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Outcomes after FFR-Guided PCI vs. CABG:

Final 5-Year Follow-up of the FAME 3 Trial

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Background

- Previous studies in patients with 3-vessel coronary artery disease (3V-CAD) have shown that coronary artery bypass grafting (CABG) results in lower rates of the composite of death, stroke, or myocardial infarction (MI) compared with percutaneous coronary intervention (PCI) at long-term follow-up.[1]

- These results, however, are outdated given improvements in percutaneous and surgical techniques, and in medical therapy.

[1]Head SJ, et al. Eur Heart J 2014;35:2821-30

Background

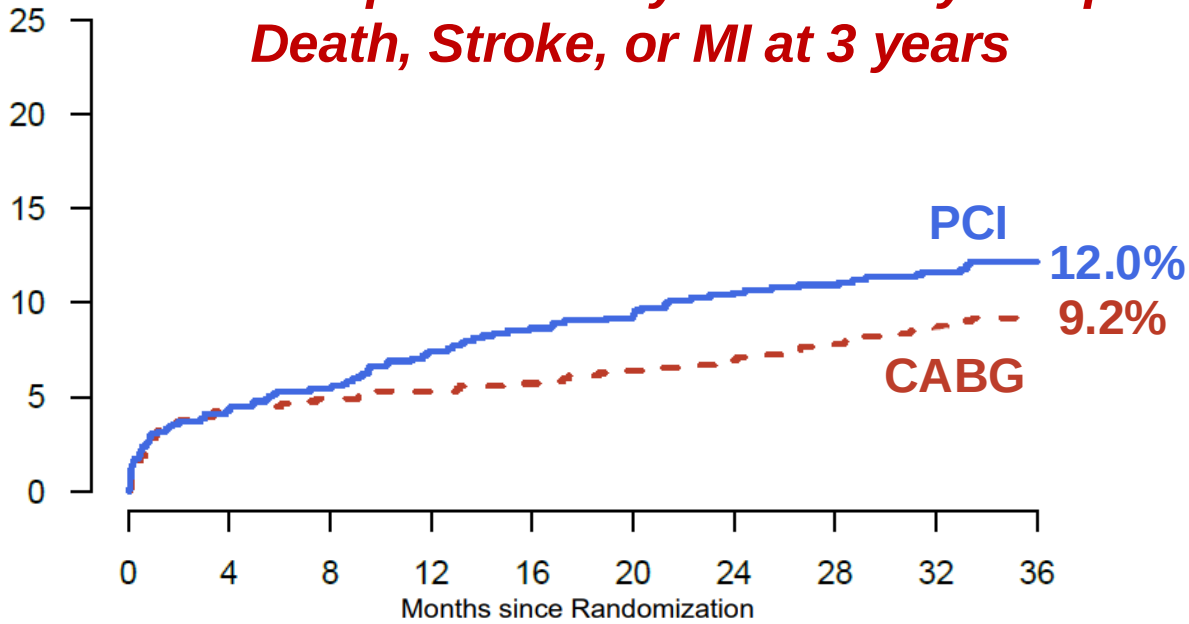
- The Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME) 3 trial compares fractional flow reserve (FFR)-guided PCI using a current-generation drug-eluting stent (DES) with contemporary CABG, both in conjunction with guideline-directed medical therapy.

- At one year, PCI failed to meet the primary endpoint of non-inferiority compared with CABG with respect to the composite of death, stroke, MI, or repeat revascularization.[1]

[1]New Engl J Med 2022;386:128-137

Background

Prespecified Key Secondary Endpoint:
Death, Stroke, or MI at 3 years



HR 1.3 (0.98−1.83)
p=0.07

Zimmermann FM, et al. Circulation 2023;148:950-958

Background

- In older studies, the improved outcomes after CABG continued to increase with longer-term follow-up.[1]

- In this study, we report the prespecified, final 5-year follow-up of the FAME 3 trial for the clinically important outcome of death, stroke, or MI.

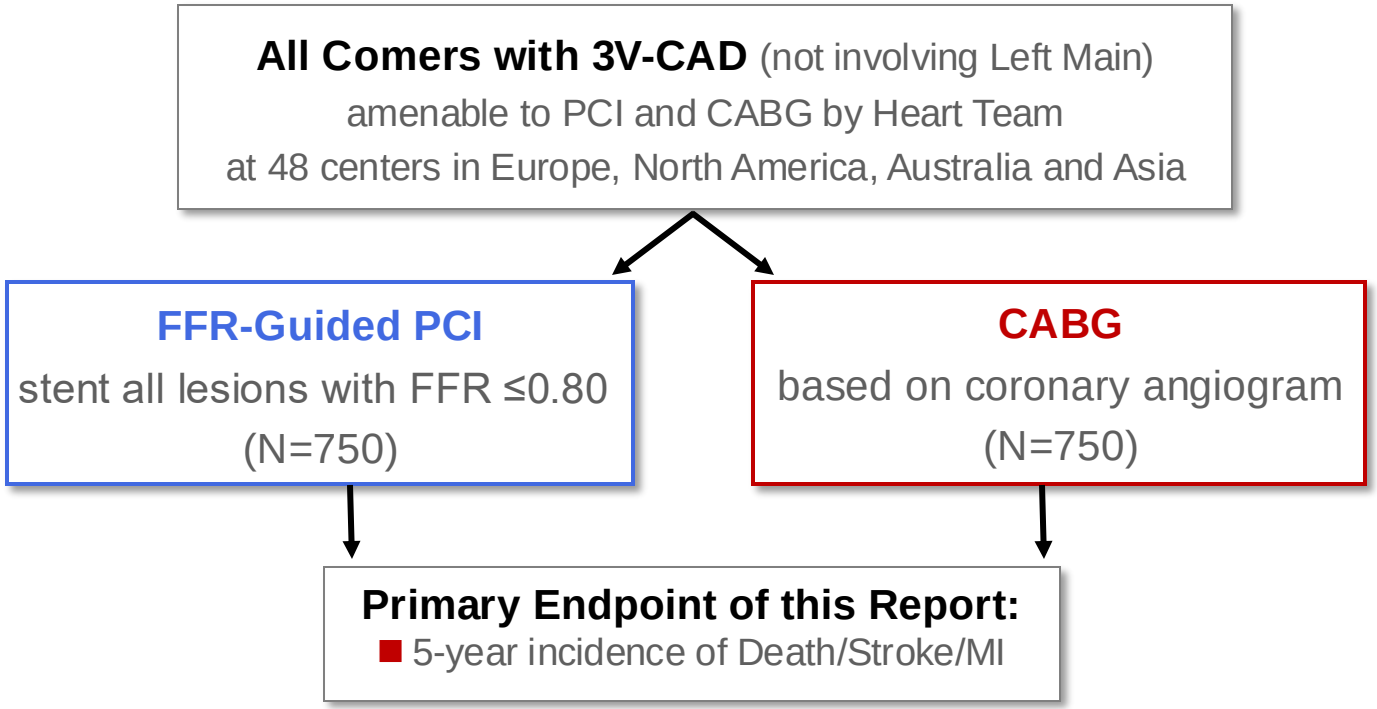
[1]Head SJ, et al. Eur Heart J 2014;35:2821-30

Study Organization

Sponsor	Stanford University
Funding	Research grants from Medtronic, Inc. and Abbott Vascular, Inc.
Steering Committee	William Fearon, MD (Chair), Bernard De Bruyne, MD, PhD, Nico Pijls, MD, PhD, Keith Oldroyd, MD, Michael Reardon, MD, Joseph Woo, MD, Olaf Wendler, MD, Alan Yeung, MD
Study Coordination	genae (now IQVIA) and Frederik Zimmermann, MD
Clinical Events Committee	Ken Mahaffey, MD (Chair), Stanford University
Data Safety Monitoring Board	Morton Kern, MD (Chair), University of California, Irvine
Angio Core Lab	Yuhei Kobayashi, MD, Stanford University/Albert Einstein
Data Analysis	Manisha Desai, PhD (Chair), Victoria Ding, MS, Stanford University

Study Design

Investigator-initiated, multicenter, randomized, controlled study



Patient Eligibility

Key Inclusion Criteria

- Three vessel CAD:
  - ≥ 50% diameter stenosis in 3 major epicardial vessels (visual estimation, no Left Main involvement)
  - Amenable to revascularization by both PCI and CABG (Heart Team)

Key Exclusion Criteria

- Cardiogenic shock
- Recent STEMI (within 5 days)
- LV ejection fraction < 30%

Procedural Requirements

FFR-Guided PCI

- Preload with P2Y12 inhibitor and high dose statin
- FFR measured with intracoronary or intravenous adenosine
- PCI (Medtronic Resolute stent) only if FFR ≤ 0.80 (Abbott pressure wire)
- Post-PCI FFR measurement recommended
- DAPT for ≥ 6 months

CABG

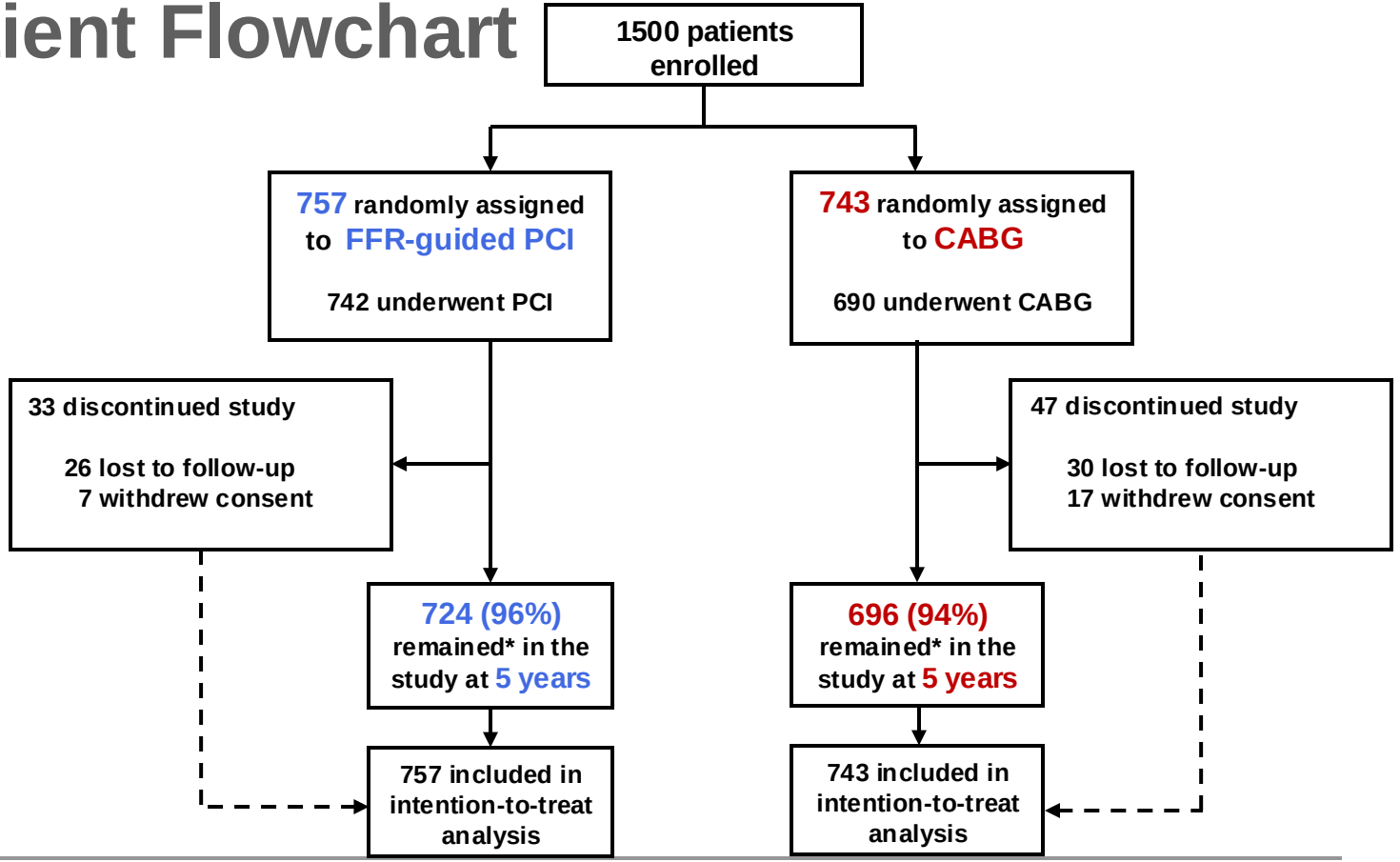
- FFR-guided CABG not mandated, but FFR information from diagnostic angiogram could be used
- Pre-treatment with aspirin and high dose statin recommended
- On- or off-pump CABG acceptable
- LIMA graft attempted in all cases
- Complete arterial revascularization strongly recommended

Statistical Analysis

- Data were analyzed on an intention to treat basis.
- Original trial assumptions:[1,2]
  - 12% event rate with CABG (based on SYNTAX)
  - Noninferiority margin set at a hazard ratio of 1.65
  - One-sided 2.5% significance level
  - Original sample size: 712 subjects (1,424 total) with 90% power
- The primary outcome of this analysis, the composite of death, stroke, or MI assessed at five years was prespecified, but not explicitly powered or adjusted for multiple comparisons.

[1] Zimmermann FM, et al. Am Heart J 2015;170:619-626
[2] Zimmermann FM, et al. Am Heart J 2019;214:156-157

Patient Flowchart



* Randomised patients who had either completed follow-up within the protocol-specified timeframe or were deceased.

Baseline Characteristics

Variable	PCI (n=757)	CABG (n=743)
Age	65 ± 8 years	65 ± 8 years
Male	81%	83%
Caucasian	94%	92%
HTN	71%	75%
Dyslipidemia	69%	72%
Current Tobacco Use	19%	18%
Diabetes	28%	29%
Insulin dependent	7%	8%
ACS presentation	40%	39%
EF≤50%	18%	18%
Prior PCI	13%	14%

Procedural Characteristics

Variable	PCI (n=757)	CABG (n=743)
Time to procedure	4 days	13 days
Procedure duration	87 min	197 min
Length of hospital stay	3 days	11 days
Number of lesions	4.3	4.2
≥1 Chronic occlusion	21%	23%
≥1 Bifurcation lesion	69%	66%
SYNTAX Score	26	26
Low (0-22)	32%	35%
Intermediate (23-32)	50%	48%
High (>33)	18%	17%

Procedural Characteristics

Variable	PCI (n=757)
% Lesions FFR measured	82%
FFR>0.80	24%
Staged procedure	22%
Number of stents	3.7±1.9
Total stent length	80 mm
Intravascular imaging	12%
FFR measured after PCI	60%

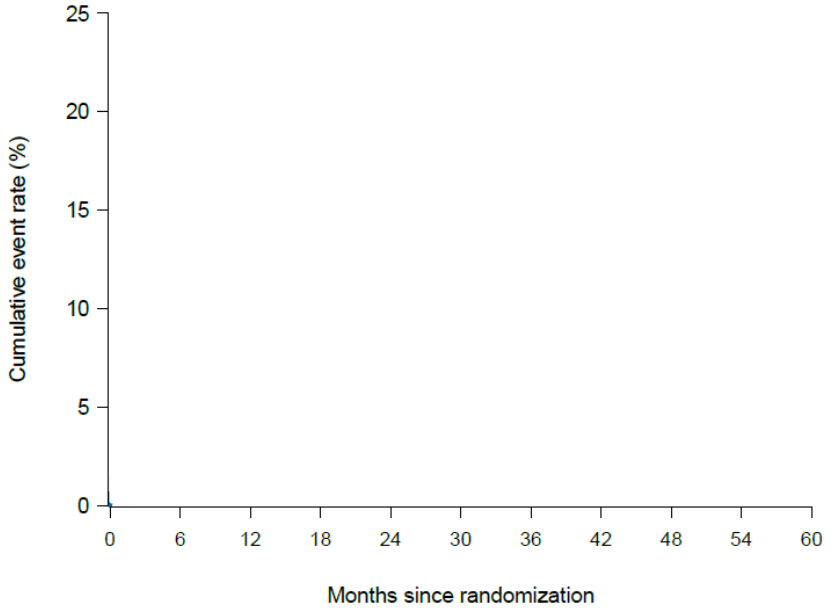
Variable	CABG (n=743)
FFR measured prior to CABG	10%
# of distal anastomoses	3.4±1.0
Multiple arterial grafts	25%
LIMA	97%
Off-Pump surgery	24%

Medical Therapy at Five Years

- Any antiplatelet agent ~90% (anticoagulants not recorded)
- Statin >91%
- Beta blocker >70%
- ACE I/ARB >70%

- No major differences between the two groups

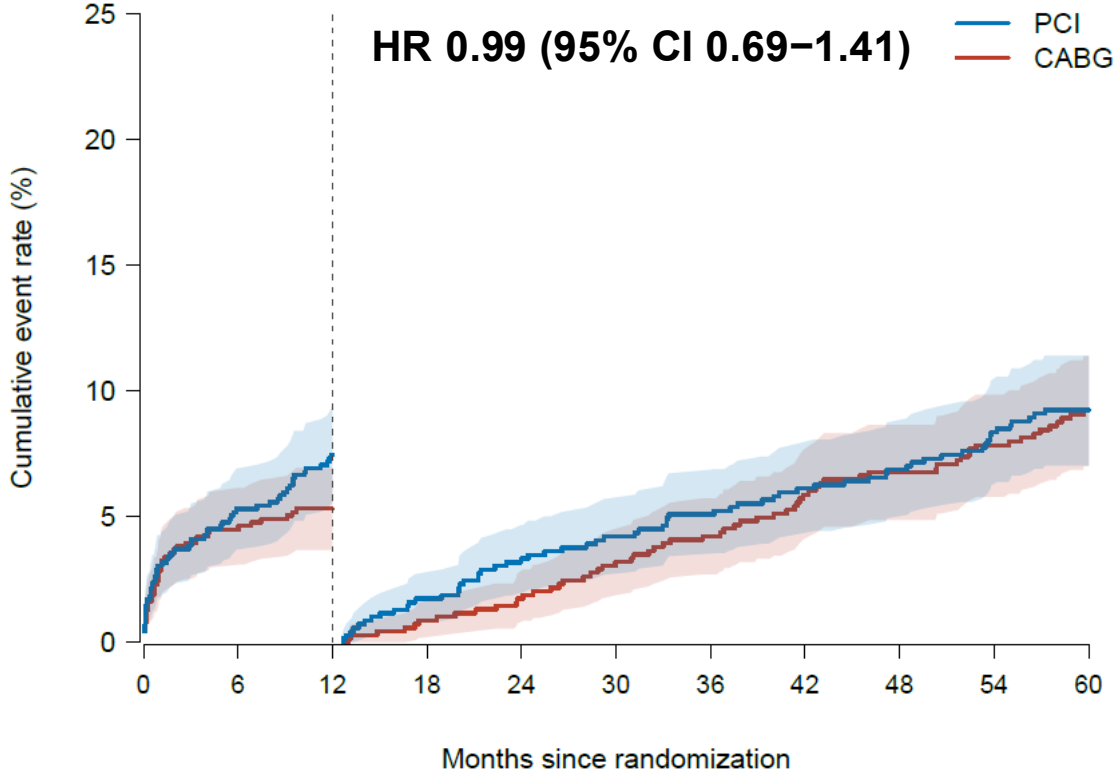
Primary Endpoint: *Death, Stroke, or MI at 5 years*



Number at risk

PCI	757	709	692	678	665	655	649	632	626	615	566
CABG	743	697	690	683	676	661	650	624	617	605	561

Landmark Analysis of Death, Stroke, or MI

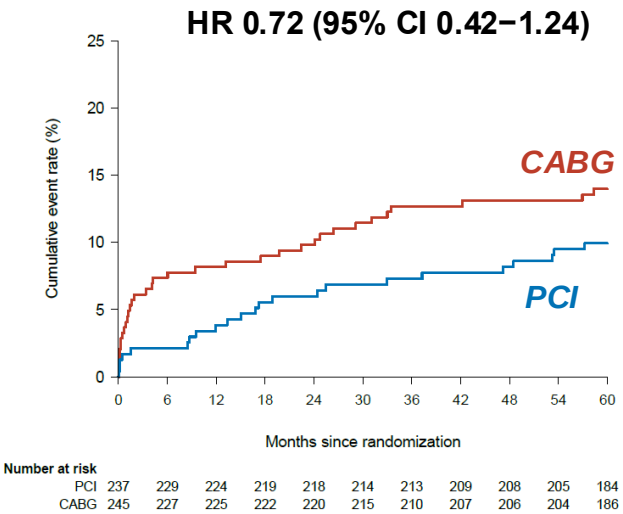


Secondary Endpoints

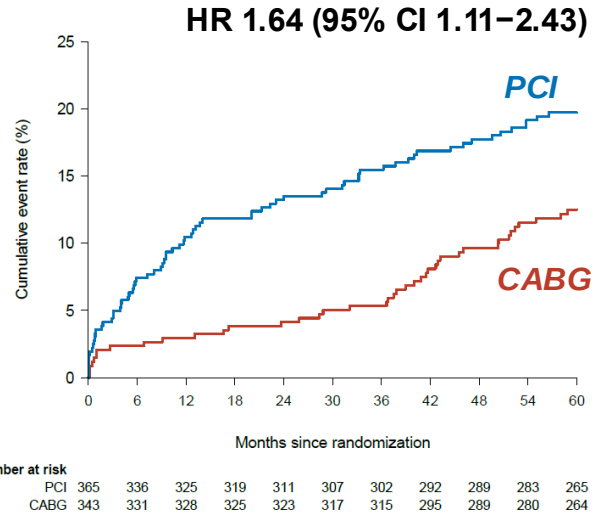
Endpoint	PCI (n=757)	CABG (n=743)	Hazard Ratio
Death	7.2%	7.2%	1.0 (0.7-1.5)
Cardiac death	2.0%	1.4%	
Stroke	1.9%	3.0%	0.7 (0.3-1.3)
MI	8.2%	5.3%	1.6 (1.0-2.4)
Procedural	1.9%	1.2%	
Spontaneous	6.3%	4.1%	
Repeat Revascularization	15.6%	7.8%	2.0 (1.5-2.8)
Death, stroke, MI, or repeat revascularization	25.3%	18.2%	1.4 (1.2-1.8)
Death, stroke, or MI (SCAI)*	20.0%	23.7%	0.9 (0.7-1.1)

*Using the Society for Cardiovascular Angiography and Interventions definition for procedural MI

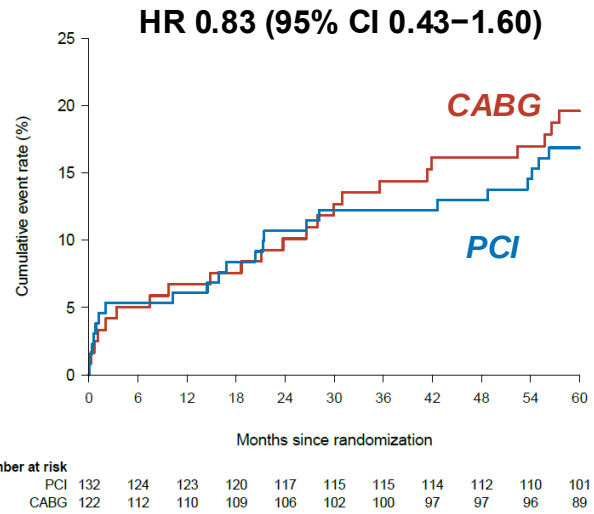
Death, Stroke, or MI Based on SYNTAX Score



LOW (<23) SYNTAX SCORE



INTERMEDIATE (23-32) SYNTAX SCORE



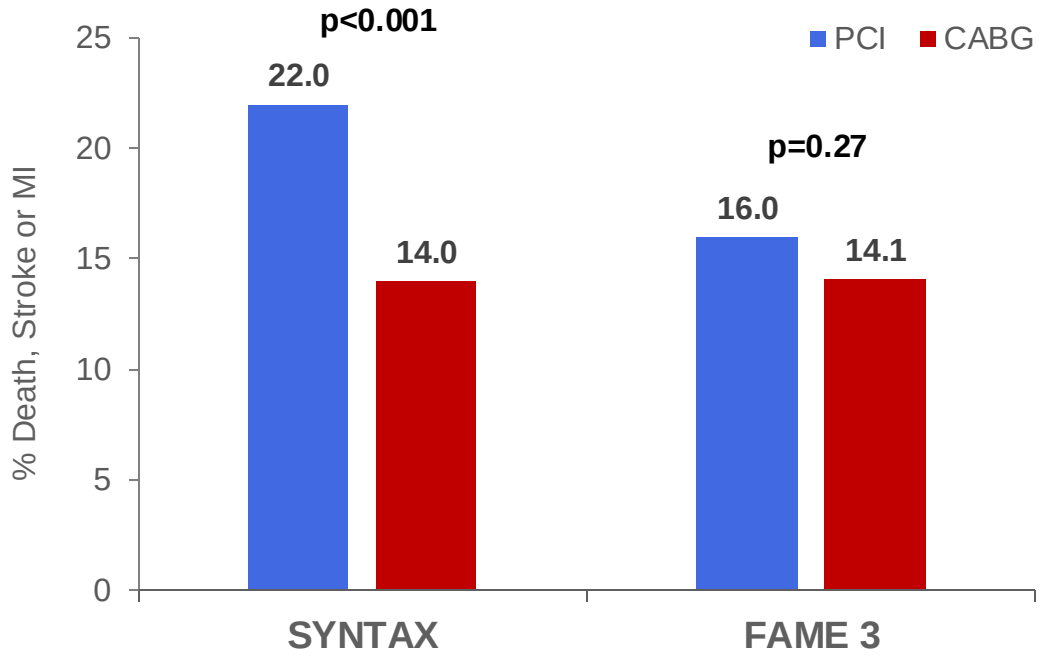
HIGH (>32) SYNTAX SCORE

FAME 3 Compared with the SYNTAX Trial

Variable	FAME 3	SYNTAX
Age	65 years	65 years
Male	82%	78%
Diabetes	29%	25%
Insulin Dependent	8%	10%
Hypertension	73%	67%
Dyslipidemia	70%	78%
Current Tobacco Use	19%	20%
ACS presentation	39%	29%
EF≤50%	18%	20%
Prior PCI	14%	0%
Number of Lesions	4.3	4.4
SYNTAX Score	26	29

FAME 3 Compared with the SYNTAX* Trial

Death, Stroke, or MI at 5 Years

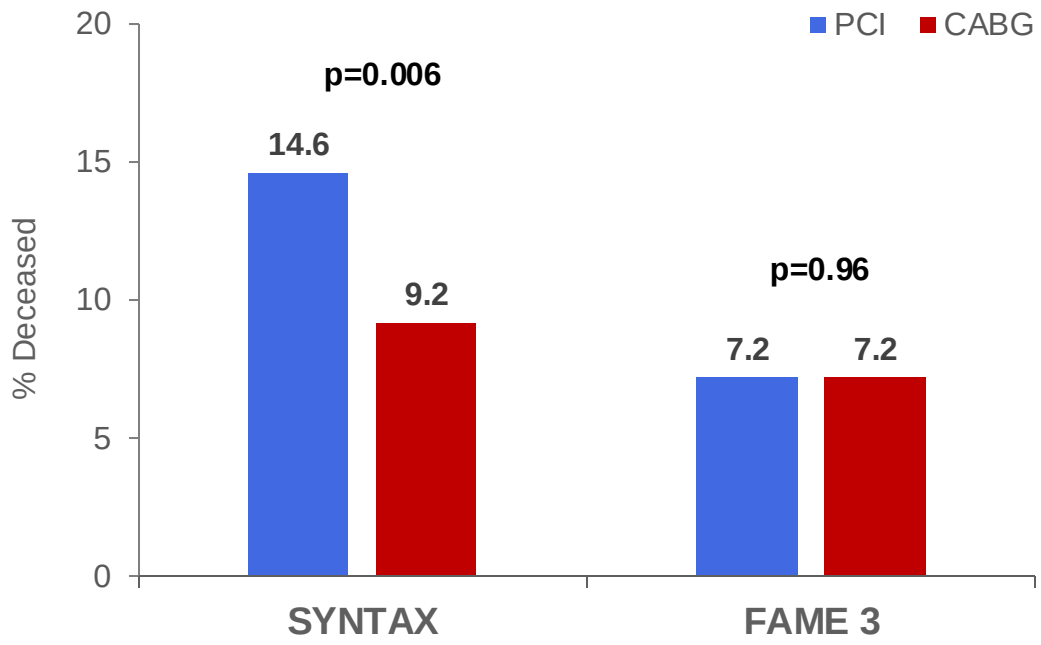


Head SJ, et al. Eur Heart J 2014;35:2821-30

*3V-CAD Cohort

FAME 3 Compared with the SYNTAX* Trial

Death at 5 Years



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*3V-CAD Cohort

Limitations

- This is a prespecified secondary endpoint of a study in which the primary endpoint was not met.
- Follow-up is limited to 5 years.
- The study included relatively few women, Black and other underrepresented patient populations.
- Intravascular imaging was utilized in only 12% in the PCI arm.

Conclusions

- In patients with 3V-CAD, there is no significant difference in the composite of death, stroke, or MI after FFR-Guided PCI with a current generation DES in comparison with CABG after 5 years.
  - The incidence of death in the two groups was the same.
  - The incidence of MI was higher after PCI (2.9% absolute difference).
  - In a landmark analysis, after one year, there was no late accrual of benefit with CABG.
  - These results differ strikingly from the 3V-CAD cohort in the SYNTAX trial, where the composite of death, stroke, or MI was significantly higher after PCI, as was the incidence of death alone.

Clinical Implications

- The difference in outcomes at 5 years between PCI and CABG has narrowed likely due to improved stent technology, the routine application of FFR-guided PCI and greater adherence to guideline-directed medical therapy.

- Patients with lower coronary anatomic complexity (based on the SYNTAX score) do better with PCI, while patients with greater anatomic complexity do better with CABG.

Clinical Implications

- The FAME 3 trial provides contemporary data regarding outcomes after FFR-guided PCI using current-generation DES compared with CABG in patients with 3V-CAD, which can facilitate improved shared decision-making between physicians and patients.

THE LANCET

Outcomes after fractional flow reserve-guided percutaneous coronary intervention versus coronary artery bypass grafting (FAME 3): 5-year follow-up of a multicentre, open-label, randomised trial

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Summary

Background Long-term outcomes following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) might be changing because of improved techniques and better medical therapy. This final prespecified analysis of the Fractional Flow Reserve (FFR) versus Angiography for Multivessel Evaluation (FAME) 3 trial aimed to reassess their comparative effectiveness at 5 years.

Thank you!

- The FAME 3 Steering Committee would like to thank the study participants, the site research coordinators and all of the co-investigators for their tireless effort.

- I would like to especially thank Dr. Frederik Zimmermann for his amazing effort and partnership on this trial for the past 11 years.

Thank You!