3 Year Clinical Outcome and Cost-Effectiveness of FFR-Guided PCI in Stable Patients with Coronary Artery Disease: *FAME 2 Trial*

William F. Fearon, MD, Takeshi Nishi, MD, Bernard De Bruyne, MD, PhD, Derek B. Boothroyd, PhD; Emanuele Barbato, MD, PhD, Pim Tonino, MD, PhD, Peter Jüni, MD, Nico H.J. Pijls, MD, PhD, and Mark A. Hlatky, MD

for the FAME 2 Trial Investigators

Disclosure Statement of Financial Interest

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, Medtronic, ACIST, CathWorks, Edwards LifeSciences
• Consulting Fees/Honoraria	
• Major Stock Shareholder/Equity	
• Royalty Income	
• Ownership/Founder	
• Intellectual Property Rights	
• Other Financial Benefit	• HeartFlow (minor stock options)

FAME 2: Background

- **The optimal treatment strategy, percutaneous coronary intervention (PCI) or medical therapy alone for patients with stable coronary disease remains controversial.**

- **Previous studies suggested little difference in clinical outcomes and quality of life between these two strategies and higher costs with PCI.**

FAME 2: Background

- **However, these studies were limited by including patients with little or no myocardial ischemia and by using older PCI techniques.**

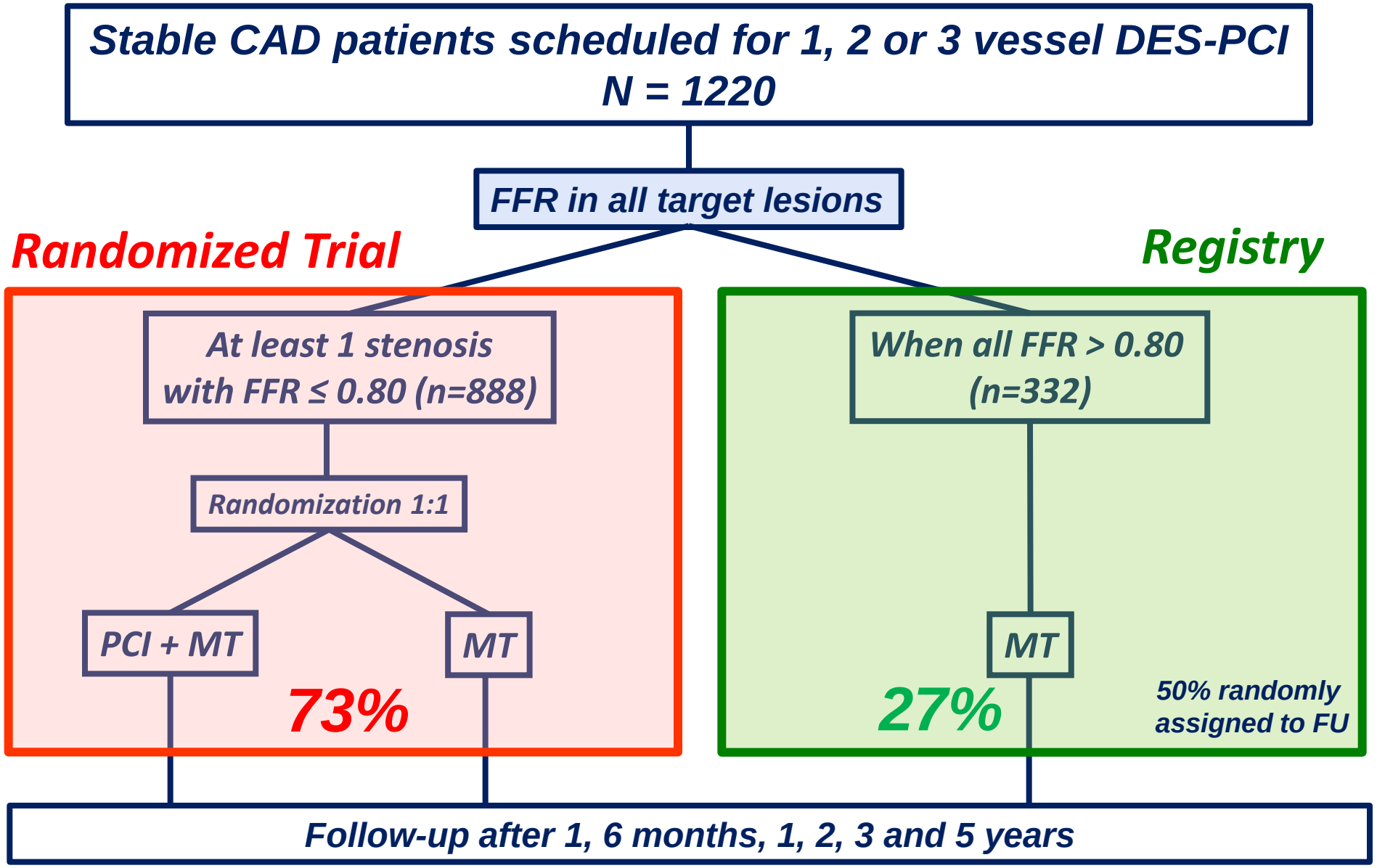
- **Measuring fractional flow reserve (FFR) at the time of angiography identifies lesions responsible for ischemia and patients most likely to benefit from PCI.**

FAME 2: Background

- **The Fractional Flow Reserve vs Angiography for Multivessel Evalation 2 (FAME 2) Trial randomized patients with stable angina and at least one lesion with an abnormal FFR to either medical therapy alone or to PCI with current generation drug-eluting stents.**

FAME 2: Design

- **Prospective, international, randomized, controlled trial conducted at 28 sites in Europe and North America.**
- **Inclusion criteria: stable angina**
- **Exclusion criteria: prior CABG, ejection fraction < 30%, or left main disease**
- **Primary endpoint: composite of death, MI and unplanned hospitalization with urgent revascularization at 2 years**


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 and 5 years

Investigators	Centers	# of Patients
Piroth	Hungarian Institute of Cardiology- Hungary	145
Jagic	Clinical Center Kragujevac- Serbia	132
Mobius-Winkler	Heart Center Leipzig- Germany	131
Pijls	Catherina-Ziekenhuis- The Netherlands	89
Rioufol	Hospices Civil de Lyon- France	86
Witt	Sodersjukhuset- Sweden	85
De Bruyne	Cardiovascular Center Aalst- Belgium	82
Kala	University Hospital Brno- Czech Republic	75
Fearon	Stanford Univ/VA Med Center Palo Alto- USA	50
MacCarthy	Kings College Hospital- UK	42
Engstroem	Rigshospitalet University Hospital- Denmark	42
Oldroyd	Golden Jubilee National Hospital- UK	37
Mavromatis	Atlanta VA Medical Center- USA	34
Manoharan	Royal Victoria Hospital- Ireland	27

Investigators	Centers	# of Patients
Ver Lee	Northeast Cardiology Associates- USA	25
Frobert	Orebro University Hospital- Sweden	25
Curzen	Southampton General Hospital- UK	18
Sohn	Klinikum der Universitat Munchen- Germany	18
Uren	Edinburgh Heart Center- Scotland	12
Samady	Emory University- USA	12
Dambrink	Isala Klinieken- Netherlands	12
Mansour	CHUM - Hotel Dieu- Canada	11
Arain	Tulane University- USA	8
Mates	Nemocnice Na Homolce- Czech Republic	8
Rensing	St. Antonius Ziekenhuis- Netherlands	5
Valgimigli	Universitaria de Ferrara- Italy	4
Rieber	Heart Center Munich- Germany	3
Schampaert	Hopital du Sacre Coeur- Canada	2

FAME 2: Initial Results

- ***Based on the recommendation of the independent DSMB*, recruitment was halted after inclusion of 1220 patients (± 54% of the initially planned number of randomized patients) and a mean follow-up of approximately 7 months, because of a highly significant difference in the primary endpoint.***

DSMB: Stephan Windecker, Chairman, Stuart Pocock, Bernard Gersh

FAME 2: Baseline Characteristics

	Randomized trial N=888		Registry N=322	P*
Patients, N	PCI+MT=447	MT=441	with FU=166	
Demographic				
Age (y)	64±9	64±10	64±10	0.89
Male sex - (%)	79.6	76.6	68.1	0.006
BMI	28.3±4.3	28.4±4.6	27.8±3.9	0.14
Risk factors for CAD				
Positive family history CAD - (%)	49	47	46	0.60
Smoking - (%)	20	20	21	0.79
Hypertension - (%)	78	78	83	0.21
Hypercholesterolemia - (%)	74	80	73	0.15
Diabetes mellitus - (%)	28	27	25	0.65

**P value compares all RCT patients with patients in registry*

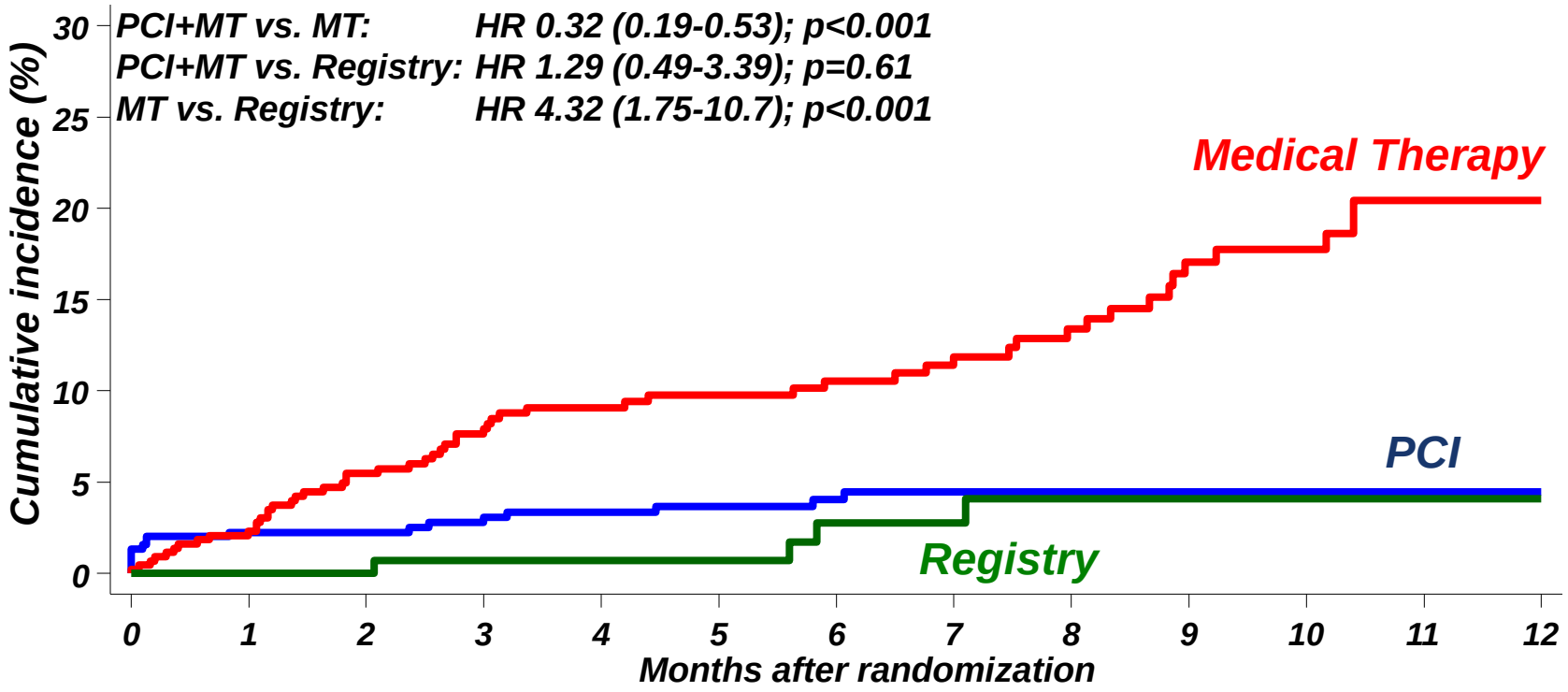
FAME 2: Baseline Characteristics

	Randomized trial N=888		Registry N=322	P*
Patients, N	PCI+MT=447	MT=441	with FU=166	
Non-Cardiac Co-Morbidity				
Renal Failure (Cr > 2.0 mg/dL) - (%)	2	3	3	0.14
History of stroke or TIA - (%)	8	7	6	0.52
Peripheral vascular disease - (%)	10	11	5	0.03
Cardiac History				
History of MI - (%)	38	39	38	0.92
History of PCI in target vessel -(%)	18	17	21	0.36
Angina - (%)				0.60
Asymptomatic	12	10	10	
CCS class I	18	22	25	
CCS class II	46	45	45	
CCS class III	18	15	14	
CCS class IV, stabilized	6	8	6	
Silent ischemia- (%)	16	17	16	0.93
LVEF < 50% - (%)	20	14	18	0.70

**P value compares all RCT patients with patients in registry*

FAME 2: Initial Results

Primary Endpoint: Composite of Death, MI, or Urgent Revascularization



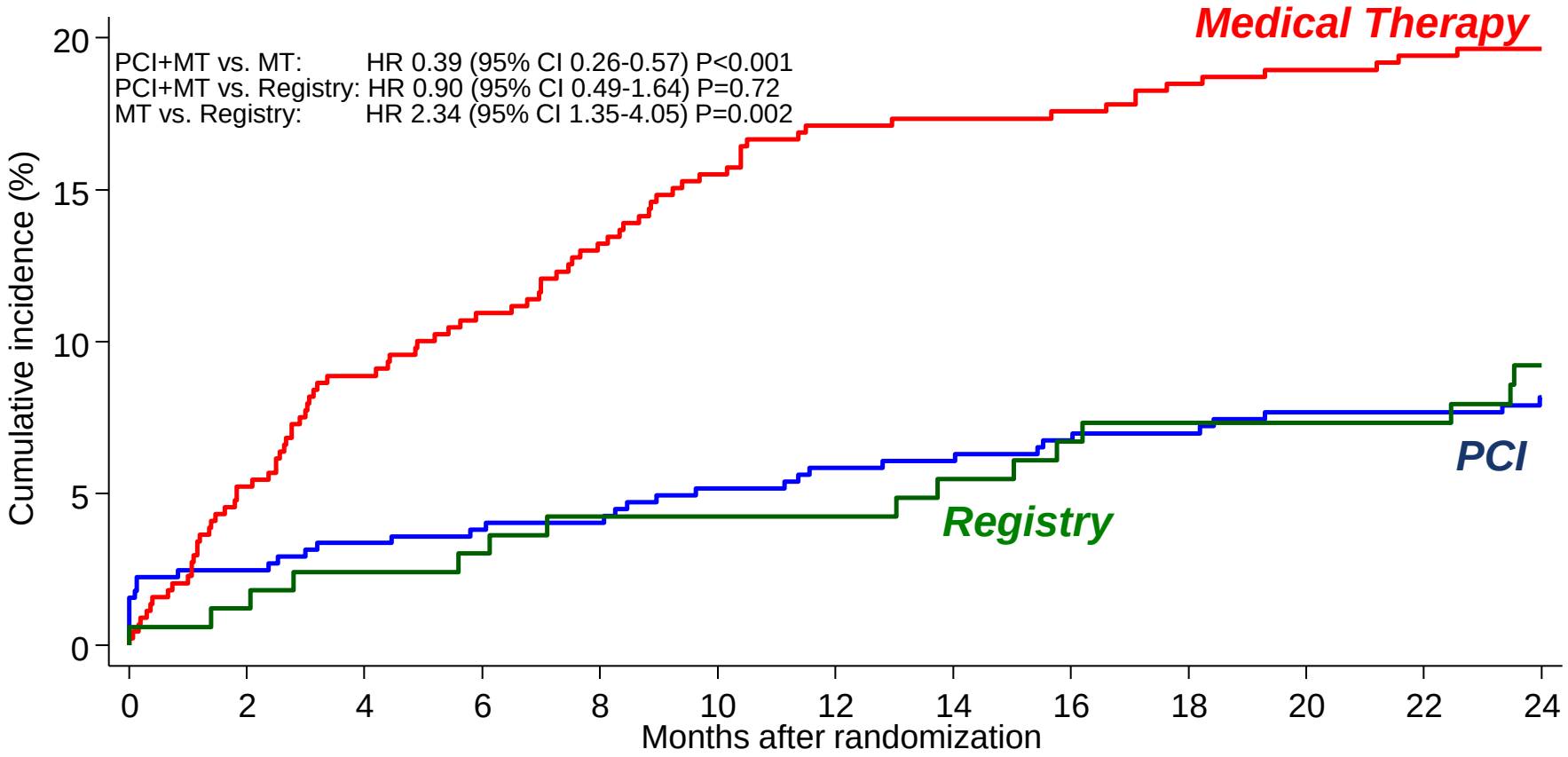
No. at risk

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.

FAME 2: Two Year Results

Primary Endpoint: Composite of Death, MI, or Urgent Revascularization



No. at risk

MT	441	417	398	389	379	369	362	360	359	355	353	351	297
PCI+MT	447	434	429	426	425	420	416	414	410	408	405	403	344
Registry	166	164	162	160	157	157	156	153	151	150	150	150	122

De Bruyne, et al. New Engl J Med 2014;371:1208-1217.

Objective

- **Evaluate the long-term clinical outcomes, effects on quality of life, and cost-effectiveness of FFR-guided PCI versus medical therapy alone in patients with stable coronary artery disease enrolled in the FAME 2 trial.**

Methods

- **Healthcare resource utilization associated with the index hospitalization, follow-up outpatient visits, diagnostic tests, medications, adverse events and hospitalizations was recorded prospectively.**
- **The actual cost of the initial angiogram and PCI (if performed) was quantified in $US.**
- **Follow-up costs were estimated based on Medicare's reimbursement rate per diagnosis-related group (DRG) and the Medicare fee schedule.**

Methods

- **Quality adjusted life years (QALY) were derived from health related quality of life and survival during the 3 year time horizon of the trial.**

- **Quality-of-life indexes (utilities) were evaluated at baseline, 1 month, and at 1, 2 and 3 years using the European Quality of Life–5 Dimensions (EQ-5D) instrument with US weights scaled from 0 (death) to 1 (perfect health).**

Methods

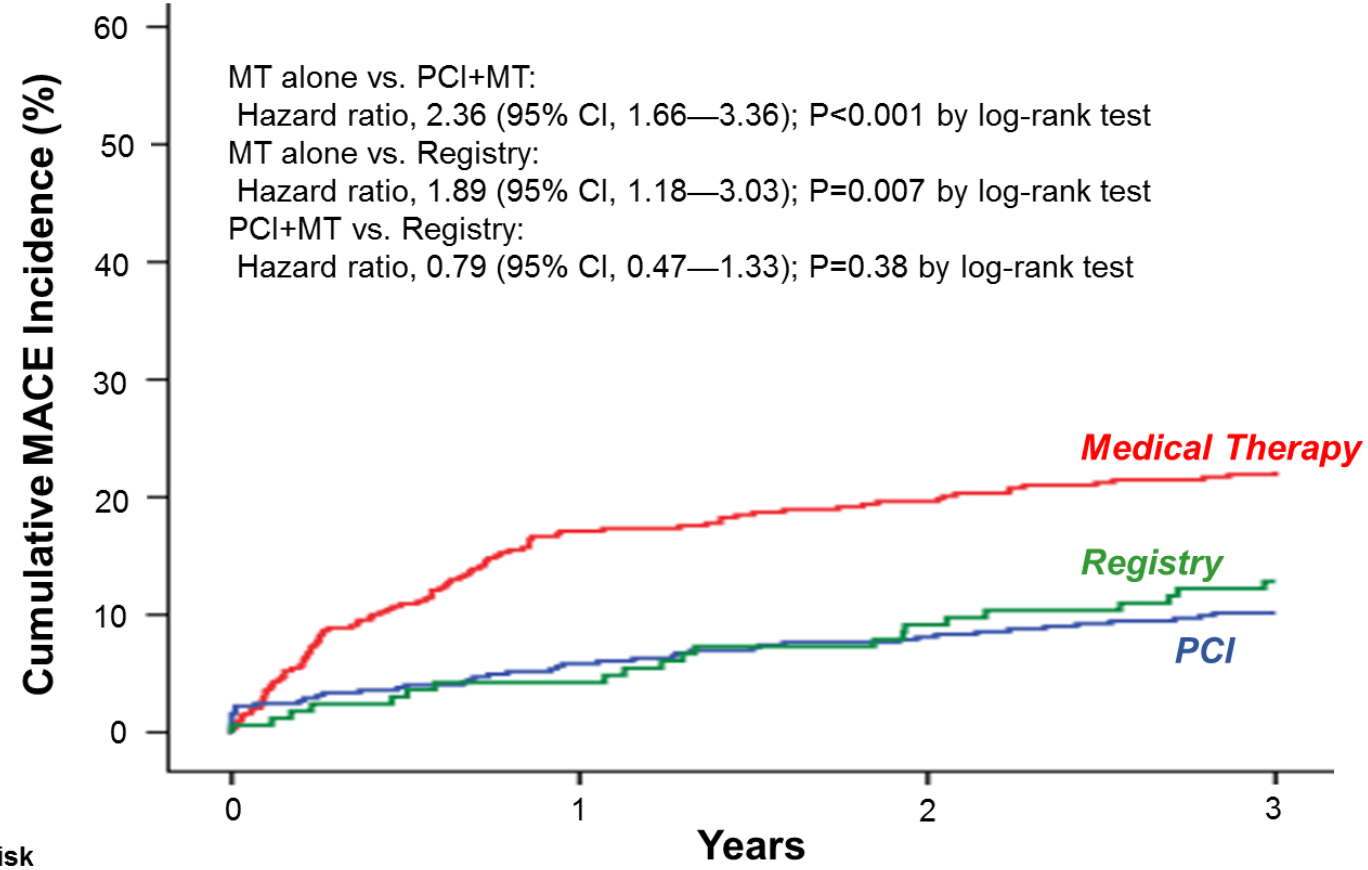
- **Because the protocol did not mandate it, only a minority completed the EQ-5D at 3 years.**
- **To account for these missing values, we employed multiple imputation.**
- **In another analysis, we used a *last value carried forward* technique to estimate utility at 3 years based on the values at 2 years.**

Methods

- **The cost-effectiveness of PCI was expressed as the incremental cost-effectiveness ratio (ICER), defined as the difference in the cumulative costs of PCI and MT, divided by the difference in cumulative QALYs of PCI and MT.**

Results: Clinical Outcome

Three Year Rate of Death, MI, or Urgent Revascularization



No. at Risk				
MT alone	441	362	350	339
PCI+MT	447	417	405	392
Registry	166	156	148	141

Results: Clinical Outcome

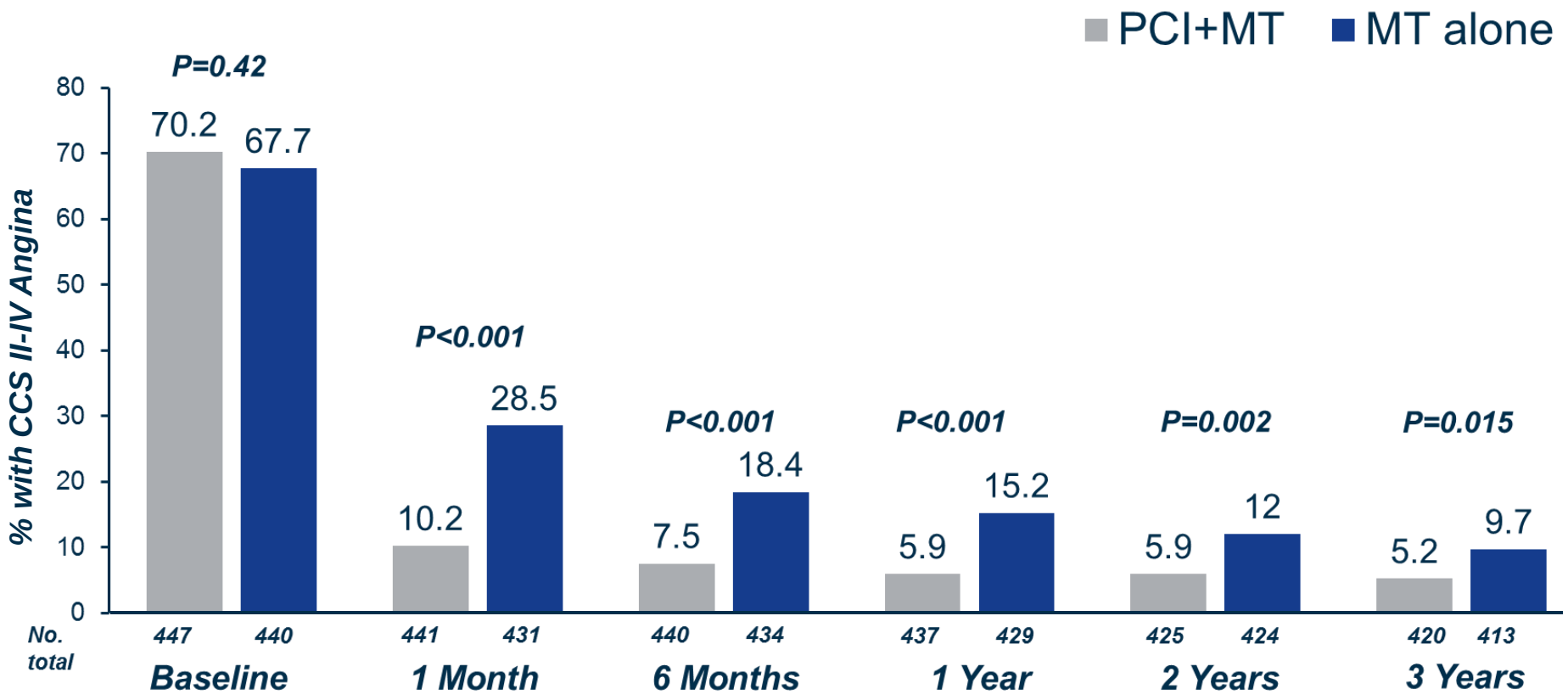
Three Year Rate of Death, MI, or Urgent Revascularization

	Randomized trial N=888		P value	Registry N=322
Event	**PCI+MT=447**	**MT=441**		**with FU=166**
MACE	**10.1%**	**22%**	**<0.001**	**12.7%**
Death	**2.7%**	**3.6%**	**0.43**	**3.0%**
Myocardial Infarction (MI)	**6.3%**	**7.7%**	**0.41**	**6.6%**
Death or MI	**8.3%**	**10.4%**	**0.28**	**9.0%**
Urgent Revascularization	**4.3%**	**17.2%**	**<0.001**	**6.6%**

P value compares PCI + MT patients with MT patients

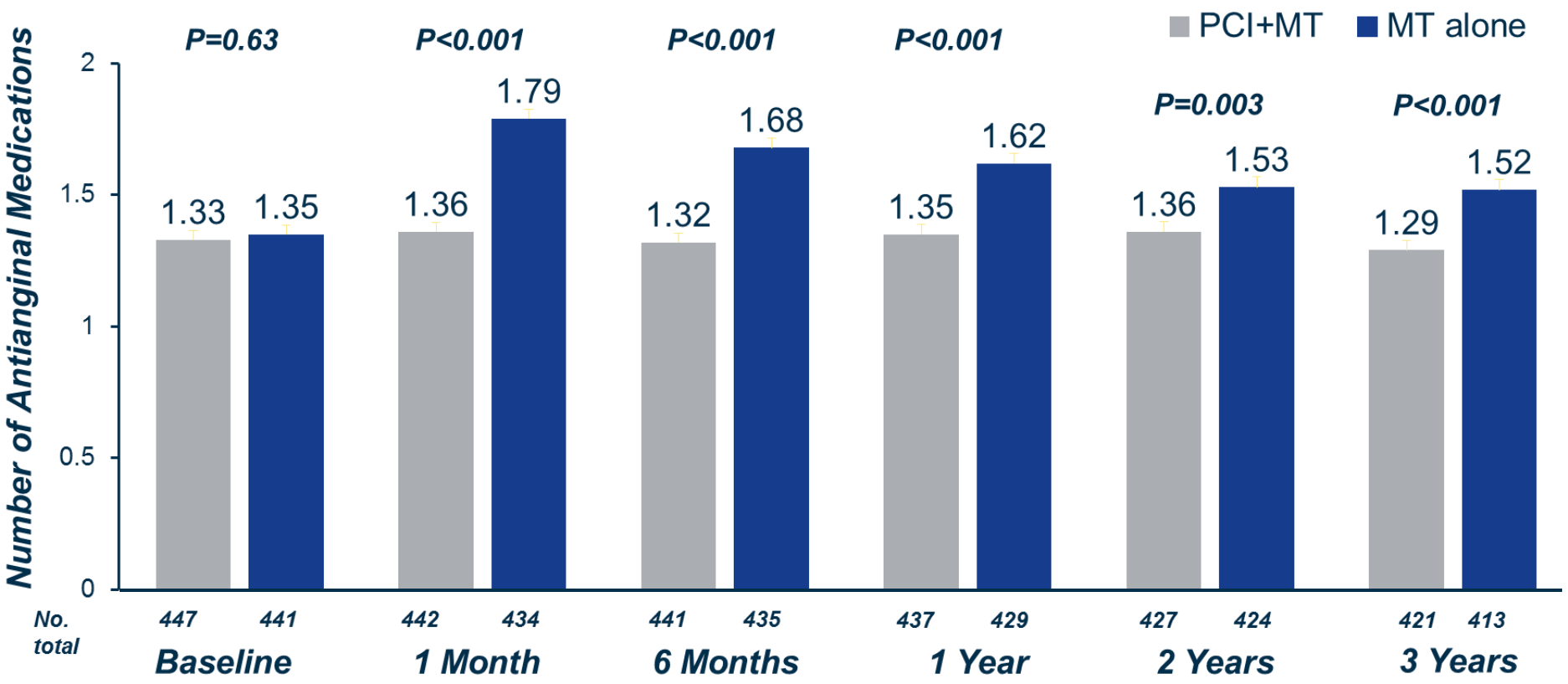
Results: Quality of Life

% of Patients with Class II-IV Angina at each Time Point



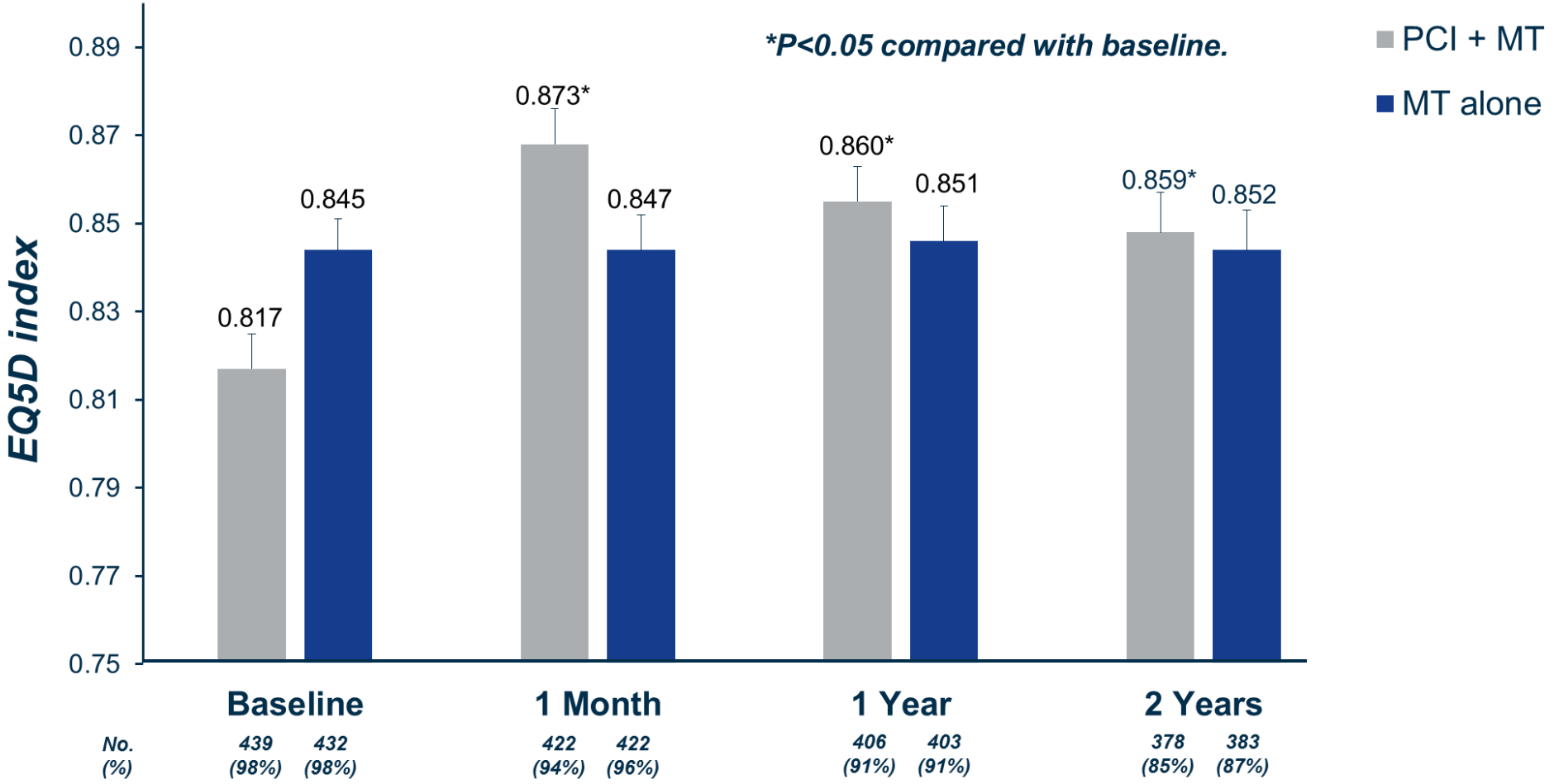
Results: Quality of Life

Mean Number of Antianginal Medications/Patient at each Time Point

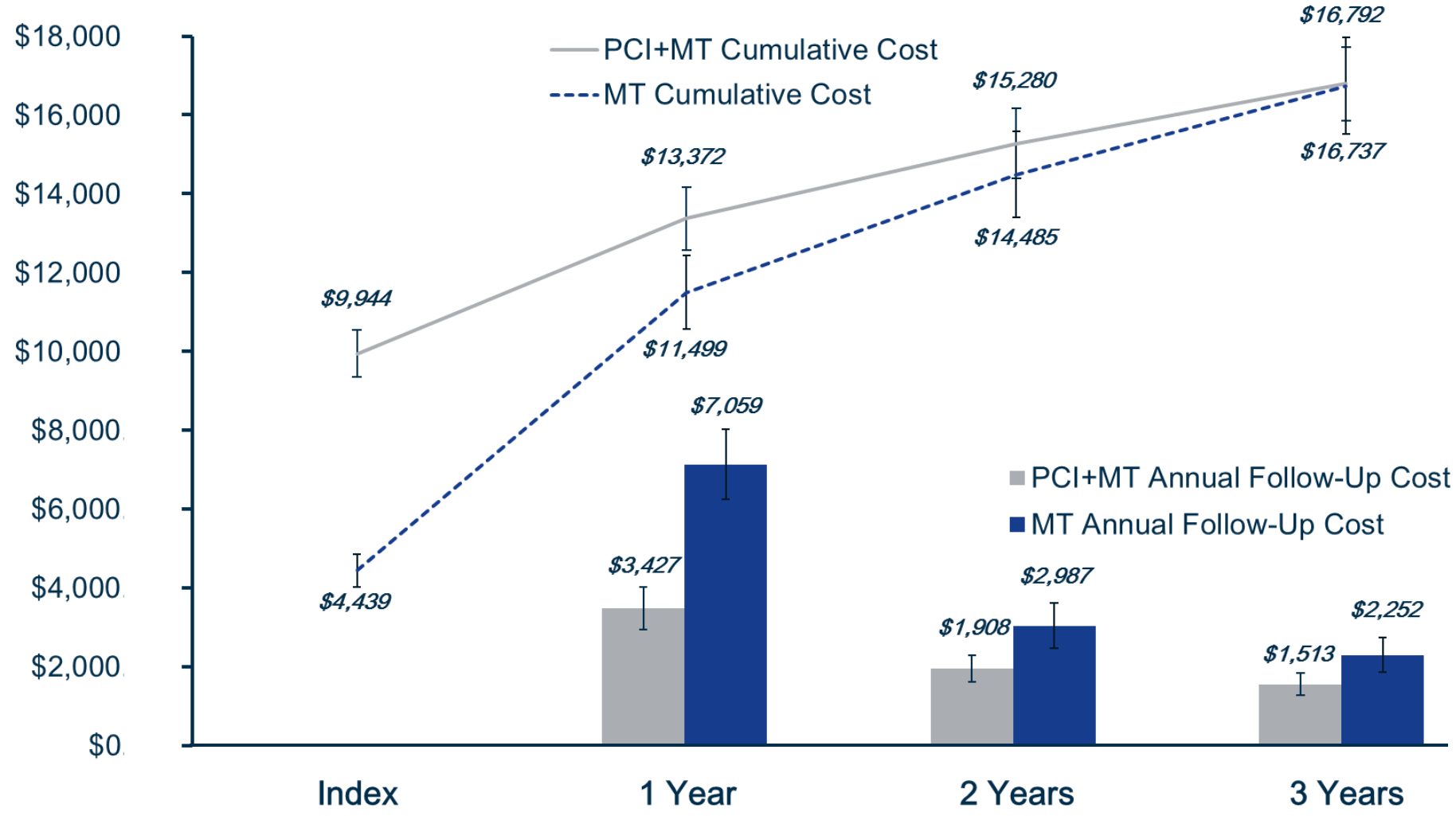


Results: Quality of Life

EQ-5D Results at each Time Point



Results: Costs



Results: Cost-Effectiveness

- At two years, QALY were higher in the PCI arm (1.716 vs. 1.691, P=0.23) and costs were higher in the PCI arm ($14,853 vs $14,421, P=0.56), resulting in an incremental cost-effectiveness ratio (ICER) for PCI of $17,300/QALY.

- At three years, the ICER for PCI was $1,600/QALY.

Results: Cost-Effectiveness

- **These findings were robust on sensitivity analysis.**
- **When quantifying QALY using a *last value carried forward* technique for the utilities rather than multiple imputation, the QALY at 3 years was numerically higher in the PCI group (2.552 vs. 2.519 P=0.34) and the costs were numerically lower ($16,376 vs. $16,664, P=0.73), and hence FFR-guided PCI was the dominant strategy.**

Limitations

- **Enrolment into FAME 2 was stopped early which might exaggerate differences between the two strategies.**
- **There was no significant difference in death and MI between the two groups.**
- **EQ-5D results were obtained in only a minority of patients at 3 years requiring the use of imputation to assess cost-effectiveness at 3 years.**

Conclusion

- **Compared with best medical therapy alone, performing PCI in patients with stable CAD and at least one coronary lesion with an abnormal FFR leads to improved clinical outcome, less angina, and improved quality of life at similar cost over three years of follow-up.**