Fractional Flow Reserve-Guided PCI Compared with Coronary Bypass Surgery:

The FAME 3 Trial

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On Behalf of the FAME 3 Investigators

Disclosures

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott, Boston Scientific, Medtronic
Consulting Fees/Honoraria	CathWorks, HeartFlow, Siemens
Major Stock Shareholder/Equity	
Royalty Income	
Ownership/Founder	
Intellectual Property Rights	
Other Financial Benefit	

Background

- Previous studies have demonstrated improved outcomes with CABG compared with PCI in patients with 3-vessel CAD.[1]
- However, most trials used BMS or 1st generation DES.[2]
- In addition, none of these studies measured fractional flow reserve (FFR) to guide PCI.[3]

[1] Serruys PW, et al. *N Engl J Med* 2009;360:961-72.
[2] Stone GW, et al. *N Engl J Med* 2010; 362:1663-1674.
[3] Tonino PAL, et al. *N Engl J Med* 2009;360:213-24.

FAME 3 Trial Hypothesis

In patients with 3V-CAD, FFR-guided PCI with a current generation DES is noninferior to CABG with respect to 1-year MACCE.

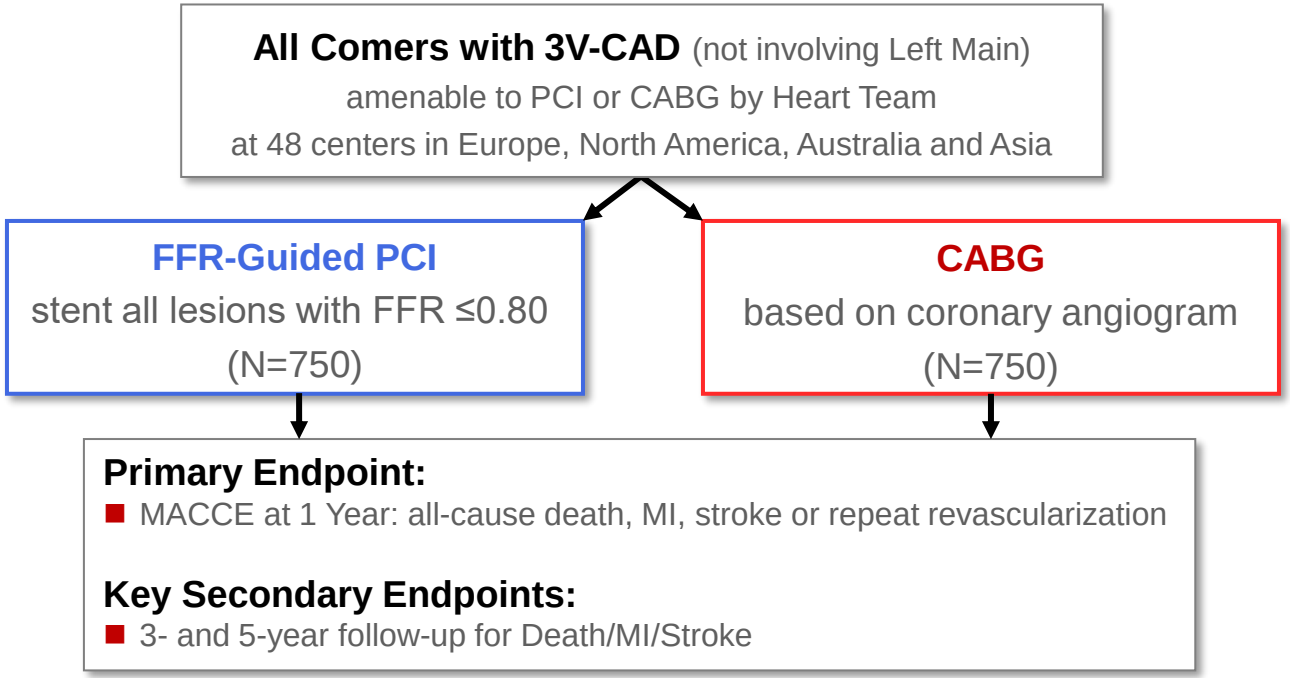
Zimmermann FM, et al. *Am Heart J* 2015;170:619-626.
Zimmermann FM, et al. *Am Heart J* 2019;214:156-157

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), Stanford University

Study Design

Investigator-initiated, multicenter, randomized, controlled study



Definition of Myocardial Infarction

Procedural

- Defined in the same way for CABG and PCI
- Troponin > 10x URL (or an increase of > 20%, if the baseline values are elevated) AND at least one of the following:
  - *New pathologic Q waves or new LBBB*
  - *Angiographic documented new graft or new major native coronary occlusion*
  - *Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality*

Spontaneous

- Rise and/or fall of cardiac biomarkers AND at least one of the following:
  - *Symptoms of ischemia*
  - *ECG changes indicative of new ischemia*
  - *Development of pathological Q waves*
  - *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality*

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

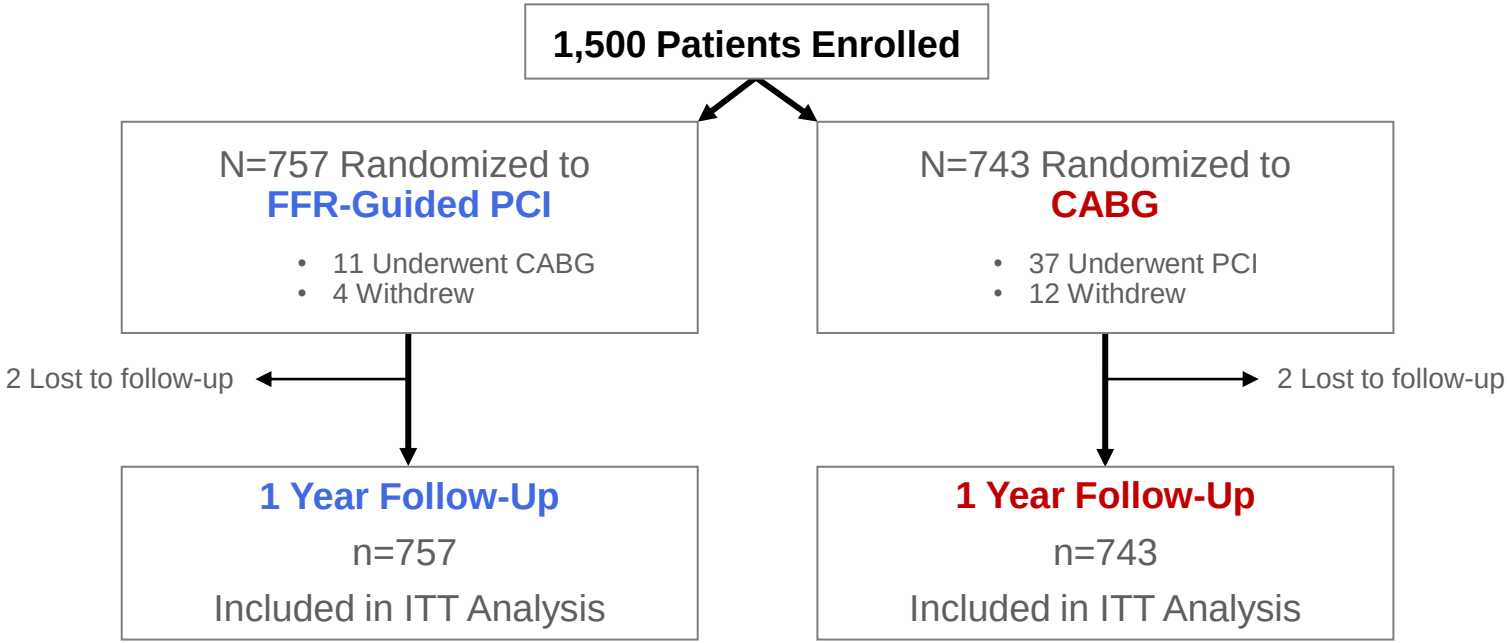
- FFR-guided CABG not mandated, but FFR information from diagnostic angiogram could be used
- Pre-treatment with aspirin and high dose statin recommended
- On- or off-pump CABG acceptable
- LIMA in all cases
- Complete arterial revascularization recommended

Statistical Analysis

- Based on intention to treat analysis
- Original assumptions:
  - 12% event rate with CABG (based on SYNTAX)
  - Noninferiority margin set at a hazard ratio of 1.45
  - One-sided 2.5% significance level
  - Original sample size: 712 subjects (1,424 total) with 90% power
- Subsequent trials comparing CABG with PCI documented 1-year MACCE rates in the CABG arm ≤10% and utilized larger noninferiority margins[1,2]
- Therefore, steering committee decided to increase HR for noninferiority margin to 1.65[3]
  - During enrolment and without knowledge of event rates
  - Maintain original sample size of 1,500 subjects to be randomized

[1] Stone GW, et al. *N Engl J Med* 2016;375:2223-2235
[2] Mäkikallio T, et al. *Lancet* 2016;388:2743-2752
[3] Zimmermann FM, et al. *Am Heart J* 2019;214:156-157

Patient Flowchart



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%

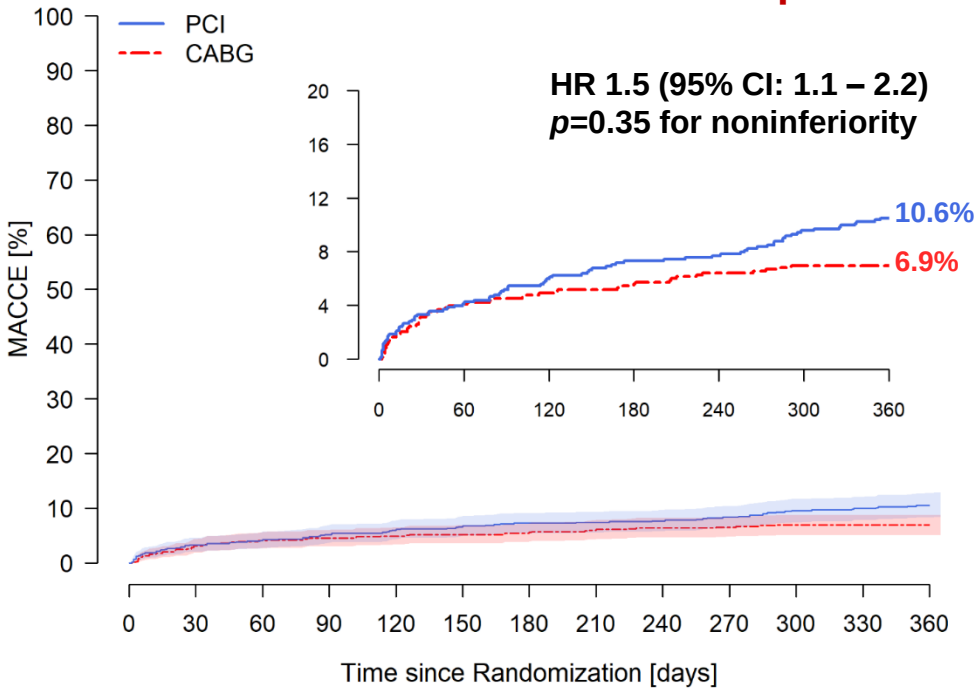
Procedural Characteristics

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%

Primary Endpoint

MACCE (Death, MI, stroke or repeat revascularization) at 1 Year



No. at Risk													
PCI	757	728	721	713	707	702	697	696	693	687	678	674	670
CABG	743	709	701	698	695	693	691	686	683	682	679	679	679

Secondary Endpoints

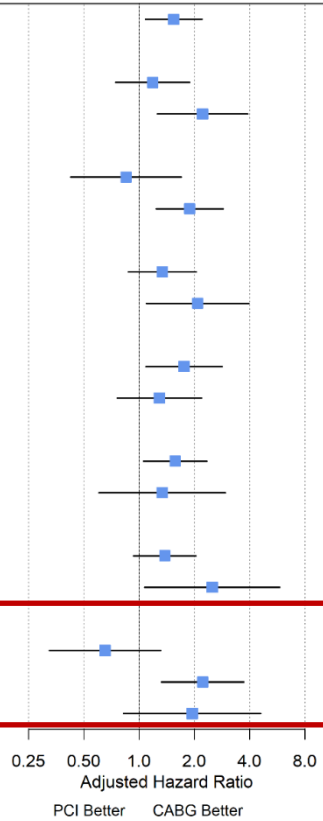
Endpoint	PCI (n=757)	CABG (n=743)	Hazard Ratio
Death	1.6%	0.9%	1.7 (0.7-4.3)
Cardiac death	0.8%	0.5%	
MI	5.2%	3.5%	1.5 (0.9-2.5)
Procedural	1.7%	1.2%	
Spontaneous	3.3%	2.3%	
Stroke	0.9%	1.1%	0.9 (0.3-2.4)
Repeat Revascularization	5.9%	3.9%	1.5 (0.9-2.3)
Death, MI or Stroke	7.3%	5.2%	1.4 (0.9-2.1)

Safety Endpoints

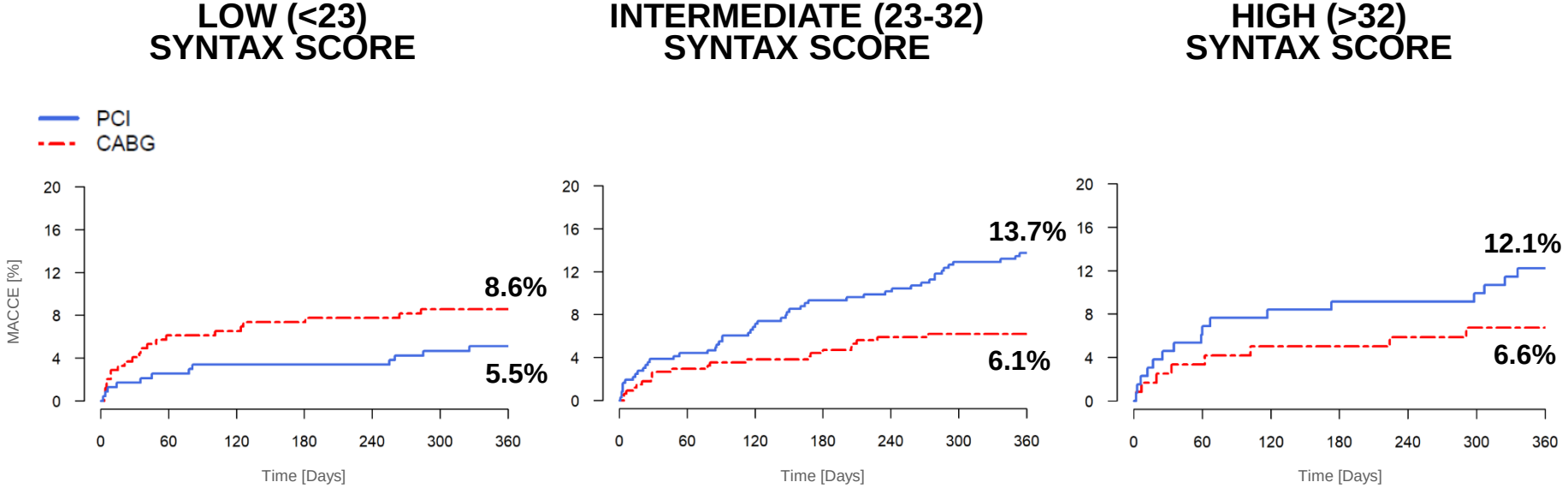
Endpoint	PCI (n=757)	CABG (n=743)	*p*-value
BARC Type 3-5 Bleeding	1.6%	3.8%	< 0.01
Acute Kidney Injury	0.1%	0.9%	< 0.04
Atrial Fibrillation/Arrhythmia	2.4%	14.1%	< 0.001
Definite Stent Thrombosis	0.8%	N/A	
Symptomatic Graft Occlusion	N/A	1.3%	
Rehospitalization w/in 30 days	5.5%	10.2%	< 0.001

Subgroup Analysis

Subgroup	PCI Total N	CABG Total N	PCI 1-yr Event Rate	CABG 1-yr Event Rate	Interaction p-value
Overall	757	743	10.6	6.9	
Age at enrollment					0.09
65+	434	409	9.4	8.1	
<65	323	334	12.1	5.4	
Sex					0.05
Female	141	124	11.3	13.7	
Male	616	619	10.4	5.5	
Diabetes					0.26
No	543	529	9.4	7.0	
Yes	214	214	13.6	6.5	
NSTE-ACS					0.40
No	456	454	10.1	5.9	
Yes	300	287	11.3	8.4	
LVEF					0.72
>50%	616	610	10.4	6.6	
30-50%	137	130	10.9	8.5	
Previous PCI					0.20
No	658	637	9.3	6.8	
Yes	98	104	19.4	7.7	
SYNTAX					0.02
0-22	237	245	5.5	8.6	
23-32	365	343	13.7	6.1	
33+	132	122	12.1	6.6	



MACCE According to SYNTAX Score

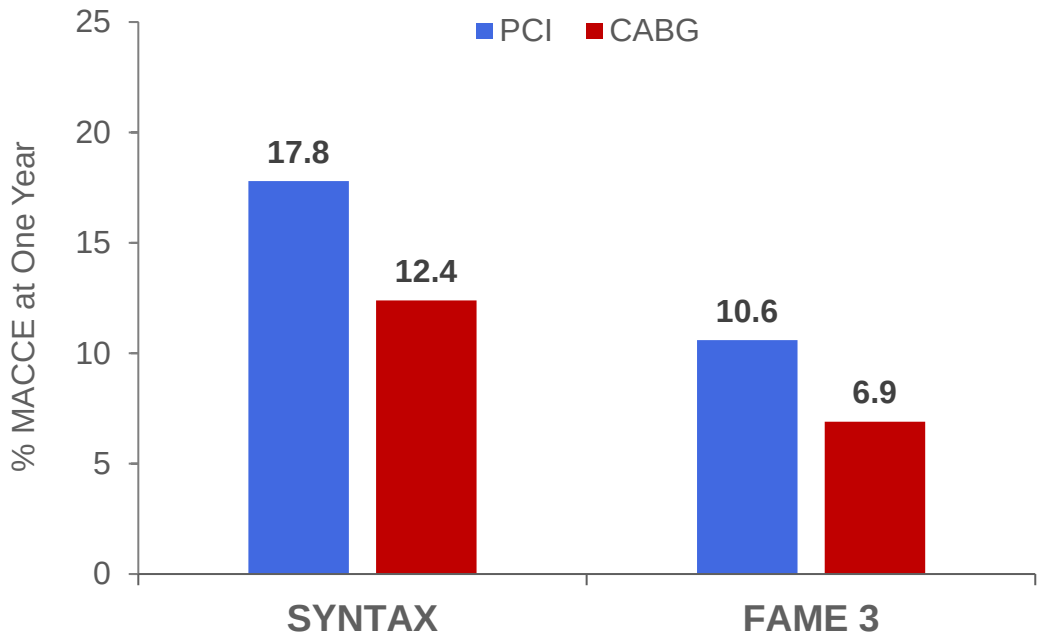


FAME 3 and SYNTAX Trials

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 and SYNTAX Trials

MACCE (Death, MI, Stroke, or Repeat Revascularization) at 1 Year



Limitations

- One year is relatively short-term follow-up
- FFR measurement not mandated in CABG arm
- Intravascular imaging utilized in only 12% in PCI arm
- Completeness of revascularization data not yet available

Conclusions

- In patients with 3V-CAD, FFR-Guided PCI with a current generation DES did not meet the criterion set for noninferiority in comparison with CABG in terms of death, MI, stroke or revascularization at one year
  - One-year rate of death, MI or stroke was not significantly different between the two groups
  - In FAME 3, MACCE rates for both FFR-guided PCI (10.6%) and CABG (6.9%) were lower than with CABG in the SYNTAX trial (12.4%)
  - FFR-guided PCI with a current generation DES performed favorably in comparison with CABG in 3V-CAD patients with less complex disease according to the SYNTAX score
  - In patients with more complex 3V-CAD, CABG remains the treatment of choice

Top 25 FAME 3 Trial Enrollers

Catharina Hospital
Eindhoven, Netherlands (Pijls/Zimmermann/Van Straten)
Hungarian Institute of Cardiology
Hungary (Piroth/Szekely)
Vilnius University Hosp
Lithuania (Davidavicius/Kalinauskas)
Centre Hosp de L'Universite de Montreal
Canada (Mansour/Noiseux)
OLV Ziekenhuis Aalst
Belgium (De Bruyne/Casselman)
Danderyds Sjukhus
Sweden (Papadogeorgos/Corascio)
Oxford University Hospital NHS
England (Kharbanda/Sayeed)
Golden Jubilee National Hospital
Scotland (Oldroyd/Al-Attar)
Clinical Center of Kragujevac
Serbia (Jagic/Rosic)
Isala Klinieken
Netherlands (Dambrink/Bruinsma)
CHU Charleroi
Belgium (Aminian/El Nakadi)
Sahlgrenska University Hospital
Sweden (Angeras/Jeppsson)

Kings College Hospital
England (MacCarthey/Wendler)
University Hospital of Brno
Czech Republic (Kala/Nemec)
Sodersjukhuset AB
Sweden (Witt/Corbascio)
Atlanta VA Medical Center,
United States (Mavromatis/Nguyen)
York PCI Group
Canada (Miner/Peniston)
University Hospital of South Manchester
England (Sarma/Barnard)
Righospitalet University Hospital
Denmark (Engstrom/Thyregod)
St. Thomas' Hospital
England (Redwood/Young)
Palo Alto VA Medical Center
United States (Yong/Giacomini/Fearon/Burdon)
Aarhus University Hospital
Denmark (Christiansen/Modrau)
University Clinical Center of Serbia
Serbia (Beleslin/Putnik)
Univ. Hosp. Coventry & Warwickshire
England (Tapp/Barker)
Hagaziekenhuis
Netherlands (Bech/Hoohenkerk)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fractional Flow Reserve–Guided PCI as Compared with Coronary Bypass Surgery

W.F. Fearon, F.M. Zimmermann, B. De Bruyne, Z. Piroth, A.H.M. van Straten, L. Szekely, G. Davidavičius, G. Kalinauskas, S. Mansour, R. Kharbanda, N. Östlund-Papadogeorgos, A. Aminian, K.G. Oldroyd, N. Al-Attar, N. Jagic, J.-H.E. Dambrink, P. Kala, O. Angerås, P. MacCarthy, O. Wendler, F. Casselman, N. Witt, K. Mavromatis, S.E.S. Miner, J. Sarma, T. Engstrøm, E.H. Christiansen, P.A.L. Tonino, M.J. Reardon, D. Lu, V.Y. Ding, Y. Kobayashi, M.A. Hlatky, K.W. Mahaffey, M. Desai, Y.J. Woo, A.C. Yeung, and N.H.J. Pijls, for the FAME 3 Investigators*

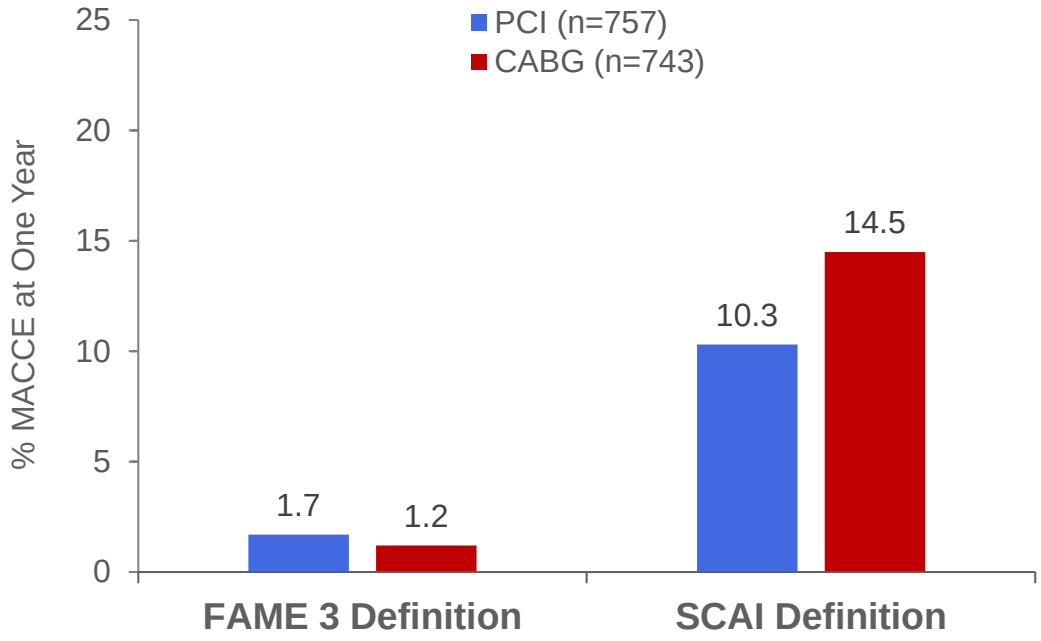
FAME 3

Thank You!

BACKUP

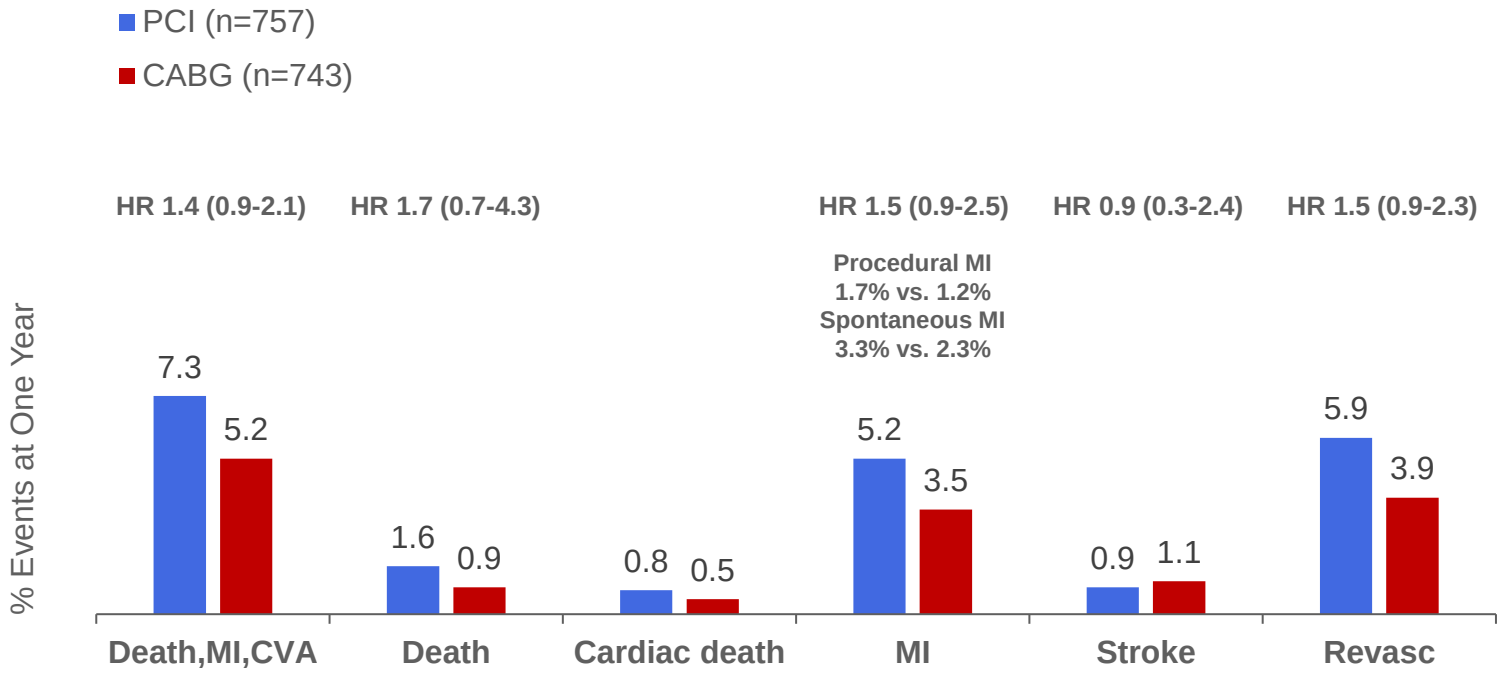
Procedural MI Definitions

SCAI definition[1] for procedural MI results in higher rates at 1 year



[1] Moussa ID, et al. *J Am Coll Cardiol* 2013;62:1563-70.

Secondary Endpoints at 1 Year



Safety Endpoints at 1 Year