# FAME and PROMISE Trials

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**Stent Save a life Regional Africa Board**

**Chairman of ICC Hospital, Alexandria**

# FRACTIONAL FLOW RESERVE *versus* ANGIOGRAPHY FOR GUIDING PCI IN PATIENTS WITH MULTIVESSEL CORONARY ARTERY DISEASE

***Late Breaking Trial at***
***TCT, October 14 th , 2008***


Nico H.J.Pijls, MD, PhD
Catharina Hospital, Eindhoven
The Netherlands,
on behalf of the ***FAME investigators***

# FLOW CHART


Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% considered for stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

1-year follow-up

# *FAME study: PRIMARY ENDPOINT*

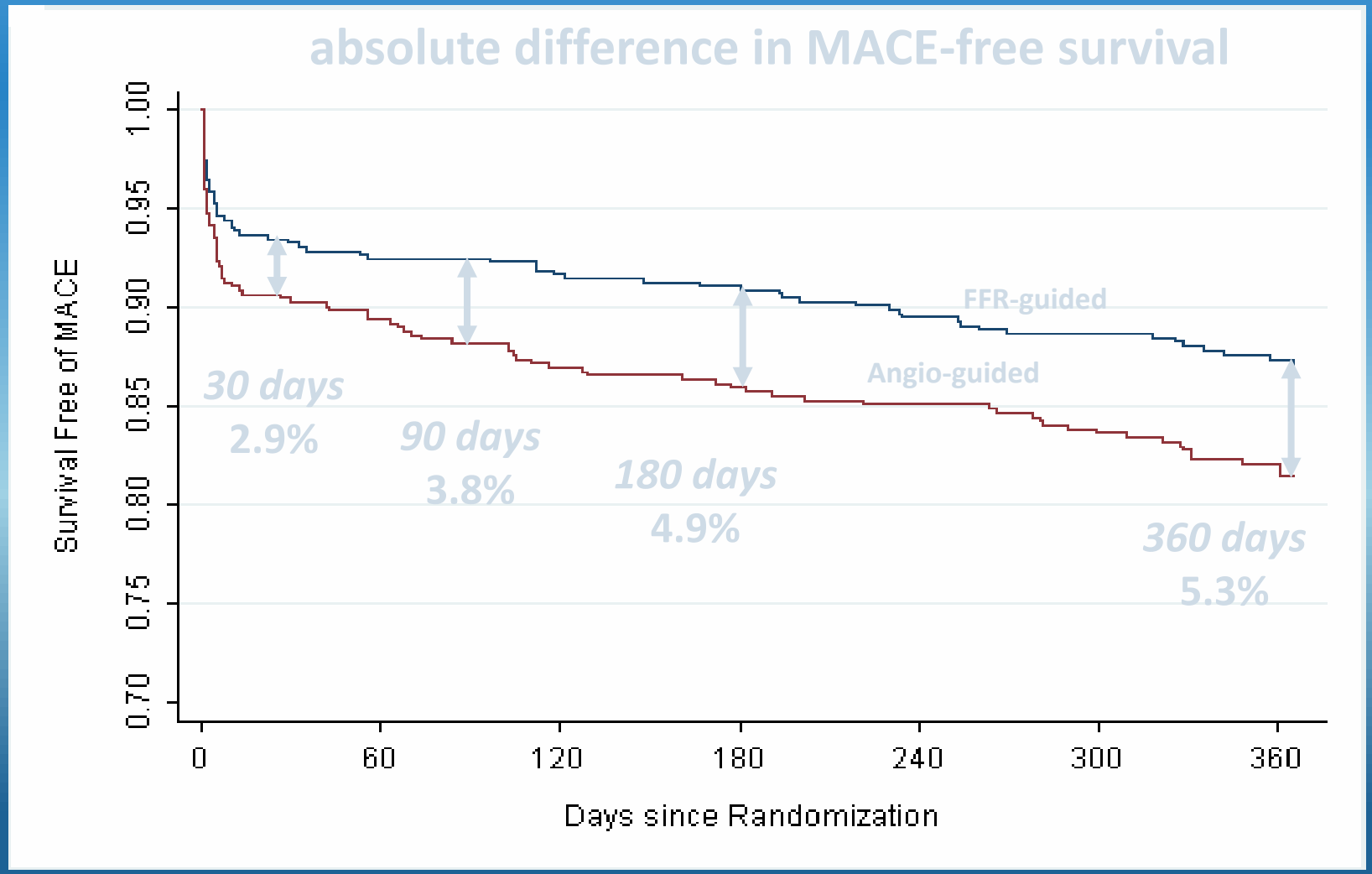
***Composite of death, myocardial infarction, or repeat revascularization ("MACE") at 1 year***

# *FAME study: SECONDARY ENDPOINTS*

- individual components of MACE at 1 year
- functional class
- use of anti-anginal drugs
- health-related quality of life (EuroQOL-5D)

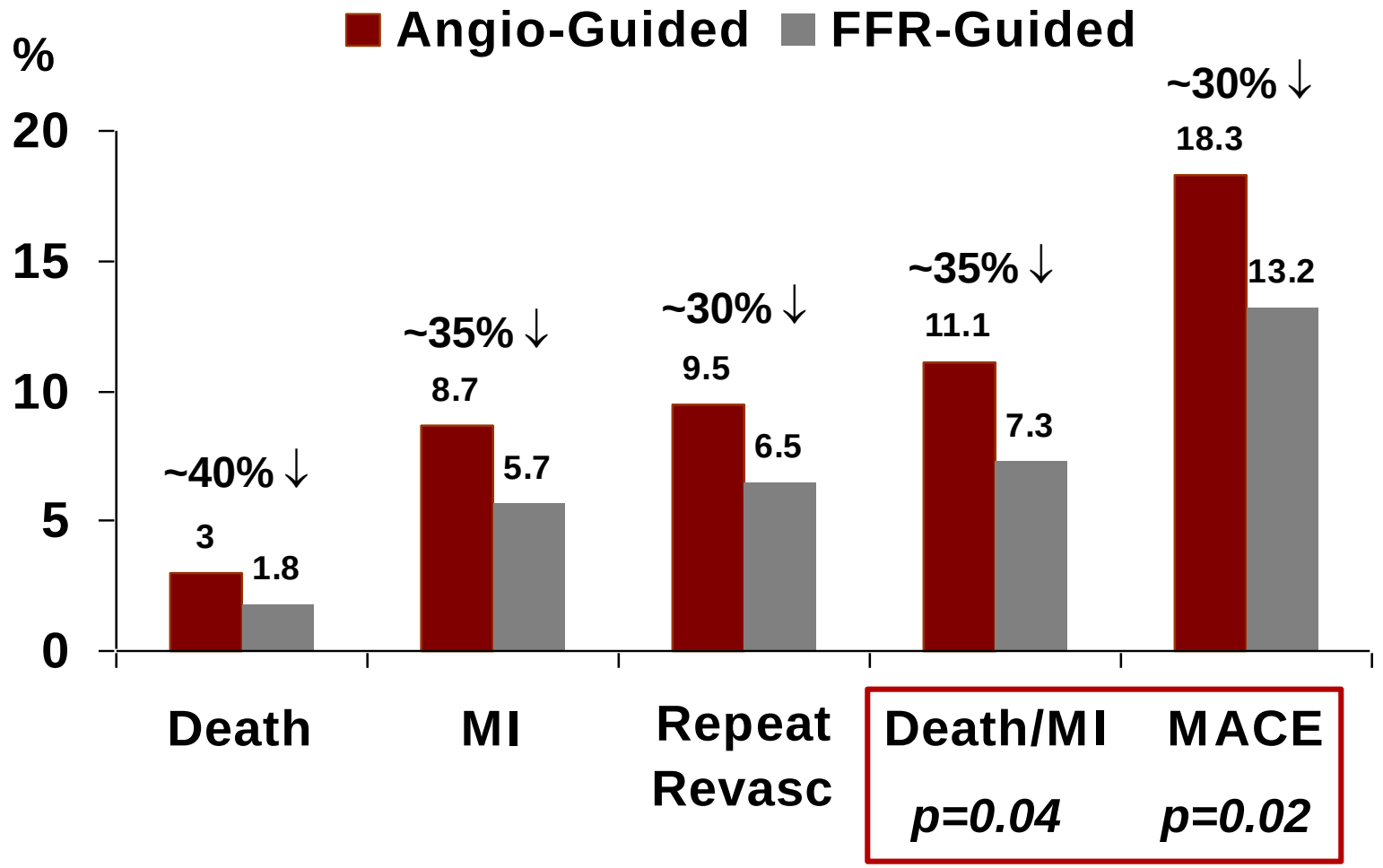
- procedure time
- amount of contrast agent used during procedure
- cost of the procedure

# FAME study: Event-free Survival



# FAME Study: One Year Outcomes

***1,005 patients with MVD randomized to FFR or Angio-guided PCI***




Tonino, et al. New Engl J Med 2009;360:213-24.

# *FAME study: CONCLUSIONS (1)*

**Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy**

- ***reduces the rate of the composite endpoint of death, myocardial infarction, re-PCI and CABG at 1 year by ~ 30%***

- ***reduces mortality and myocardial infarction at 1 year by ~ 35 %***

# FAME 2 Trial:
## *Results and Lessons Learned*

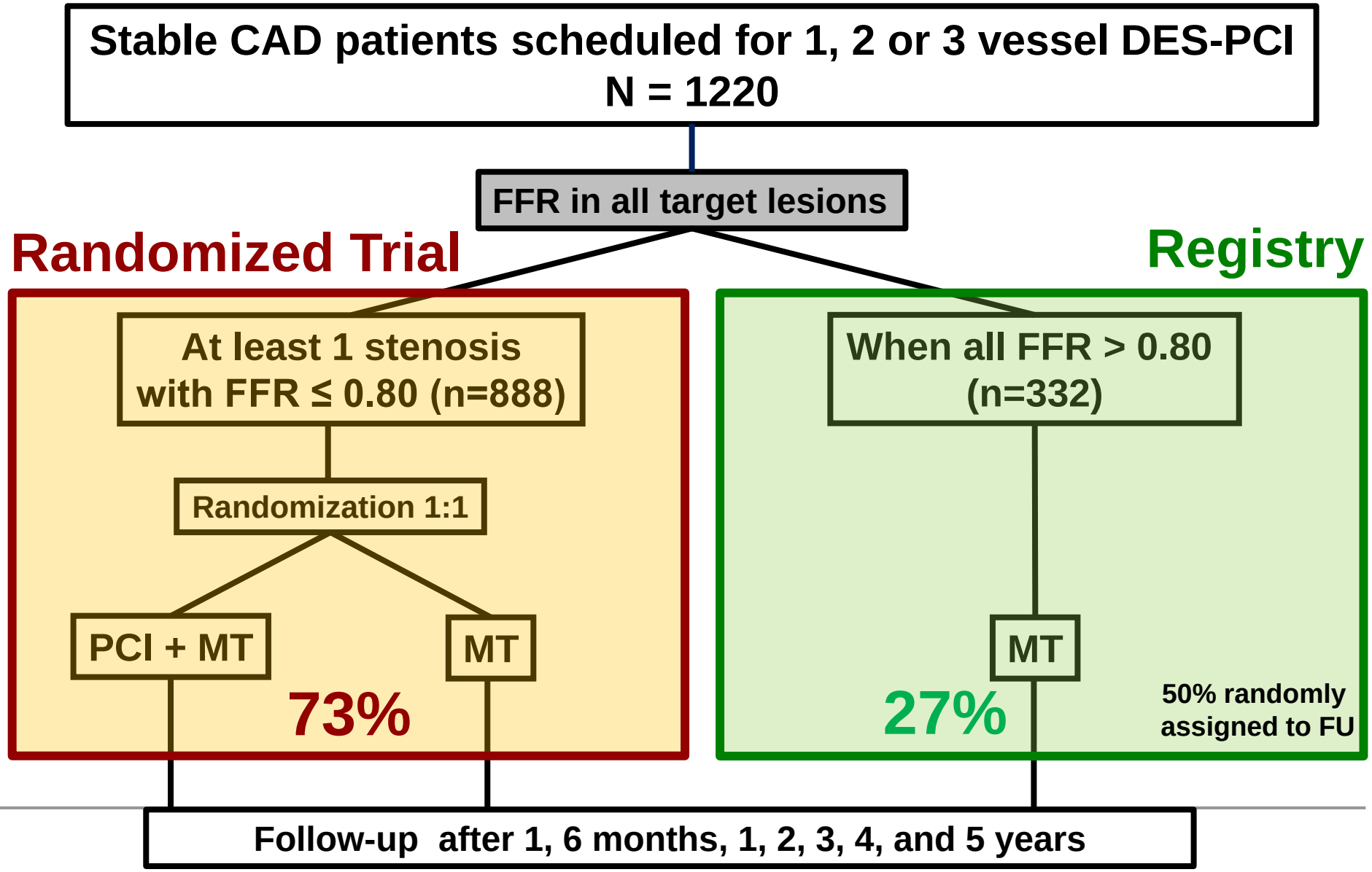
William F. Fearon, MD
Associate Professor of Medicine
Director, Interventional Cardiology
Stanford University Medical Center

# FAME 2: Design

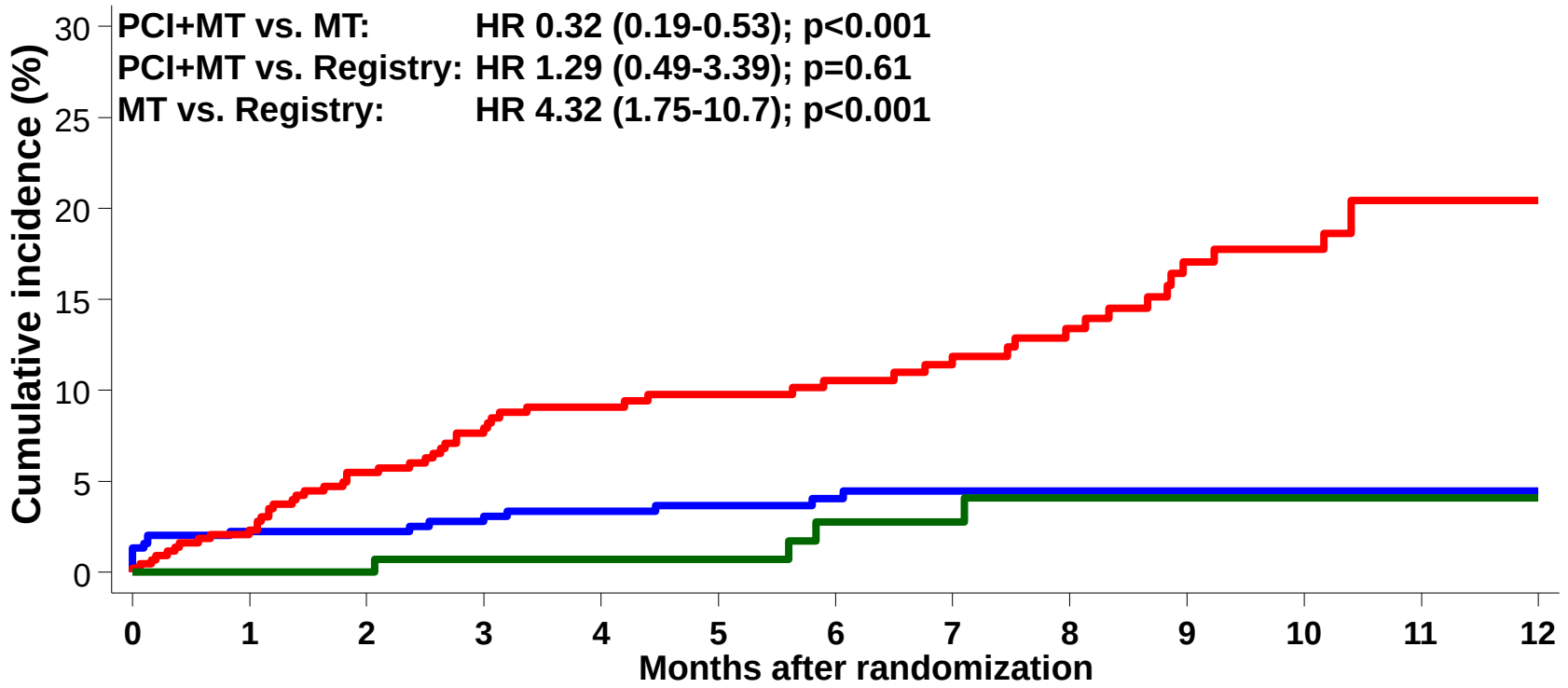
- Hypothesis:
  - Optimal medical therapy plus FFR-guided PCI improves outcomes compared to optimal medical therapy alone in patients with stable coronary artery disease.

De Bruyne, et al. New Engl J Med 2012;367:991-1001

# Flow Chart


Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI
N = 1220
FFR in all target lesions
Randomized Trial
Registry
At least 1 stenosis with FFR ≤ 0.80 (n=888)
Randomization 1:1
PCI + MT
MT
73%
When all FFR > 0.80 (n=332)
MT
27%
50% randomly assigned to FU
Follow-up after 1, 6 months, 1, 2, 3, 4, and 5 years

# Primary Endpoint: Death, MI, Urgent Revasc




No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MT | 441 | 414 | 370 | 322 | 283 | 253 | 220 | 192 | 162 | 127 | 100 | 70 | 37 |
| PCI+MT | 447 | 414 | 388 | 351 | 308 | 277 | 243 | 212 | 175 | 155 | 117 | 92 | 53 |
| Registry | 166 | 156 | 145 | 133 | 117 | 106 | 93 | 74 | 64 | 52 | 41 | 25 | 13 |

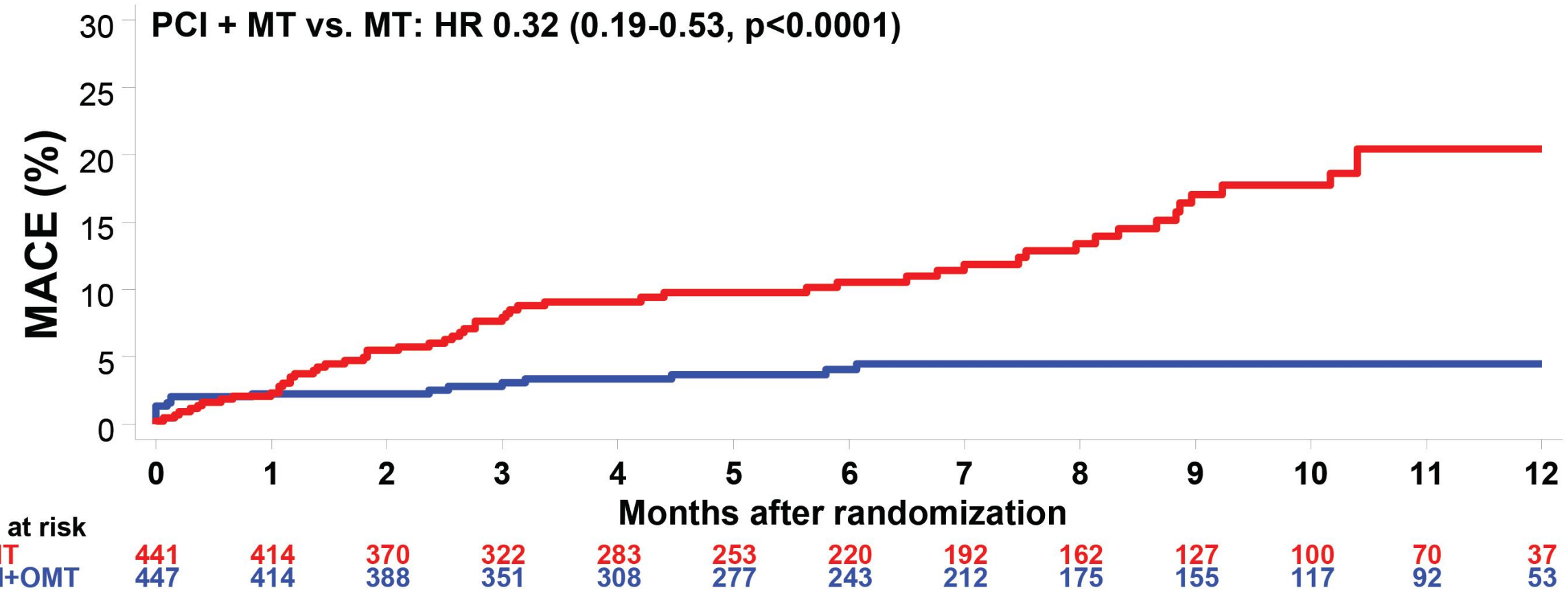
De Bruyne, et al. New Engl J Med 2012;367:991-1001

Cardiovascular Center Aalst

# FAME 2 trial

## FFR-guided PCI vs. OMT in stable CAD pts

1 year




Munich 2018

B De Bruyne B, Barbato E et al et al NEJM 2012

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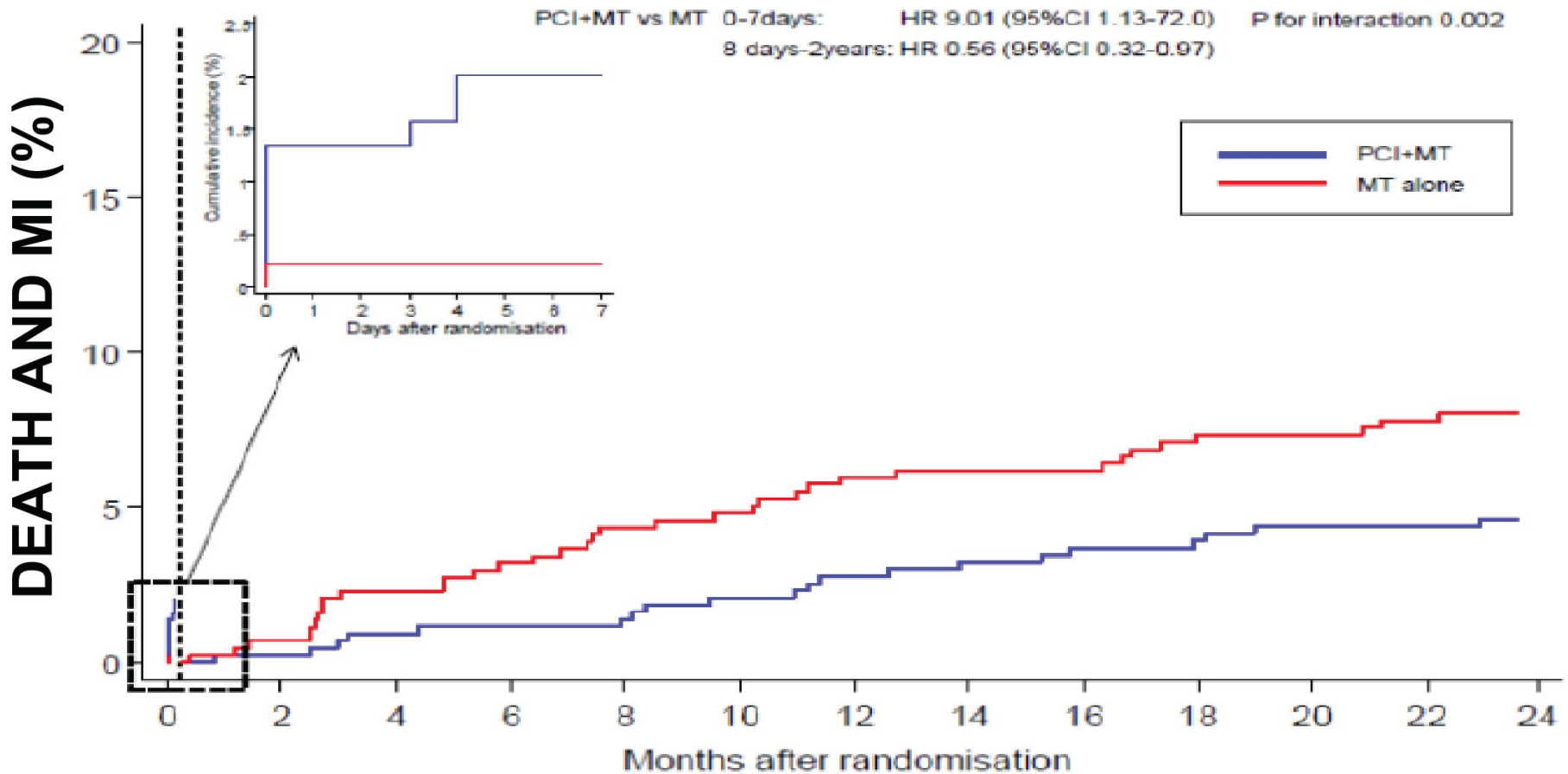
# FAME 2 trial

## FFR-guided PCI vs. OMT in stable CAD pts

2 years



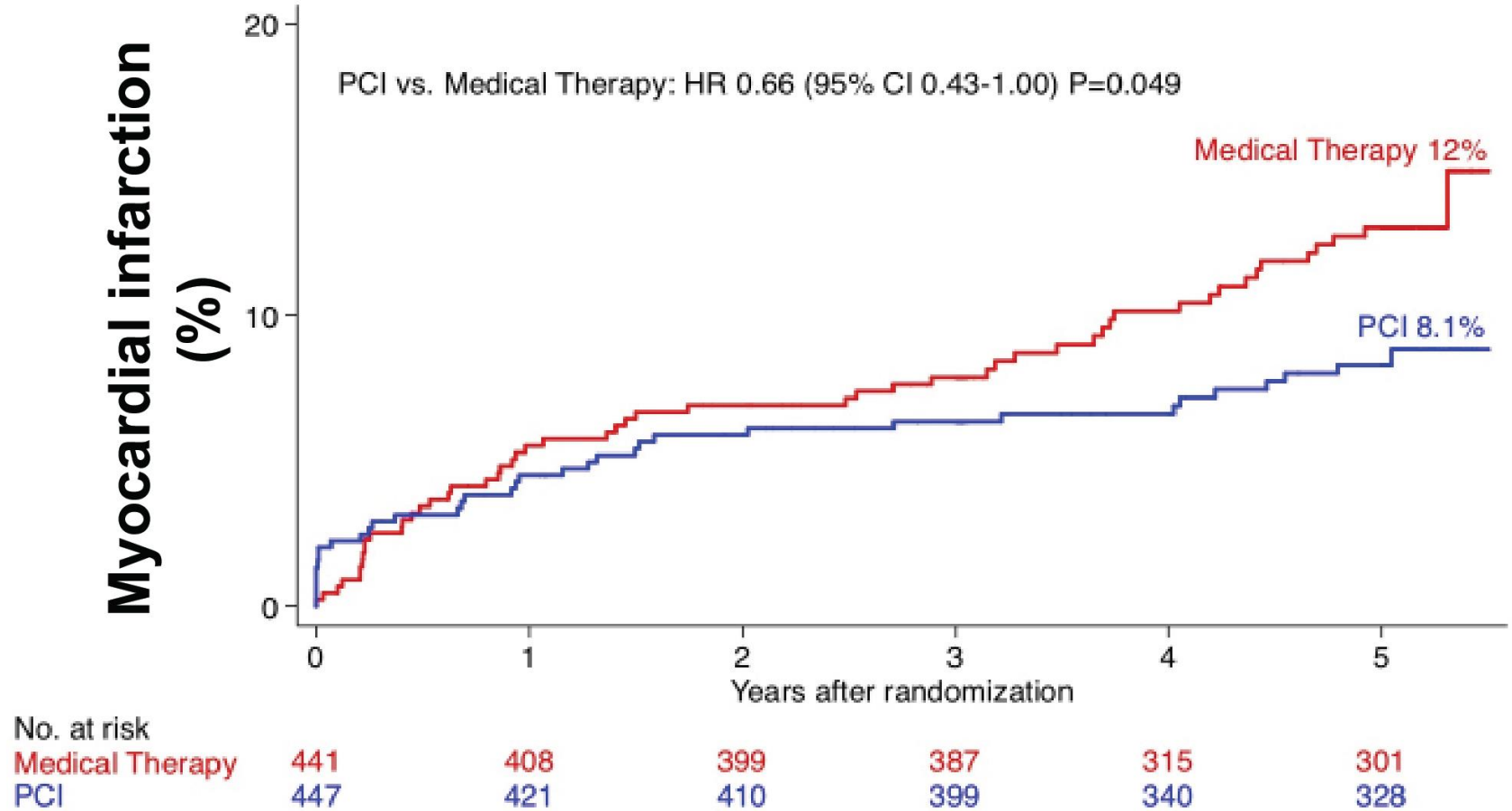

Munich 2018

B De Bruyne B, Barbato E et al et al NEJM 2014

# FAME 2 trial

## FFR-guided PCI vs. OMT in stable CAD pts

5 years






Xaplanteris P, Barbato E et al et al NEJM 2018

# FAME 2 Trial

***Take Home Messages:***

- **In patients with stable coronary artery disease, FFR-guided PCI improves patient outcome and is cost-effective when compared to medical therapy alone.**

- **This improvement is driven by a dramatic decrease in the need for urgent revascularization for ACS.**

- **In patients with functionally non-significant stenoses, medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses.**

# FAME 3 Trial:
## *FFR-Guided PCI vs. CABG*

William F. Fearon, M.D.
Associate Professor of Medicine
Director, Interventional Cardiology
Stanford University Medical Center

# Background:

- Why should we expect a different result with FAME 3?
  - 2nd Generation DES outperform 1st Generation.
  - Fractional Flow Reserve-guided PCI outperforms angiography-guided PCI.

# FAME 3:

## ***Hypothesis***

- Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) using the 2nd generation Resolute DES in patients with multivessel coronary artery disease (CAD) will result in similar outcomes to coronary artery bypass graft surgery (CABG).

# FAME 3:

## ***Objective***

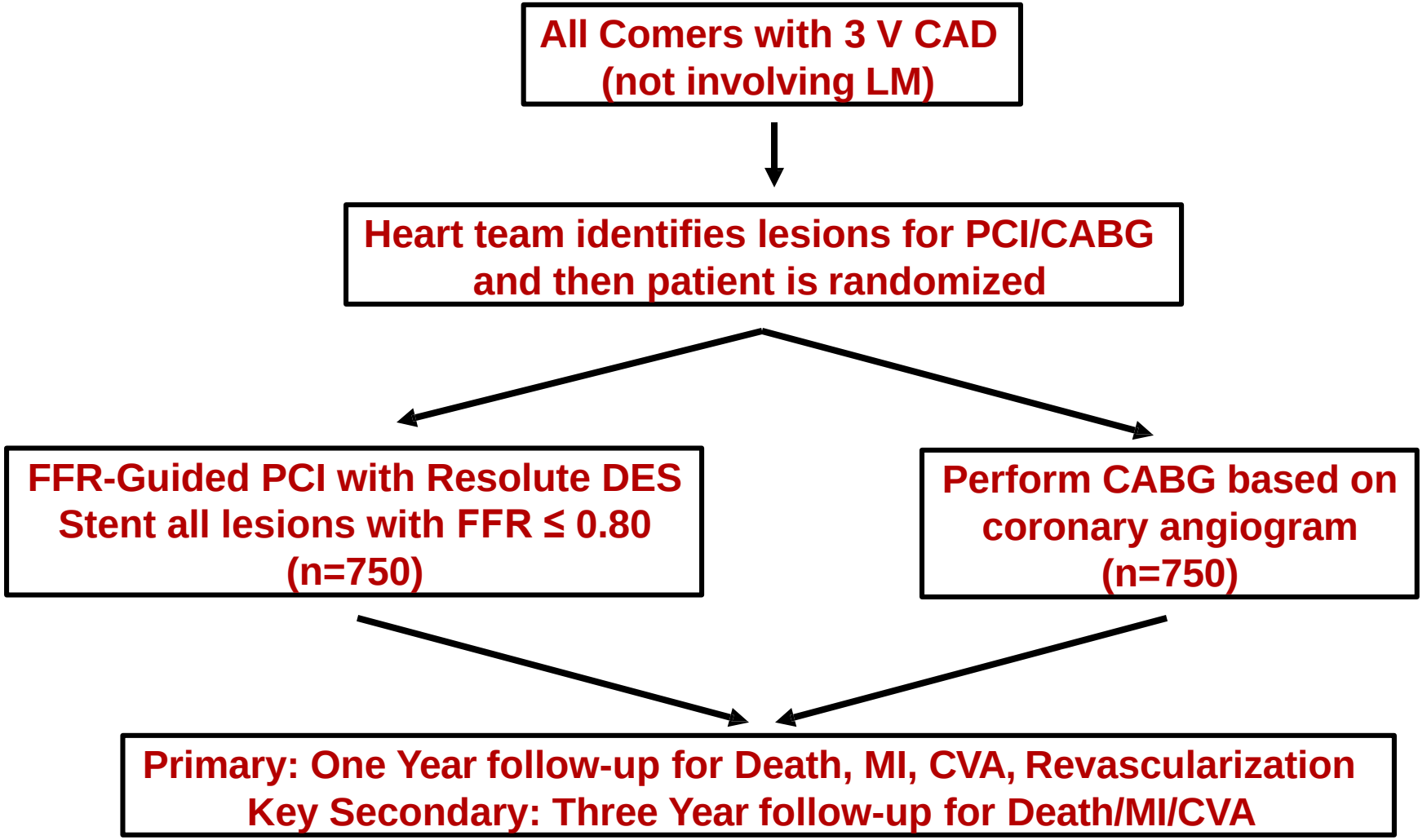
- The primary objective of the FAME 3 Trial is to demonstrate that FFR-guided PCI with the 2nd generation Resolute DES is non-inferior to CABG in patients with multivessel CAD.

# FAME 3:

## ***Design***

- Multicenter, worldwide, prospective, randomized trial
- Non-inferiority design
- 1500 patients from 50 sites
- Plan for 2 years enrolment and up to 5 year follow-up

# Study Flow:


All Comers with 3 V CAD
(not involving LM)
Heart team identifies lesions for PCI/CABG
and then patient is randomized
FFR-Guided PCI with Resolute DES
Stent all lesions with FFR ≤ 0.80
(n=750)
Perform CABG based on
coronary angiogram
(n=750)
Primary: One Year follow-up for Death, MI, CVA, Revascularization
Key Secondary: Three Year follow-up for Death/MI/CVA

# FAME 3:

## ***Inclusion Criteria***

- Age ≥ 21 years
- Three vessel CAD, defined as ≥ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels, but not involving left main coronary artery, and amenable to revascularization by both PCI and CABG as determined by the Heart Team
- Willing and able to provide informed, written consent

# FAME 3:

## ***Key Exclusion Criteria***

- Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement)
- Previous CABG
- Left main disease requiring revascularization
- Cardiogenic shock and/or need for mechanical/pharmacologic hemodynamic support
- Recent STEMI (<5 days)
- Ongoing Non STEMI with biomarkers (e.g., cardiac troponin) still rising
- Known left ventricular ejection fraction <30%

# FAME 3:

## ***Major Endpoints***

- Primary Endpoint:
  - One year rate of Death, MI, Stroke and Revascularization
- Key Secondary Endpoint:
  - Three year rate of Death, MI and Stroke

# FAME 3:

## ***Secondary Endpoints***

- MACCE rate at 1 and 6 months, 3 years and 5 years
- Stent thrombosis (ARC definition) and graft occlusion at each time point
- Bleeding complication
- Significant arrhythmia
- Development of acute renal failure
- Length of hospitalization
- Rehospitalization
- Quality of life and cost-effectiveness
- Utility of Functional SYNTAX Score

# FAME 3

## ***Study Organization***

- Investigator initiated trial
- Coordinated by Stanford with support of a CRO
- Funded by research grants from Medtronic and St. Jude Medical
- Independent DSMB and CEC

# Conclusion:

- By incorporating FFR-guided PCI and utilizing the 2nd generation Resolute Integrity stent, FAME 3 aims to demonstrate that FFR-guided PCI is non-inferior to CABG in patients with 3-vessel coronary disease not involving the left main coronary artery.

# A Randomized Comparison of Anatomic versus Functional Diagnostic Testing Strategies in Symptomatic Patients with Suspected Coronary Artery Disease

*Pamela S. Douglas, Udo Hoffmann, Manesh R. Patel, Daniel Mark, Lawton Cooper, and Kerry Lee*

*On behalf of the PROMISE Investigators*

*Duke Clinical Research Institute, Massachusetts General Hospital, and the National Heart, Lung, and Blood Institute*

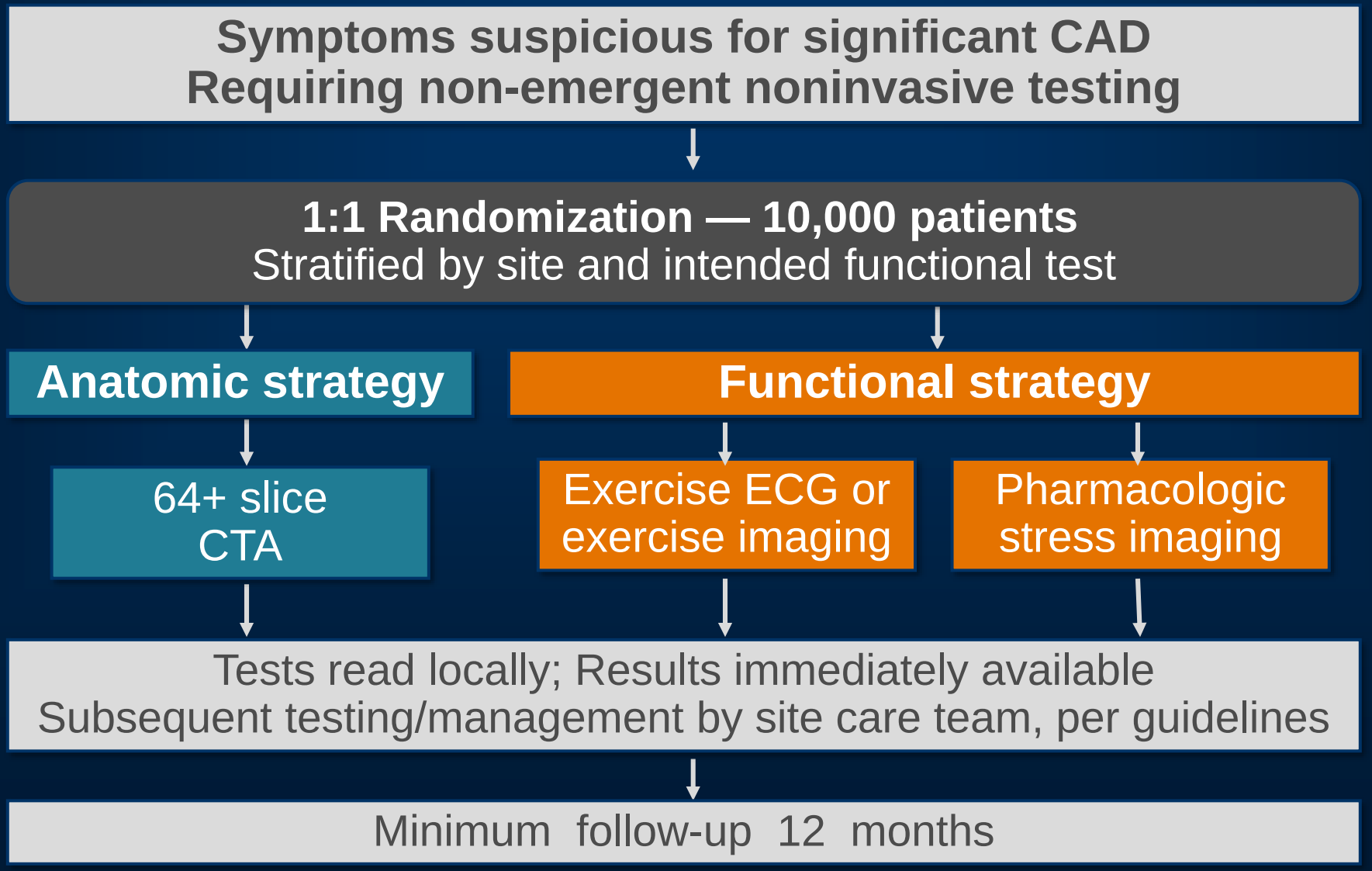
Supported by R01HL098237, R01HL098236, R01HL98305 and R01HL098235 from the National Heart, Lung, and Blood Institute

Duke Clinical Research Institute

NIH National Heart, Lung, and Blood Institute

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

# PROMISE Trial Design



# Study Population

## Inclusion criteria

- Non-urgent, noninvasive CV testing clinically necessary
- No history of CAD or recent CAD evaluation
- Age ≥55 years (men) or ≥65 years (women)  OR
- Age 45–54 years (men) or 50–64 years (women) with ≥1 major cardiac risk factor

## Exclusion criteria

- Unstable hemodynamics or arrhythmias
- Urgent evaluation for R/O ACS
- Known significant congenital, valvular or cardiomyopathic heart disease
- Any reason the patient could not be safely randomized

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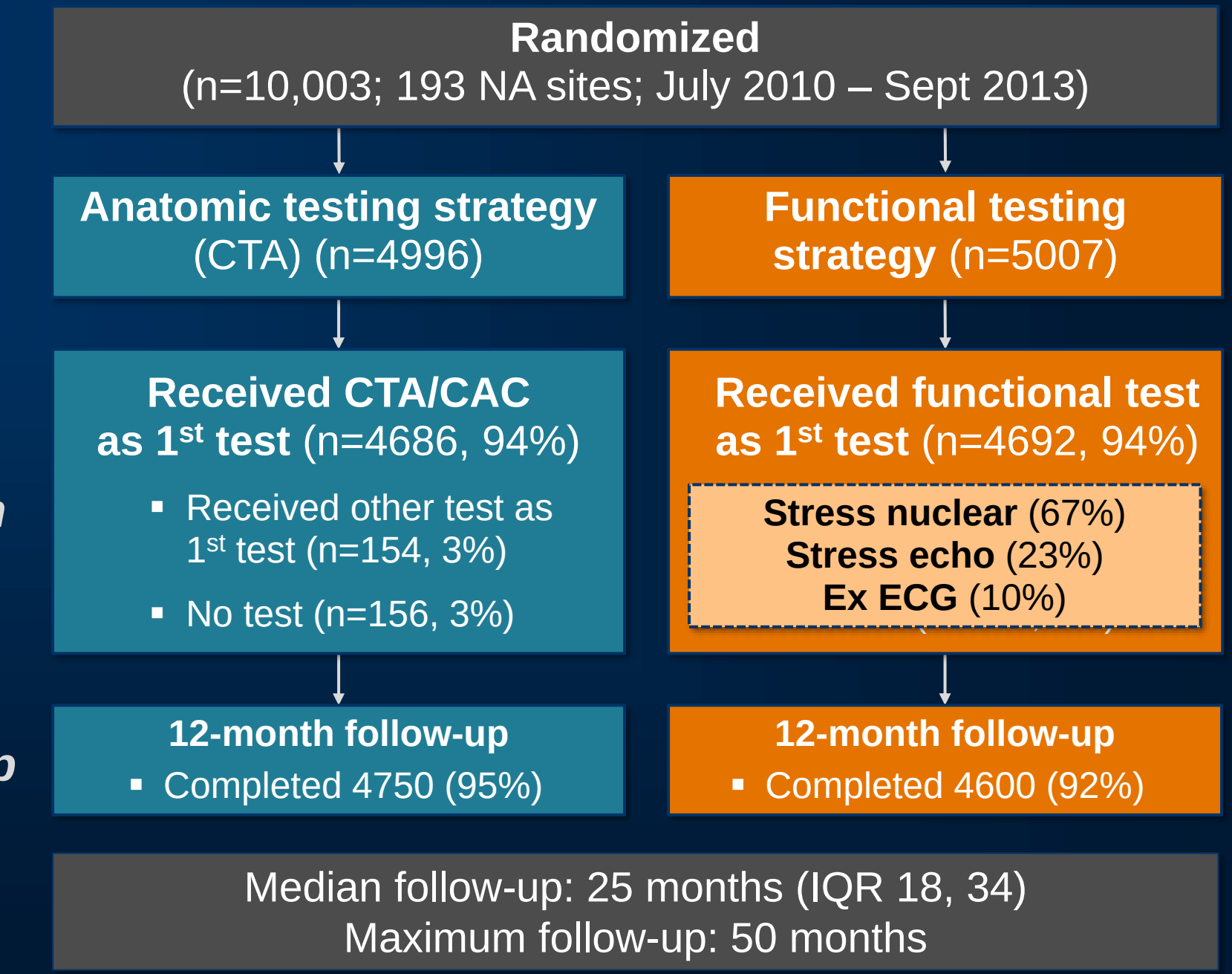
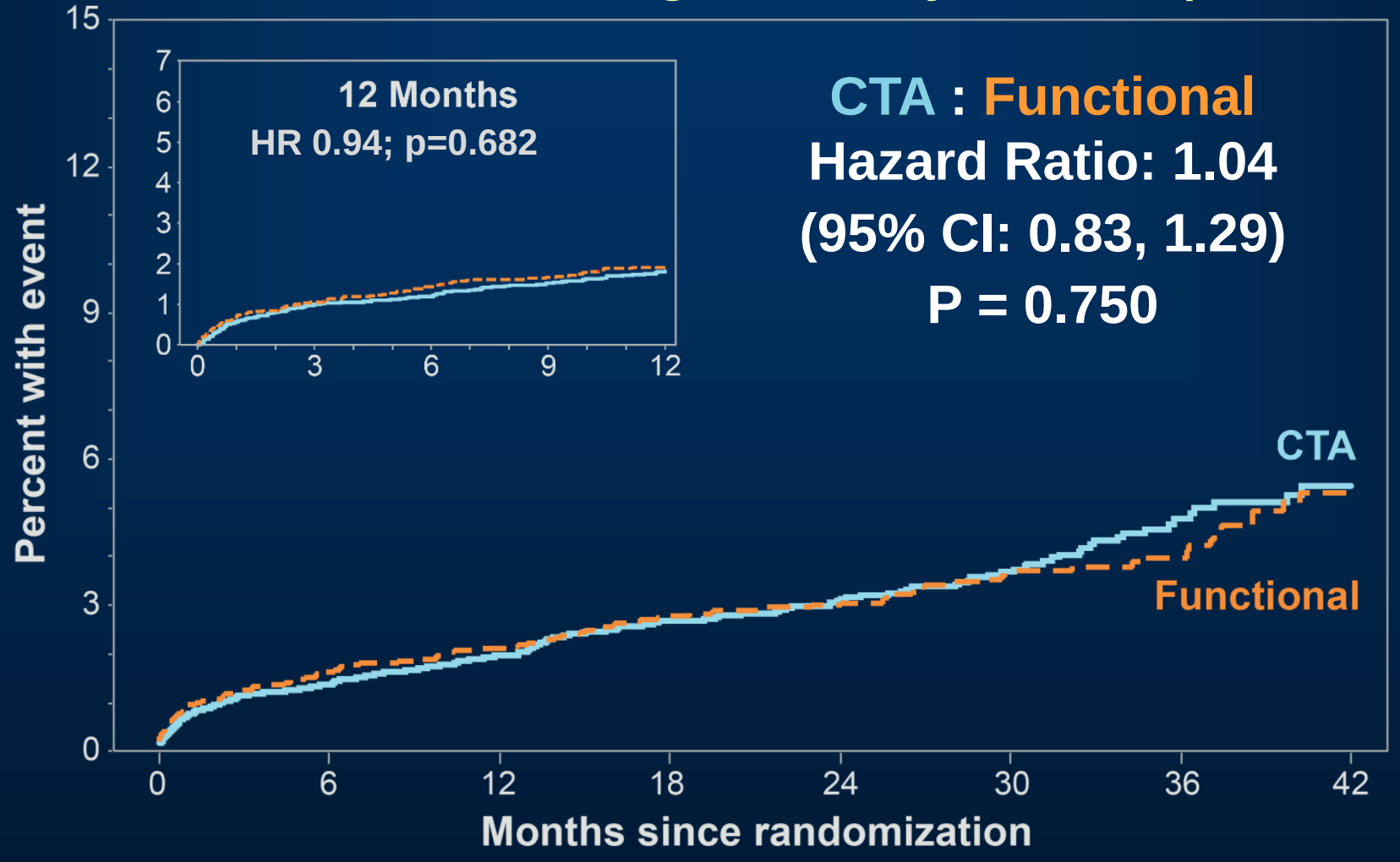
# Randomization and Follow-up

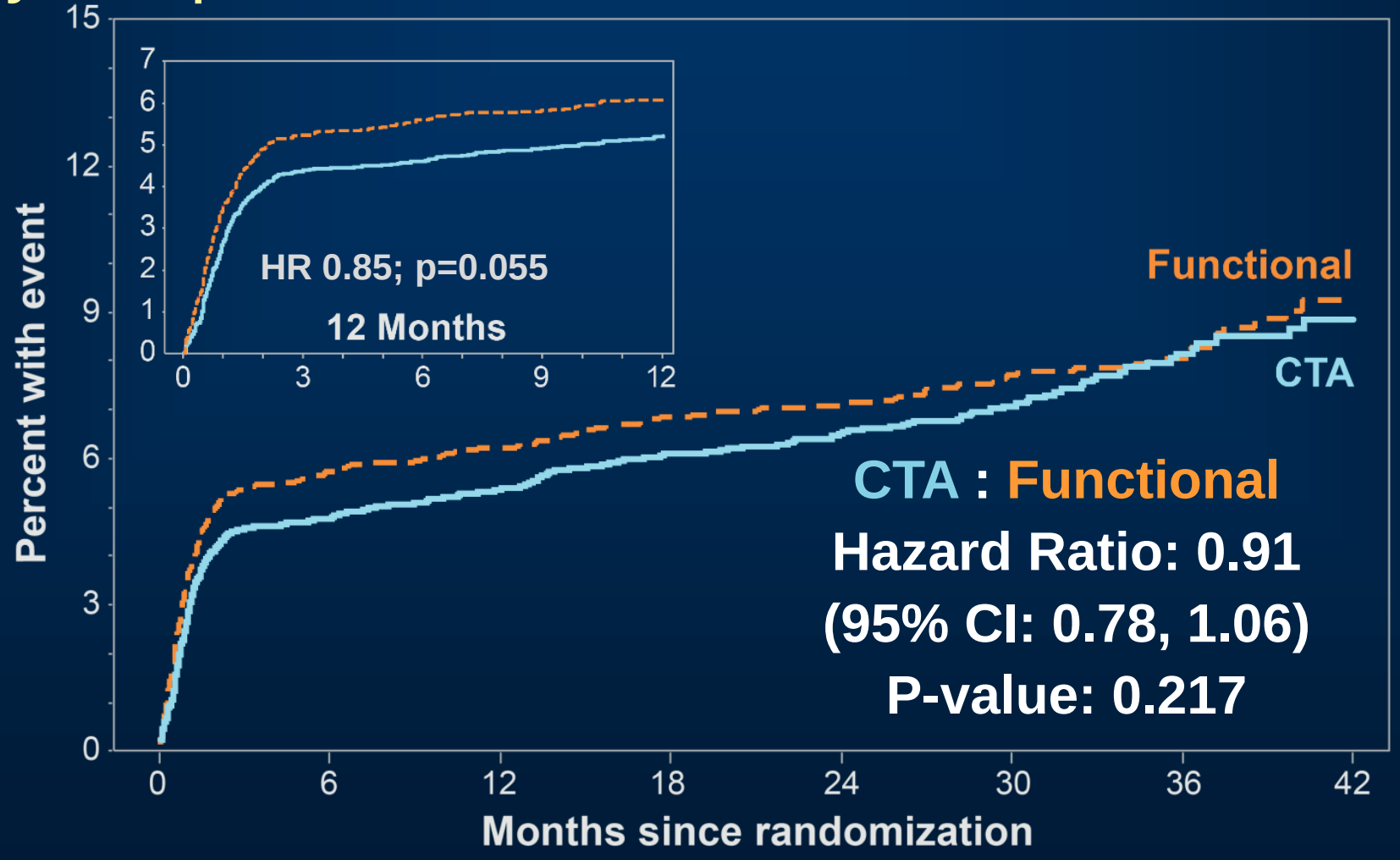


# Primary Endpoint:
## Death, MI, Unstable Angina, Major Complications



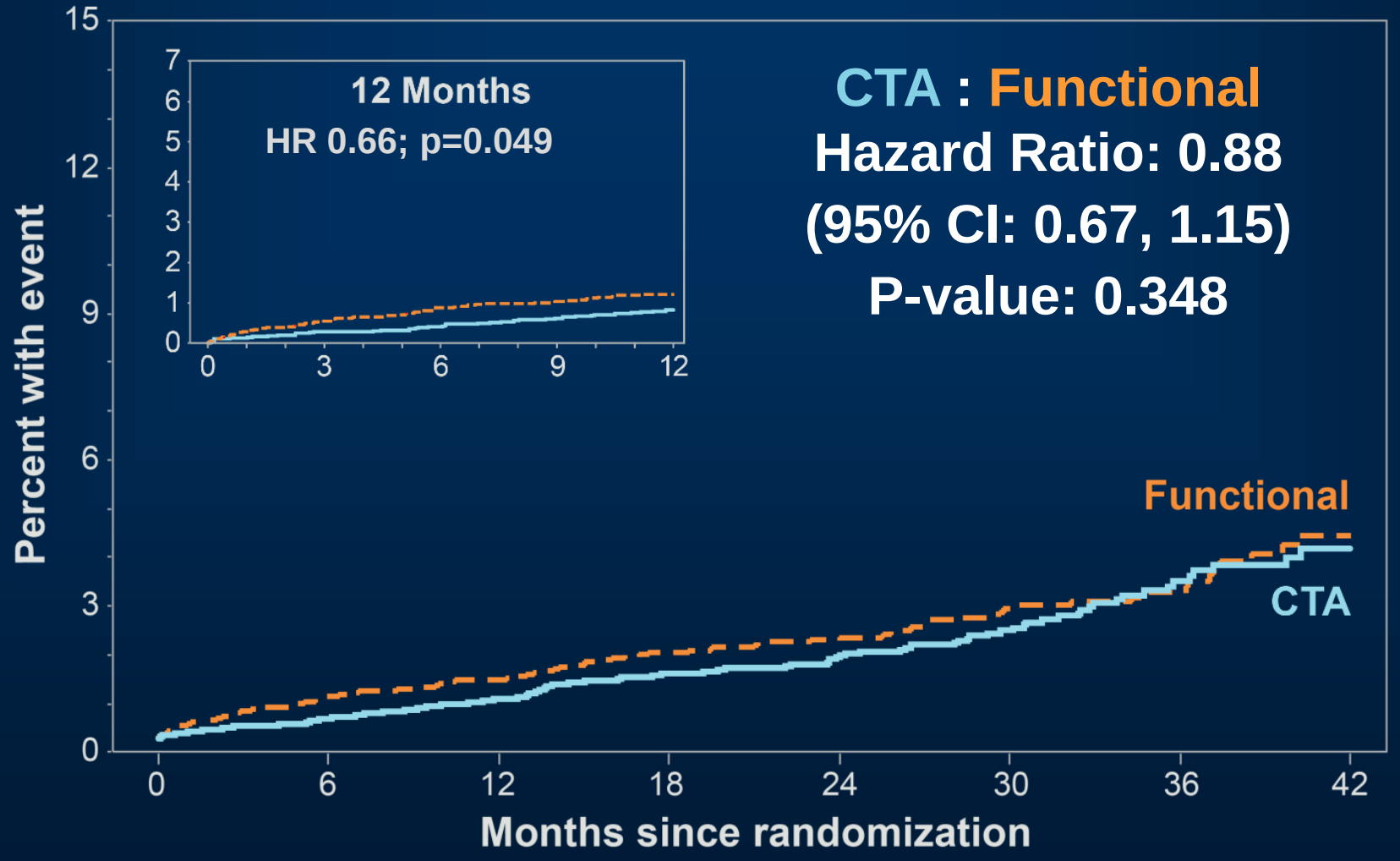

| # at risk | Baseline (0) | 6 Mo. | 12 Mo. | 18 Mo. | 24 Mo. | 30 Mo. | 36 Mo. | 42 Mo. |
|---|---|---|---|---|---|---|---|---|
| CTA | 4996 | 4703 | 4362 | 3551 | 2652 | 1705 | 902 | 269 |
| Functional | 5007 | 4536 | 4115 | 3331 | 2388 | 1518 | 832 | 258 |

# Secondary Endpoint:
## Primary Endpoint + Catheterization w/o Obstructive CAD




| # at risk | Baseline (0) | 6 Mo. | 12 Mo. | 18 Mo. | 24 Mo. | 30 Mo. | 36 Mo. | 42 Mo. |
|---|---|---|---|---|---|---|---|---|
| CTA | 4996 | 4540 | 4211 | 3430 | 2565 | 1645 | 868 | 255 |
| Functional | 5007 | 4341 | 3934 | 3179 | 2276 | 1438 | 781 | 244 |

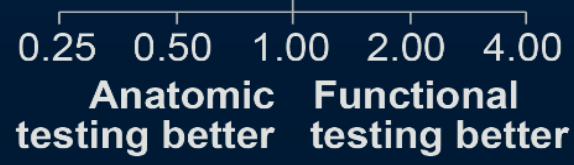
# Secondary Endpoint:
## Death or Non-fatal MI




| # at risk | Baseline (0) | 6 Mo. | 12 Mo. | 18 Mo. | 24 Mo. | 30 Mo. | 36 Mo. | 42 Mo. |
|---|---|---|---|---|---|---|---|---|
| CTA | 4996 | 4739 | 4409 | 3599 | 2686 | 1732 | 918 | 276 |
| Functional | 5007 | 4563 | 4148 | 3365 | 2415 | 1540 | 846 | 262 |

# **Primary Endpoint:** Subgroup Analyses

| Subject group | | Interaction P-value | N | Hazard ratio | 95% CI |
|---|---|---|---|---|---|
| **All subjects** | | | 10,003 | 1.04 | 0.83, 1.29 |
| **Age** | <65 | 0.591 | 7111 | 1.10 | 0.82, 1.47 |
| | ≥65 | | 2892 | 0.97 | 0.69, 1.36 |
| **Sex** | Male | 0.698 | 4733 | 0.99 | 0.74, 1.32 |
| | Female | | 5270 | 1.08 | 0.76, 1.51 |
| **Race** | White | 0.100 | 8371 | 0.95 | 0.74, 1.20 |
| | Non-white | | 1545 | 1.62 | 0.89, 2.92 |
| **Pre-test risk assessment** | Low risk (≤30%) | 0.341 | 3755 | 1.33 | 0.88, 2.00 |
| | Intermediate risk (31–70%) | | 5750 | 0.92 | 0.69, 1.23 |
| | High risk (>70%) | | 481 | 0.94 | 0.51, 1.74 |
| **CAD equivalent** | Yes | 0.142 | 2531 | 0.83 | 0.57, 1.20 |
| | No | | 7472 | 1.17 | 0.89, 1.54 |
| **Pretest probability of CAD** | Low risk (<10%) | 0.603 | 250 | 2.30 | 0.45, 11.88 |
| | Intermediate risk (10–90%) | | 9258 | 1.00 | 0.79, 1.26 |
| | High risk (>90%) | | 495 | 1.08 | 0.53, 2.23 |
| **Functional test randomization stratum** | Stress nuclear | 0.293 | 6781 | 0.93 | 0.72, 1.21 |
| | Stress echo | | 2236 | 1.27 | 0.78, 2.05 |
| | Exercise ECG | | 986 | 1.80 | 0.66, 4.86 |

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# Summary

- PROMISE enrolled a symptomatic, intermediate risk population for whom testing is currently recommended
- There is a low event rate in this contemporary population
- There were no significant differences in outcomes between an initial anatomic (CTA) or functional testing strategy with respect to the primary endpoint overall or in any subgroup
- An initial CTA strategy was associated with a lower rate of invasive catheterization without obstructive CAD
- Radiation exposure was higher in CTA arm overall, but lower in those patients for whom a nuclear test was specified at randomization as the intended functional test, and who were then randomized to CTA

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# Conclusions

- Compared to usual care using a functional testing strategy, use of an initial anatomic testing strategy employing CTA did not improve clinical outcomes in patients with suspected CAD
- Our results suggest that CTA is a viable alternative to functional testing
- These real-world results should inform noninvasive testing choices in clinical care as well as provide guidance to future studies of diagnostic strategies in suspected heart disease

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# Results Published Online Today

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

Pamela S. Douglas, M.D., Udo Hoffmann, M.D., M.P.H., Manesh R. Patel, M.D., Daniel B. Mark, M.D., M.P.H., Hussein R. Al-Khalidi, Ph.D., Brendan Cavanaugh, M.D., Jason Cole, M.D., Rowena J. Dolor, M.D., Christopher B. Fordyce, M.D., Megan Huang, Ph.D., Muhammad Akram Khan, M.D., Andrzej S. Kosinski, Ph.D., Mitchell W. Krucoff, M.D., Vinay Malhotra, M.D., Michael H. Picard, M.D., James E. Udelson, M.D., Eric J. Velazquez, M.D., Eric Yow, M.S., Lawton S. Cooper, M.D., M.P.H., and Kerry L. Lee, Ph.D., for the PROMISE Investigators*

ABSTRACT

BACKGROUND

Many patients have symptoms suggestive of coronary artery disease (CAD) and are often evaluated with the use of diagnostic testing, although there are limited data from randomized trials to guide care.

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