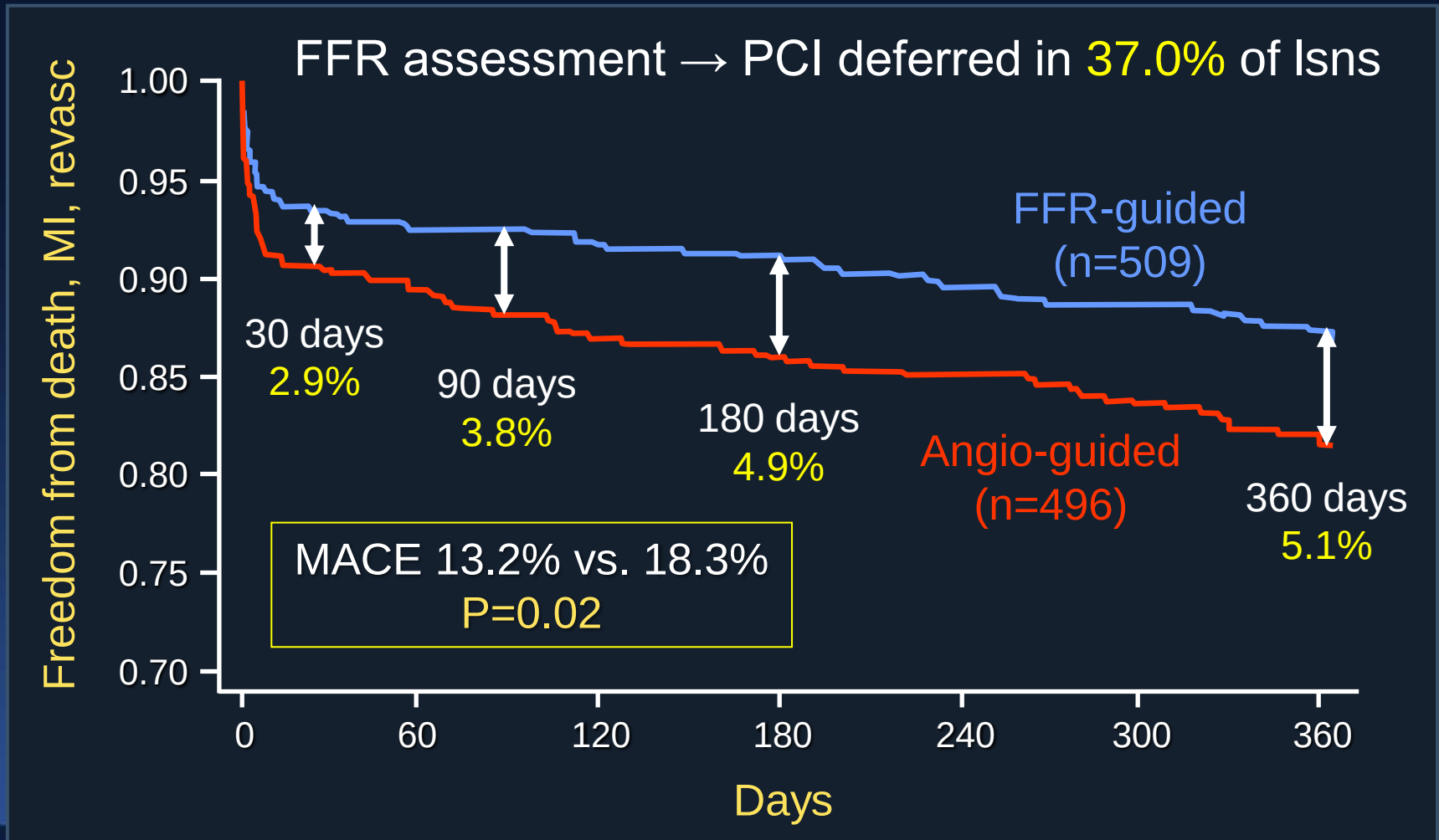
- Pts with ischemia by noninvasive imaging or FFR -  
n=1,557 randomized



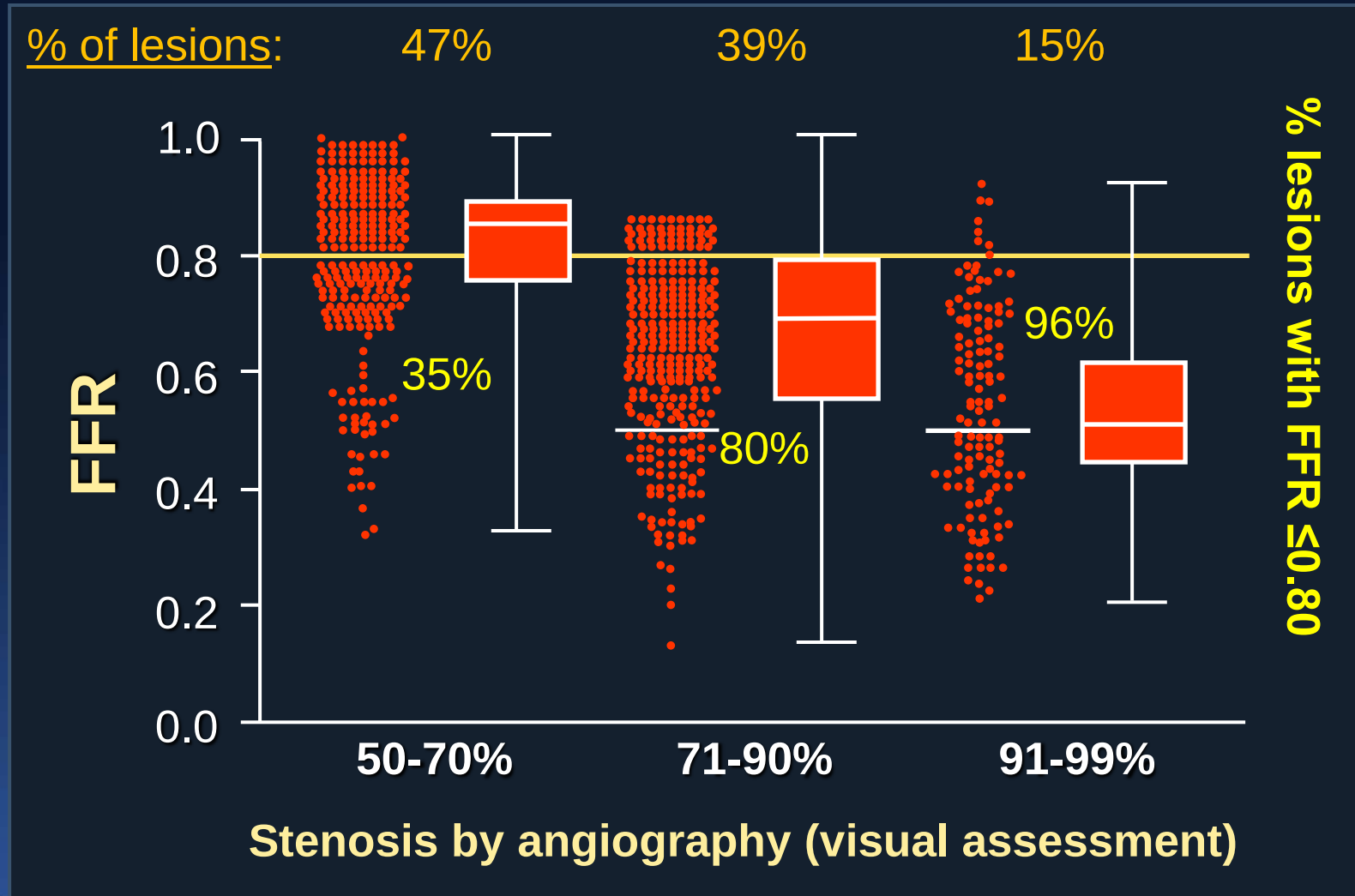
# FAME: Primary Endpoint



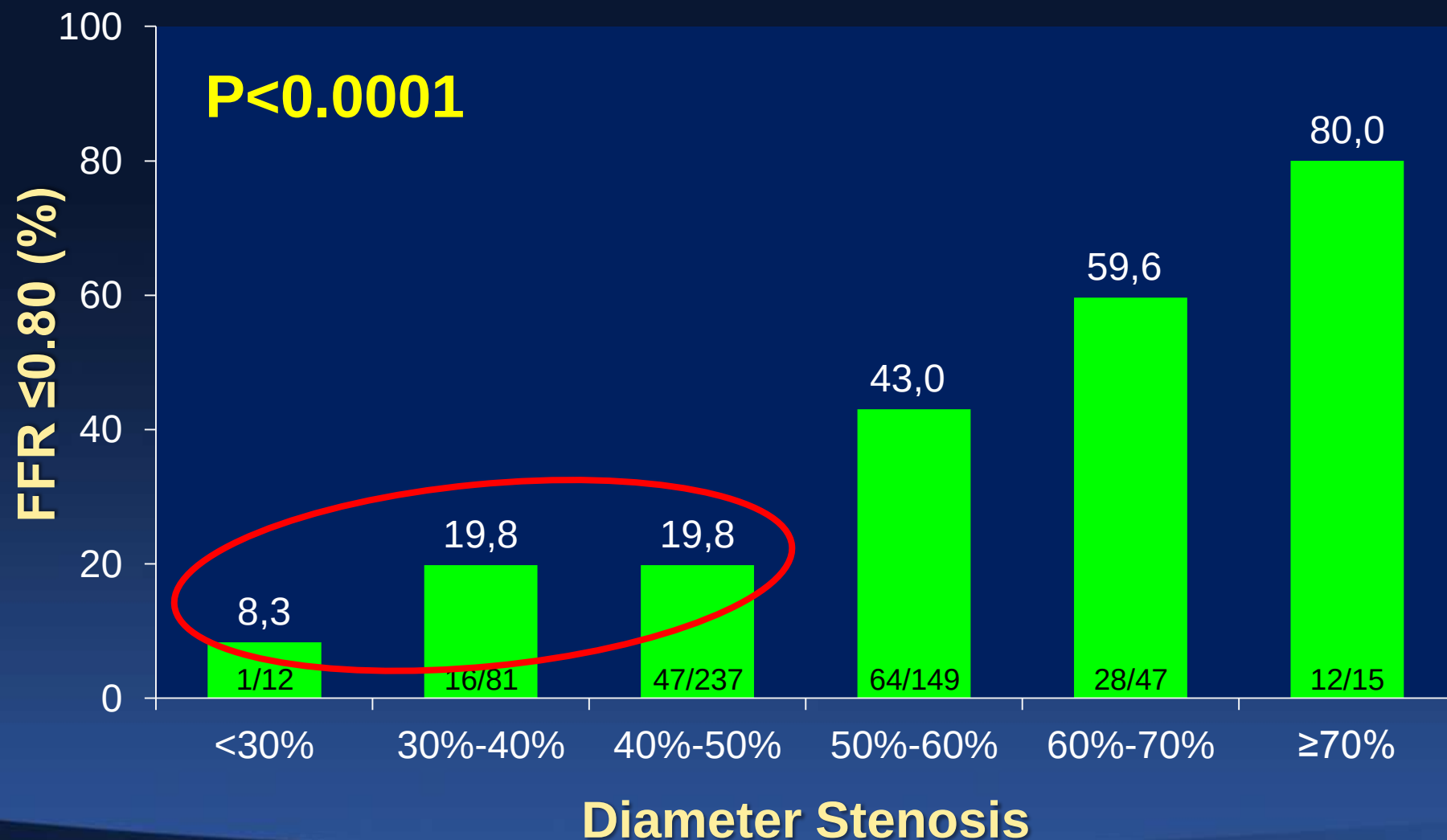
1005 pts with MVD undergoing PCI with DES were randomized to FFR-guided vs. angio-guided intervention



# Relationship Between Visual Angiographic %DS and FFR (n=1,329)



# Correlation Between QCA DS% and FFR $\leq 0.80$ (n=544)



# The ISCHEMIA Trial

~8,000 pts with moderate to severe  
ischemia by non-invasive testing

Blinded CT scan to rule out LM ds or normal coronaries

R

```
graph TD; R((R)) --> A[Optimal Medical Therapy (OMT - cath reserved for refractory ischemia)]; R --> B[Invasive Strategy (OMT + cath, followed by PCI or CABG as appropriate)];
```

Optimal Medical  
Therapy (OMT -  
cath reserved for  
refractory ischemia)

Invasive Strategy  
(OMT + cath, followed by  
PCI or CABG as  
appropriate)

Primary endpoint: CV death or MI

Major secondary endpoint: QOL

# **Conclusions:** Optimal Therapy in Pts with Stable Coronary Artery Disease?

- The presence of ischemia identifies pts at ↑ risk for future death and MI: The greater the ischemia, the greater the risk
- Moderate-sized randomized trials have suggested that mortality and spontaneous MI are reduced after PCI in pts with documented ischemia
- The ISCHEMIA trial is being conducted to evaluate a strategy of ischemia-guided revascularization in pts with moderate or severe ischemia
- Pending the results of ISCHEMIA (~7 years), PCI (or CABG) may be considered the preferred initial treatment strategy in pts with documented ischemia by non-invasive testing or FFR, or in those with life-style limiting angina