The FUTURE Trial and Current Evidence for FFR-Guided PCI: *Is there a warning sign?*

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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:	**St. Jude Medical** **Medtronic** **Acist Medical** **CathWorks**
Consulting Fees/Honoraria:	**HeartFlow**
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	
Intellectual Property Rights:	
Other Financial Benefit:	

FUTURE Trial

Background:

- Fractional flow reserve (FFR)-guided PCI has been proven to be beneficial when compared with angiography-guided PCI in patients with multivessel CAD (FAME 1).
- FFR-guided PCI has been proven to be beneficial when compared with medical therapy in patients with stable angina and single or multivessel CAD (FAME 2).

Rioufol G, et al. AHA 2016

FUTURE Trial

Objective:

- Determine whether FFR is superior when compared with noninvasive testing and coronary angiography for guiding the decision between medical therapy, PCI or CABG in patients multivessel CAD including the left anterior descending coronary artery and stable angina or stabilized acute coronary syndrome.

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FUTURE Trial

Design:

- Multicenter, randomized, open-label study in 31 French medical centers.
- Primary endpoint of death, myocardial infarction (MI), repeat revascularization and stroke at one year.
- Superiority design
- Assuming a 30% relative risk reduction with FFR guidance, 1,721 patients total necessary to show a significant difference.

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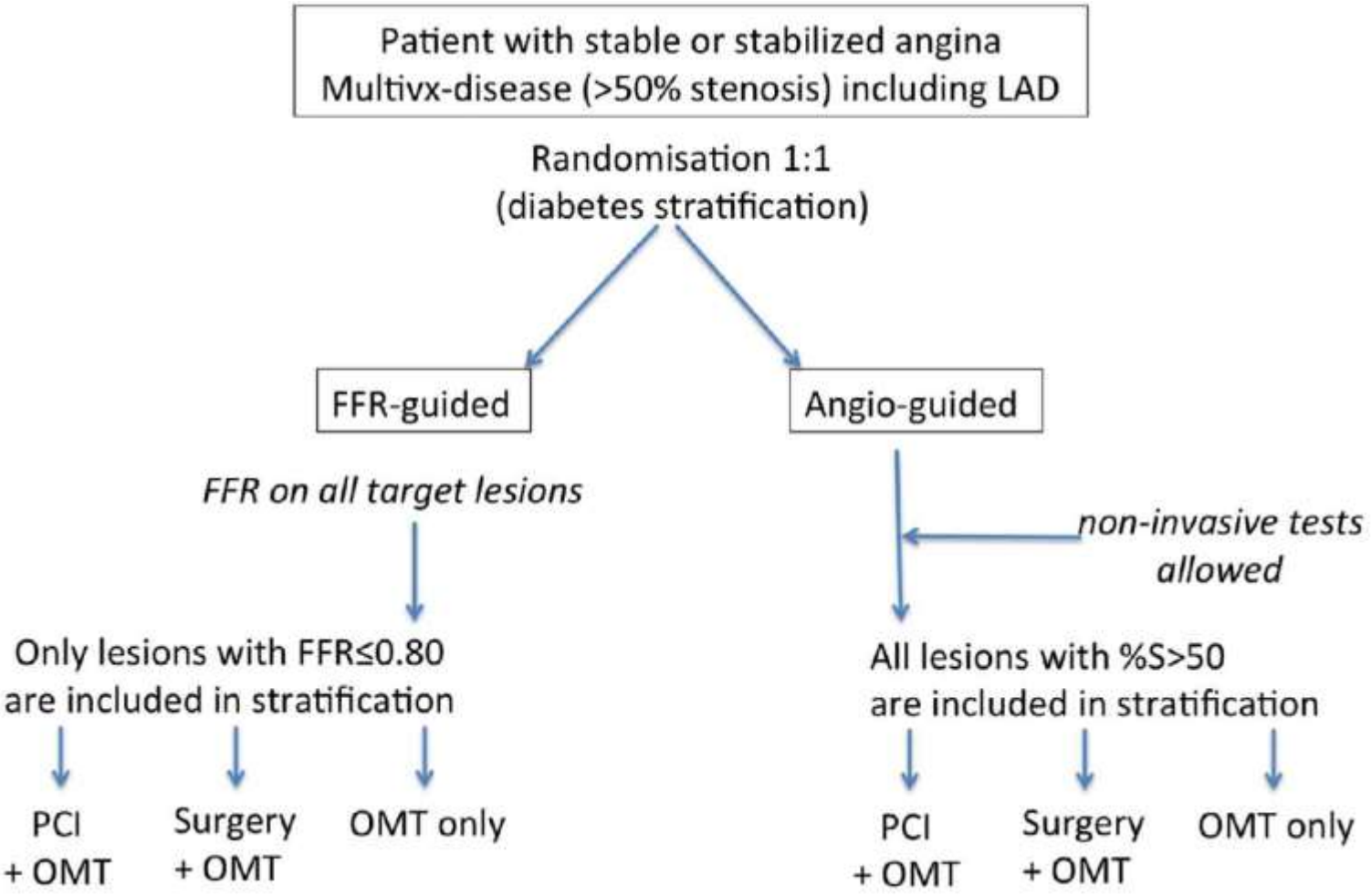
FUTURE Trial

Study Flow:



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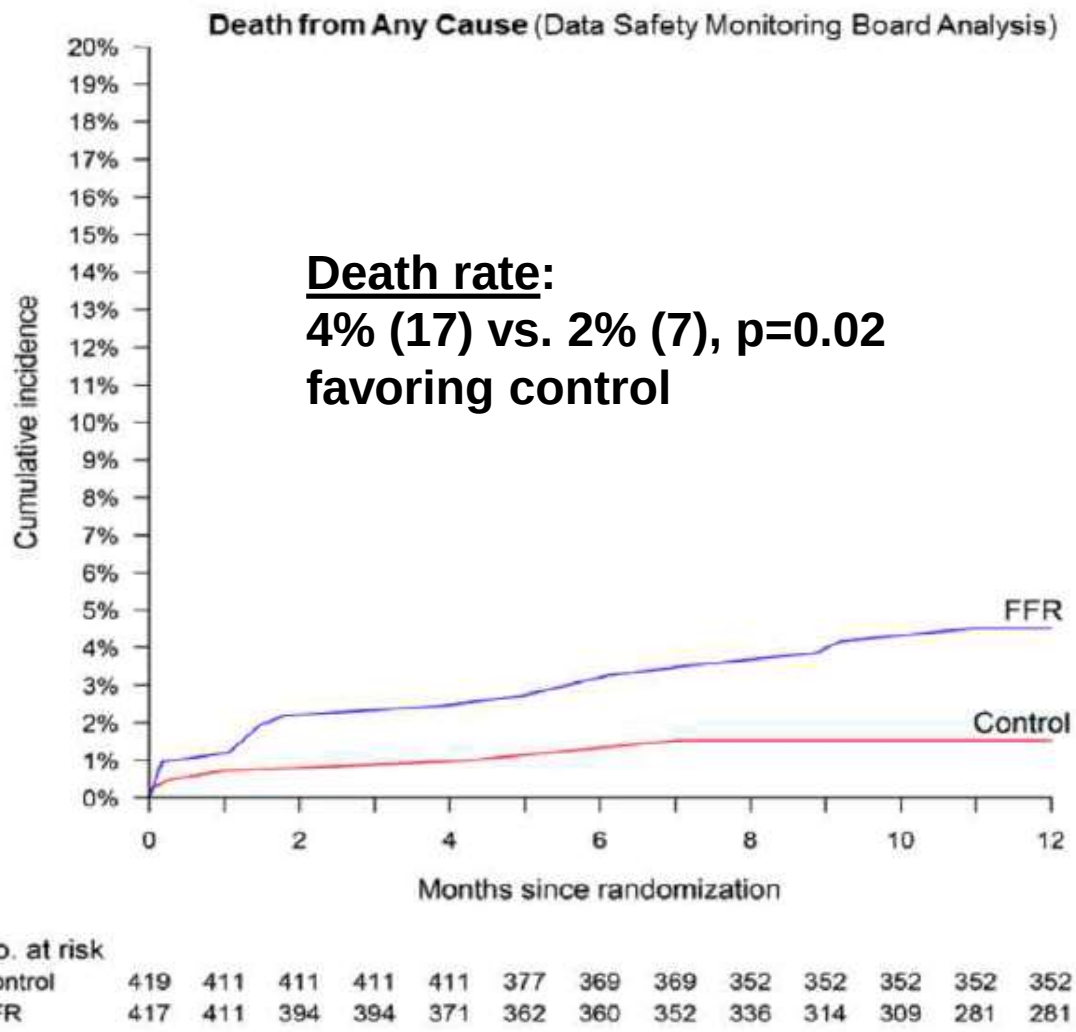
FUTURE Trial



<u>Death rate</u>:
4% (17) vs. 2% (7), p=0.02
favoring control

- ***On interim analysis after 836 patients enrolled, the DSMB found a higher mortality rate in the FFR-guided arm and recommended stopping the study.***
- ***Study enrolment stopped after including 936 patients***

Rioufol G, et al. AHA 2016

FUTURE Trial

Clinical Characteristics:

Variable	Control group (n=469)	FFR group (n=465)	P-value
Age (yr)	66±11	65±10	0.16
Male (%)	386/469 (82)	399/465 (86)	0.14
BMI	27±5	28±5	0.07
Current smoking (%)	118/469 (26)	110/465 (24)	0.78
HTA (%)	285/469 (61)	269/465 (58)	0.34
Dyslipidemia (%)	288/469 (61)	278/465 (60)	0.58
Diabetes (%)	148/469 (32)	146/465 (31)	0.96
Renal failure (%)	182/469 (39)	191/465 (41)	0.48
History of MI (%)	100/469 (21)	93/465 (20)	0.64
History of PCI (%)	127/469 (27)	117/465 (25)	0.52
History of stroke (%)	27/469 (6)	13/465 (3)	0.03

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FUTURE Trial

Clinical Presentation:

Variable	Control group (n=469)	FFR group (n=465)	P-value
ACS (%)	213/467 (46)	217/464 (47)	0.76
Including STEMI (%)	88/467 (19)	91/464 (20)	0.77
Stable angina (%)	105/467 (23)	88/464 (19)	0.19
Silent Ischemia (%)	149/467 (32)	159/464 (34)	0.44
CCS ≥ 2 (%) ¶	200/469 (43)	178/465 (39)	0.19
Previous NI Test (%)	196/465 (42)	176/461 (38)	0.24
% positive test (%)	157/196 (80)	141/176 (80)	0.40
LVEF %	56±11 (343)	55±12 (336)	0.56

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FUTURE Trial

Variable	Control group (n=469)	FFR group (n=465)	P-value
2-vessel disease (%)	225/469 (48)	201/465 (43)	0.34
3-vessel disease (%)	229/469 (49)	251/465 (54)	
LAD involved (%)	453/469 (97)	448/465 (96)	0.84
Left main (%)	51/469 (11)	59/465 (13)	0.39
SYNTAX score	18±8 (442)	19±8 (446)	0.15
Nb FFR measures	NA	1141	
FFR-related complications (%)	NA	4 (0.8)	
Nb FFR / patient	NA	2.4±0.9	
Mean FFR	NA	0.77±0.13	
FFR>0.80 Lesions (%)	NA	474/1103 (43)	

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FUTURE Trial

Medical Therapy:

Variable	Control group	FFR group	P-value
Aspirin (%)	440/469 (94)	446/465 (96)	0.15
Other antiplatelet (%)	409/469 (87)	389/465 (84)	0.12
Beta-blocker (%)	383/469 (82)	388/465 (83)	0.47
Statin (%)	419/469 (89)	425/465 (91)	0.29
ACE inhibitor-ARBs (%)	353/469 (75)	349/465 (75)	0.94
Insulin (%)	39/469 (8)	59/465 (13)	0.03
Oral Antidiabetic (%)	110/469 (23)	87/465 (19)	0.07

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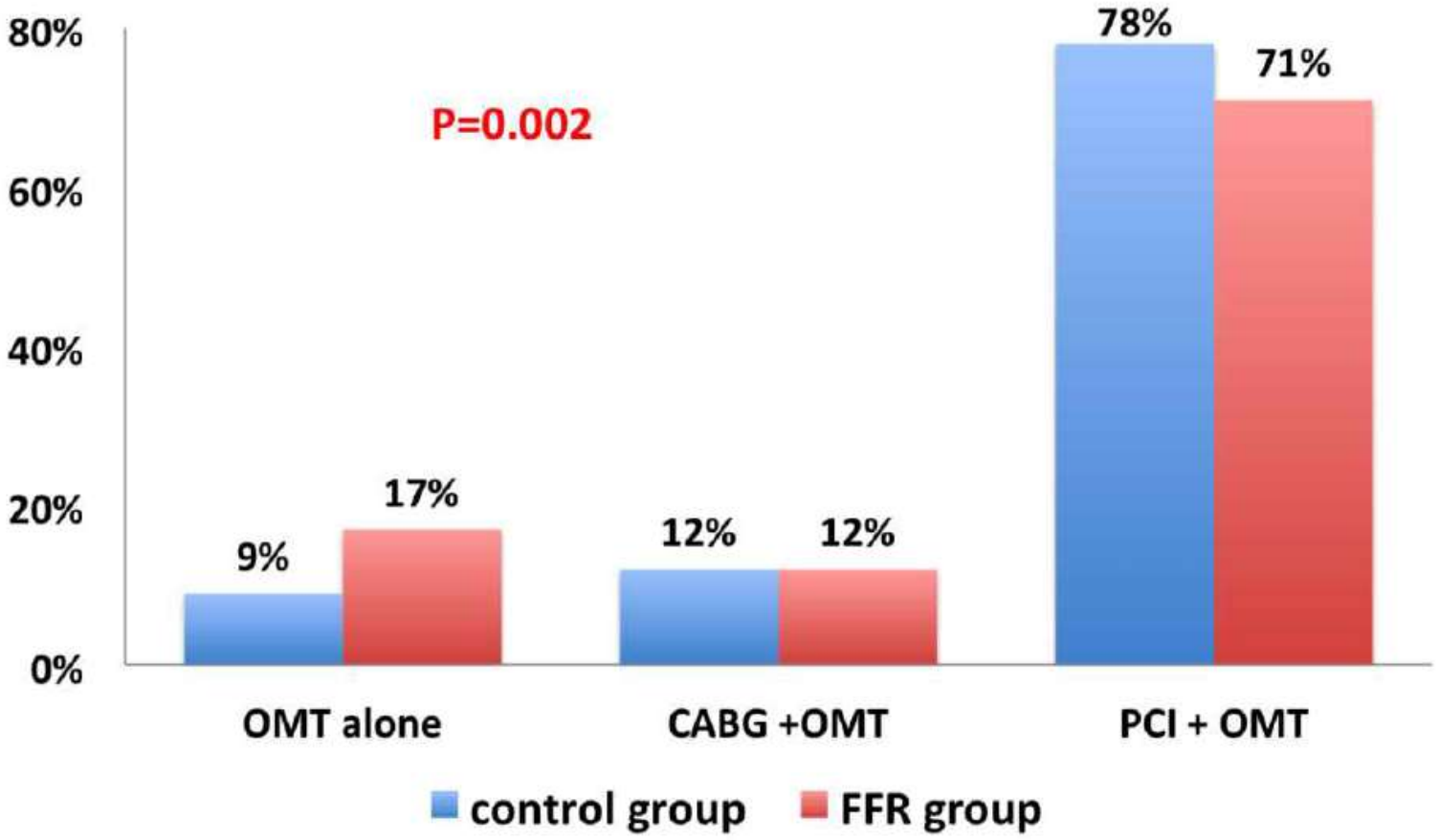
FUTURE Trial

Treatment Assignment:



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FUTURE Trial

Events at One Year:

Variable	Control group (n=398)*	FFR Group (n=399)*	HR (95%CI)	P vlue
Death from any cause (%)	8 (1.8)	17 (3.9)	1.98 (0.85–4.60)	0.07
Cardiovascular death (%)	6 (1.3)	12 (2.7)	1.88 (0.70-5.01)	0.16
MACE(%)	58 (13.2)	65 (15.1)	1.09 (0.76-1.56)	0.63
Myocardial infarction (%)	24 (5.3)	29 (6.5)	1.23 (0.71-2.11)	0.46
Stroke (%)	4 (0.9)	2 (0.4)	0.48 (0.09-2.62)	0.40
Repeat revascularization (%)	33 (7.6)	32 (7.6)	0.97 (0.60-1.58)	0.91
EQ-5D – visual analogue scale	71±18	70±17		0.51

* One year follow-up complete in 797

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FUTURE Trial

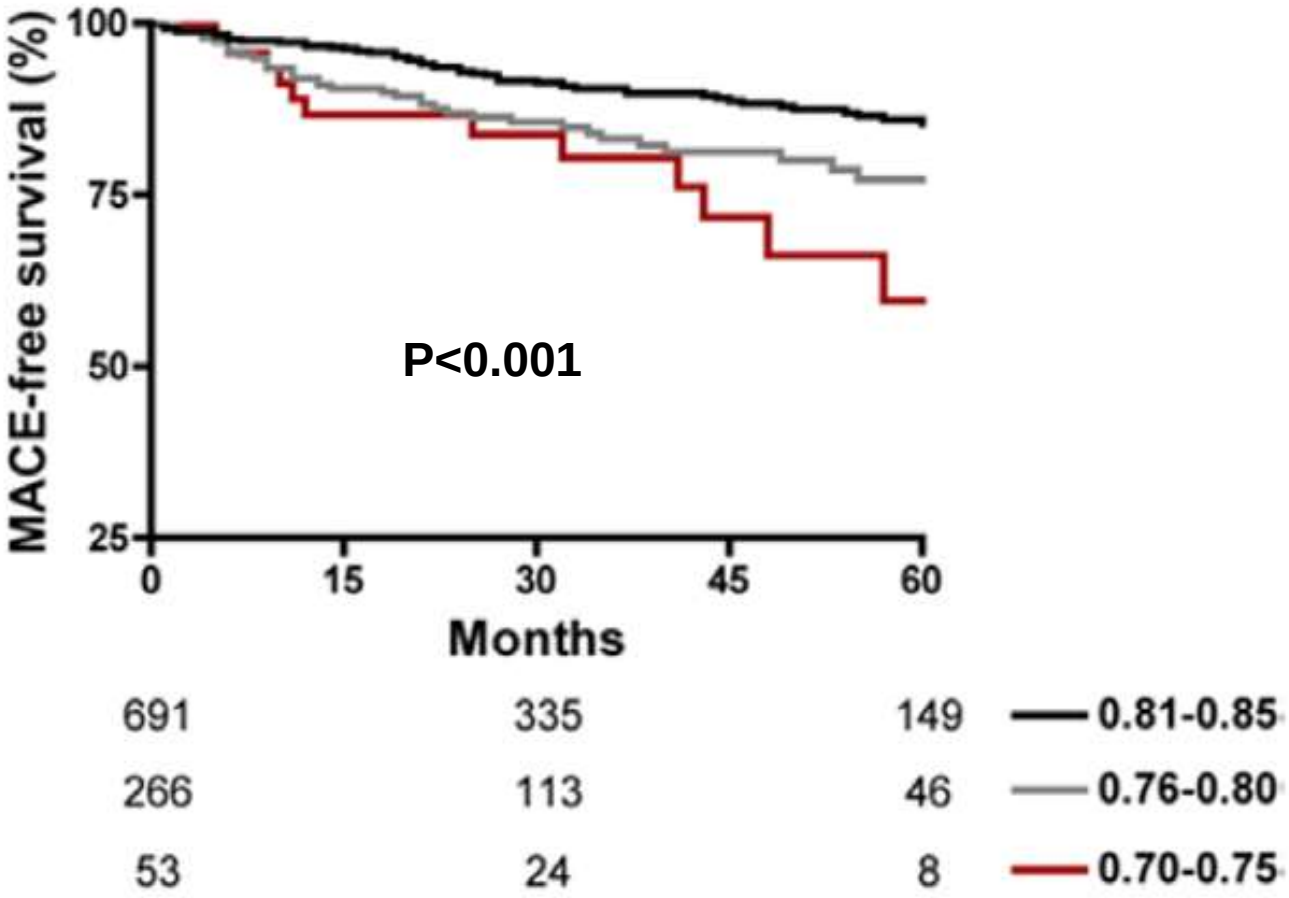
Key Points:

- Stopped prematurely which magnifies any differences
- Underpowered because it was stopped early
- Imbalances in randomization (higher SYNTAX score, more insulin dependent DM in FFR group)
- No explanation for increased mortality (no increase MI or revascularization)
- Too heterogeneous a population (≈50% STEMI or NSTEMI with culprit already treated, likely little further benefit)

Recent Data Supporting FFR

FFR and the “Grey Zone”

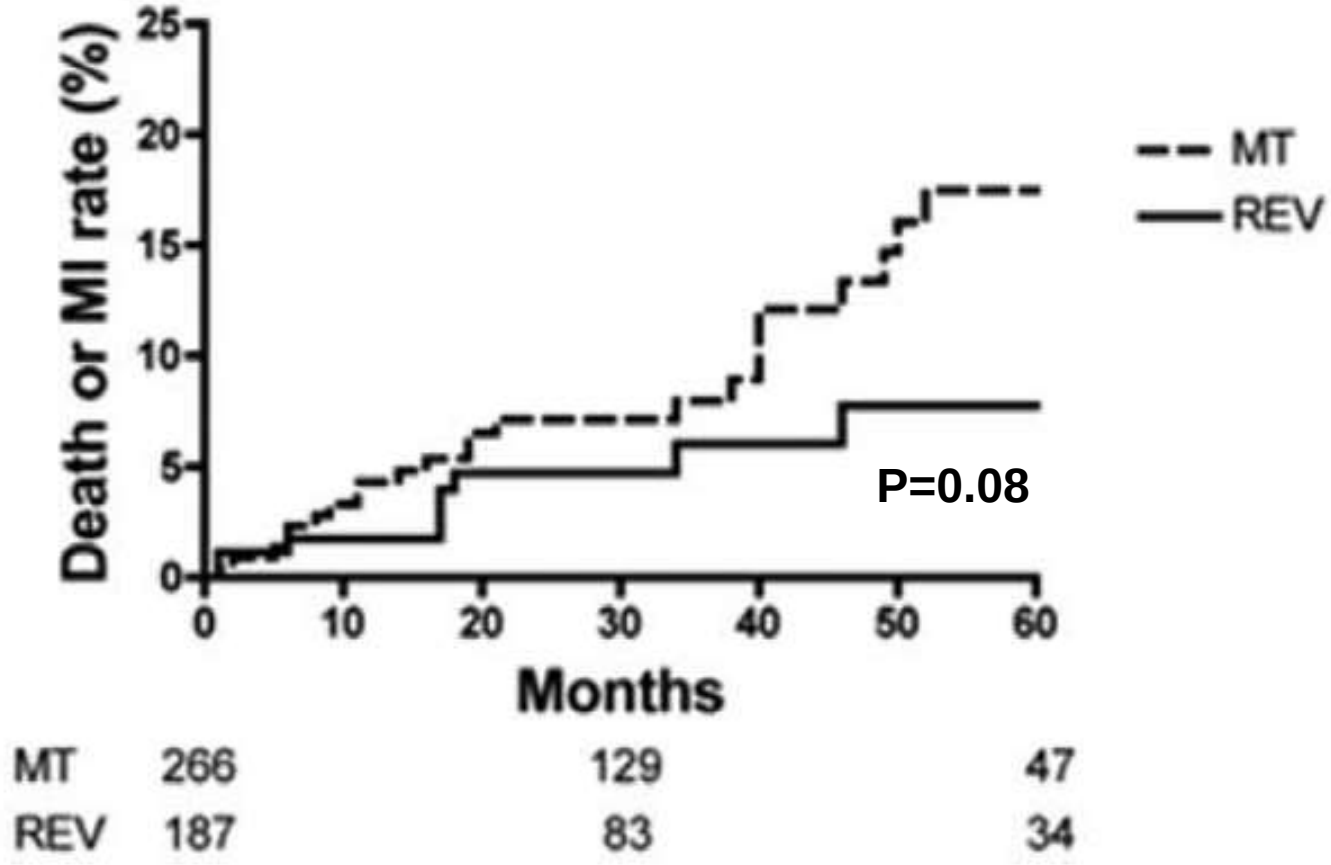
1,010 patients with FFR between 0.70 and 0.85 treated medically



Adjedj, et al. Circulation 2016;133:502-8.

FFR and the “Grey Zone”

453 patients with FFR between 0.76 and 0.80 treated medically vs revascularization



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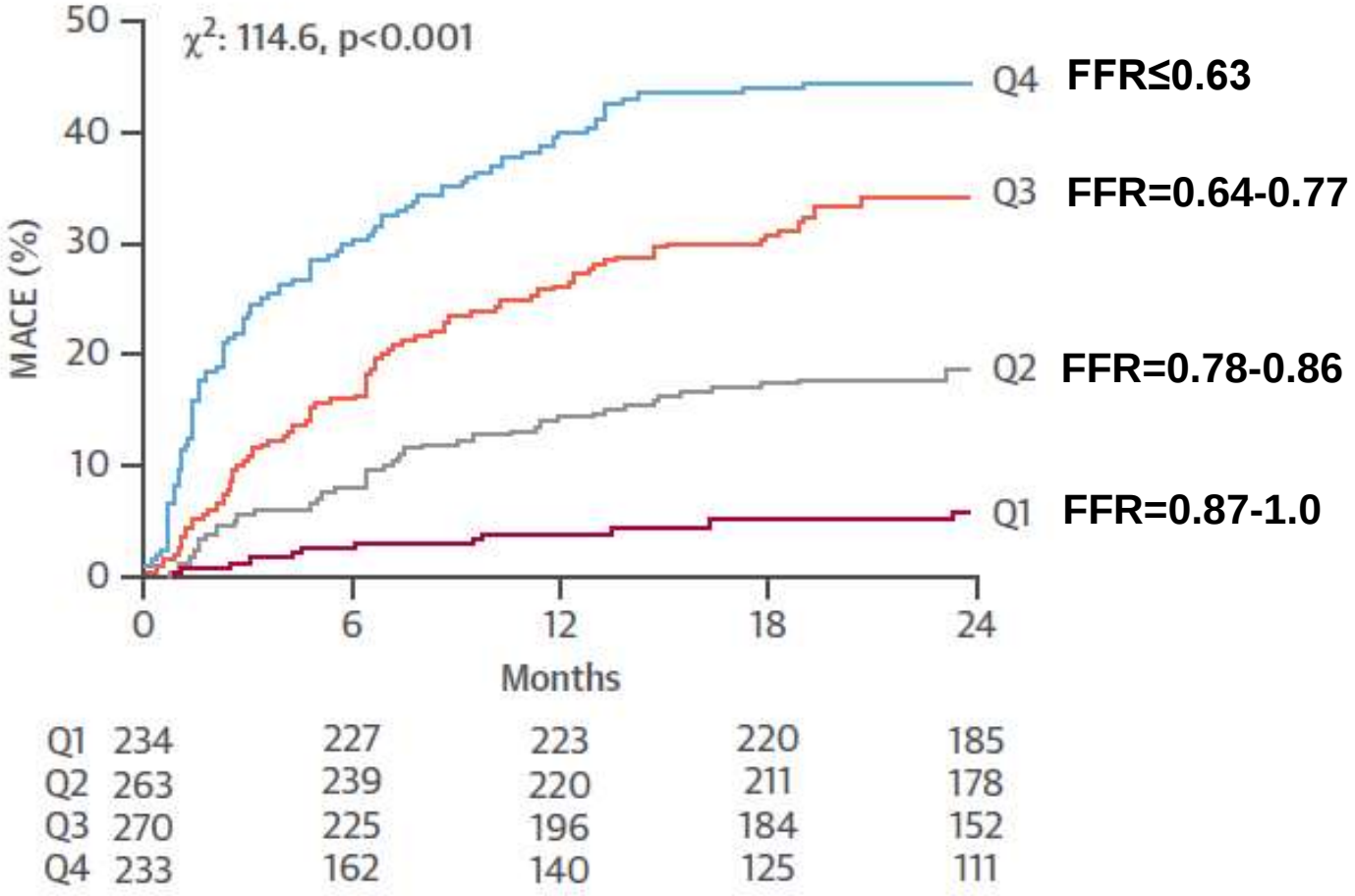
Relationship between FFR and MACE

1,029 lesions from 607 medically treated patients in FAME 2



Barbato, et al. J Am Coll Cardiol 2016;68:2247-55.

Relationship between FFR and MACE

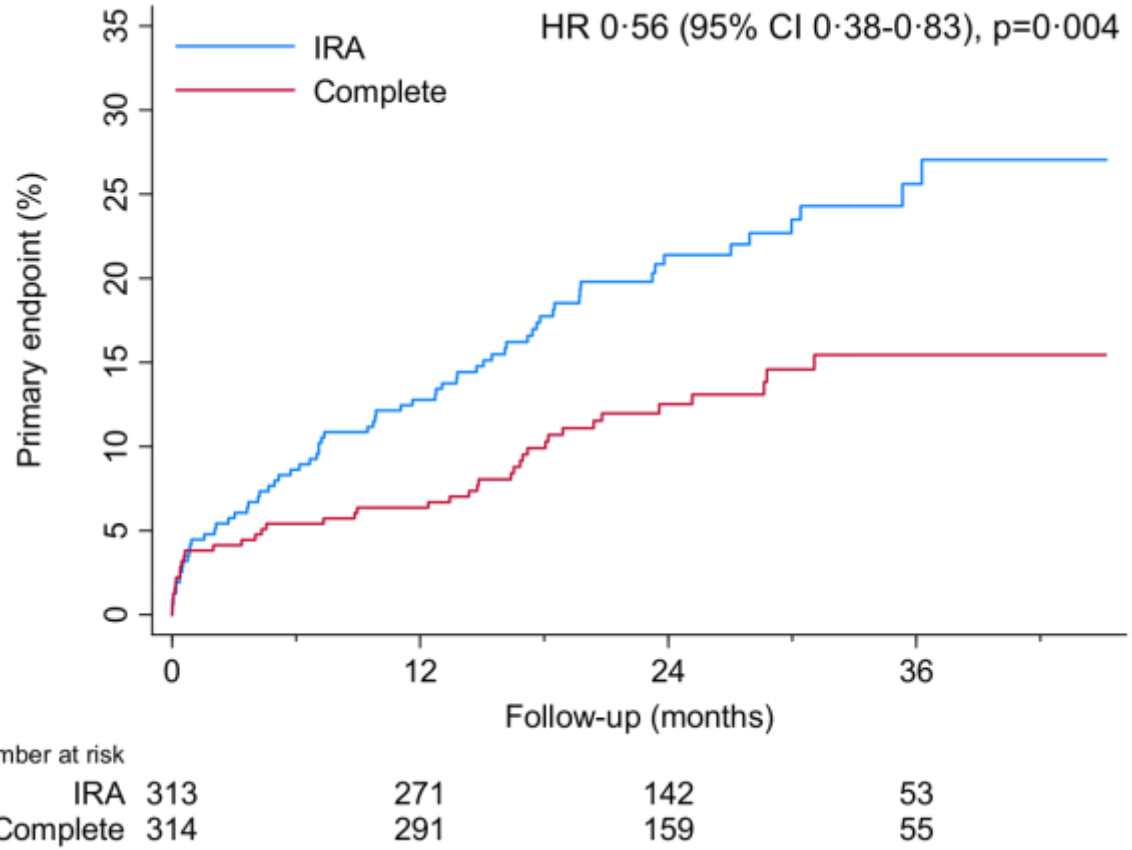
1,029 lesions from 607 medically treated patients in FAME 2

Quartile	n (%)	HR (95% CI)	p Value
MACE			
Q1 (0.87-1.00)	14 (5.4)	Ref.	–
Q2 (0.78-0.86)	50 (19.2)	3.44 (1.90-6.23)	<0.001
Q3 (0.64-0.77)	91 (35.0)	6.71 (3.82-11.78)	<0.001
Q4 (≤0.63)	105 (40.4)	9.84 (5.63-17.20)	<0.001
Death or MI			
Q1 (0.87-1.00)	6 (14.0)	Ref.	–
Q2 (0.78-0.86)	8 (18.6)	1.20 (0.41-3.45)	0.74
Q3 (0.64-0.77)	17 (39.5)	2.52 (0.99-6.39)	0.05
Q4 (≤0.63)	12 (27.9)	2.04 (0.76-5.43)	0.15
Urgent revascularization			
Q1 (0.87-1.00)	2 (2.9)	Ref.	–
Q2 (0.78-0.86)	8 (11.4)	3.61 (0.77-16.99)	0.10
Q3 (0.64-0.77)	31 (44.3)	14.29 (3.42-59.73)	<0.001
Q4 (≤0.63)	29 (41.4)	15.56 (3.71-65.20)	<0.001

Barbato, et al. J Am Coll Cardiol 2016;68:2247-55.

DANAMI 3-PRIMULTI Trial:

627 STEMI patients with MVD randomized to culprit only vs. FFR-guided nonculprit PCI during index hospitalization

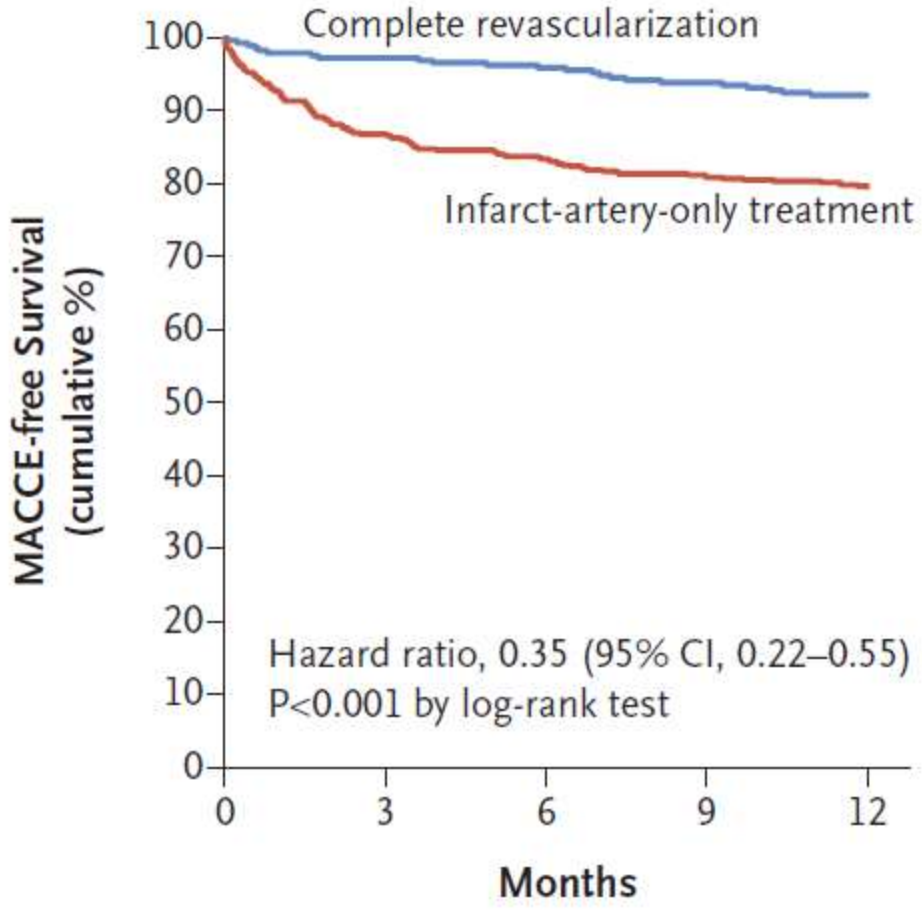


Composite of death, MI, ischemia driven revascularization of non-culprit

Engstrom T, et al. Lancet 2015;386:665-71.

COMPARE-ACUTE Trial:

885 STEMI patients with MVD randomized to 1:2 to culprit only vs. FFR-guided nonculprit PCI during index hospitalization



Smits PC, et al. New Engl J Med 2017;376:1234-44.

Conclusion:

- FUTURE Trial is not a signal
- The study has a number of critical limitations which make its findings uninterpretable
- Robust data supporting FFR-guided management of patients with CAD continues to emerge