FFR-Guided PCI for Multivessel CAD in 2022

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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:	**Abbott, Medtronic, Boston Scientific**
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Ownership/Founder:	
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Intellectual Property Rights:	
Other Financial Benefit:	**Minor Stock Options: HeartFlow**

Was 2021 a Bad Year for FFR?

FFR-Guided PCI Trials in 2021 in Patients with Multivessel CAD

- FUTURE
- FLOWER-MI
- FAME 3

FUTURE

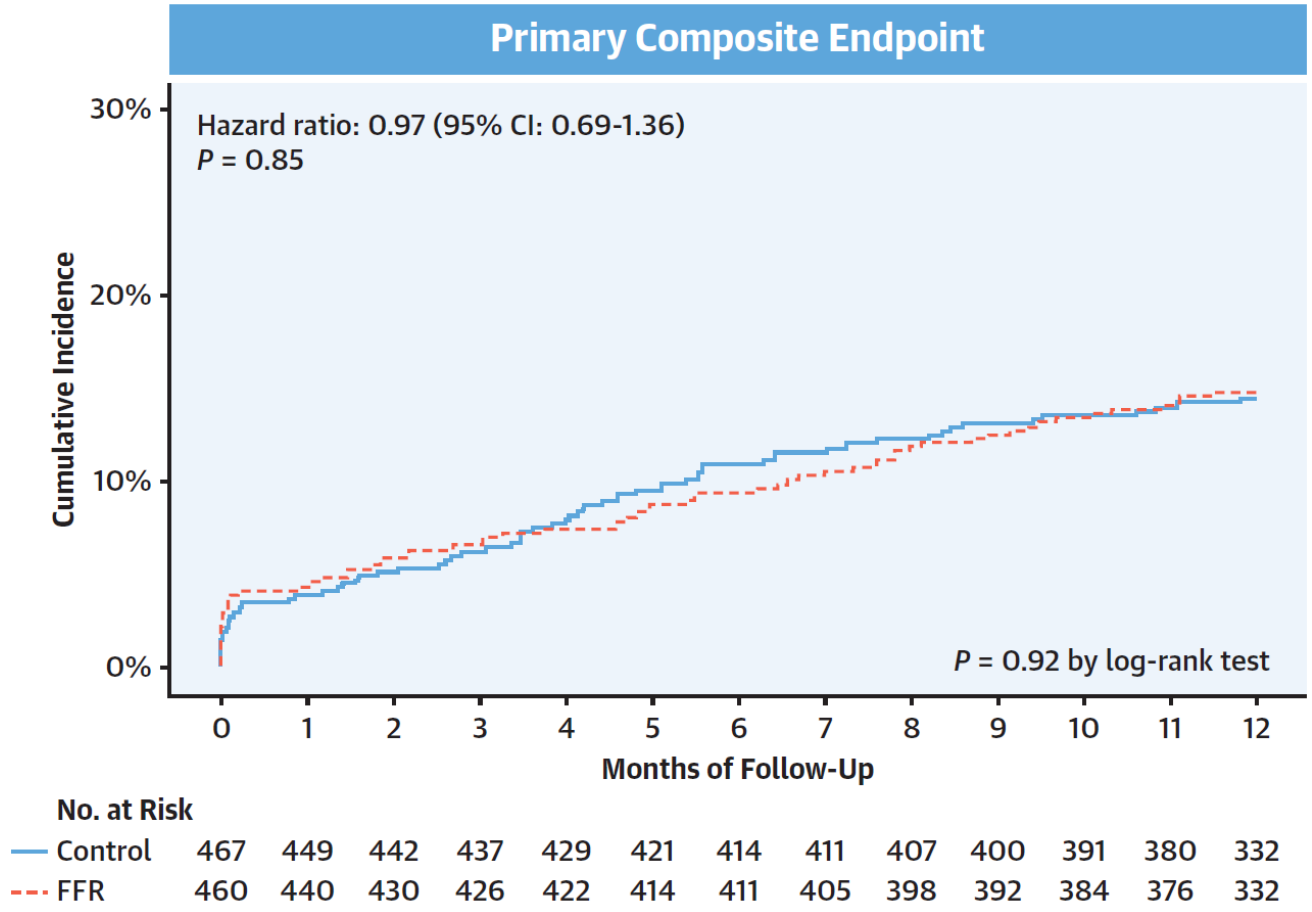
FFR-guided therapy in patients with multivessel CAD

- Multivessel CAD patients were randomly assigned to FFR-guided therapy (medical, PCI or CABG) or angio-guided therapy.
- Primary endpoint was MACCE at 1 year.
- The study was stopped prematurely after enrolment of 927 patients because of a signal for increased mortality in the FFR-guided group.

Rioufol G, et al. J Am Coll Cardiol 2021;78:1875-85.

FUTURE

Primary Endpoint: One Year MACCE



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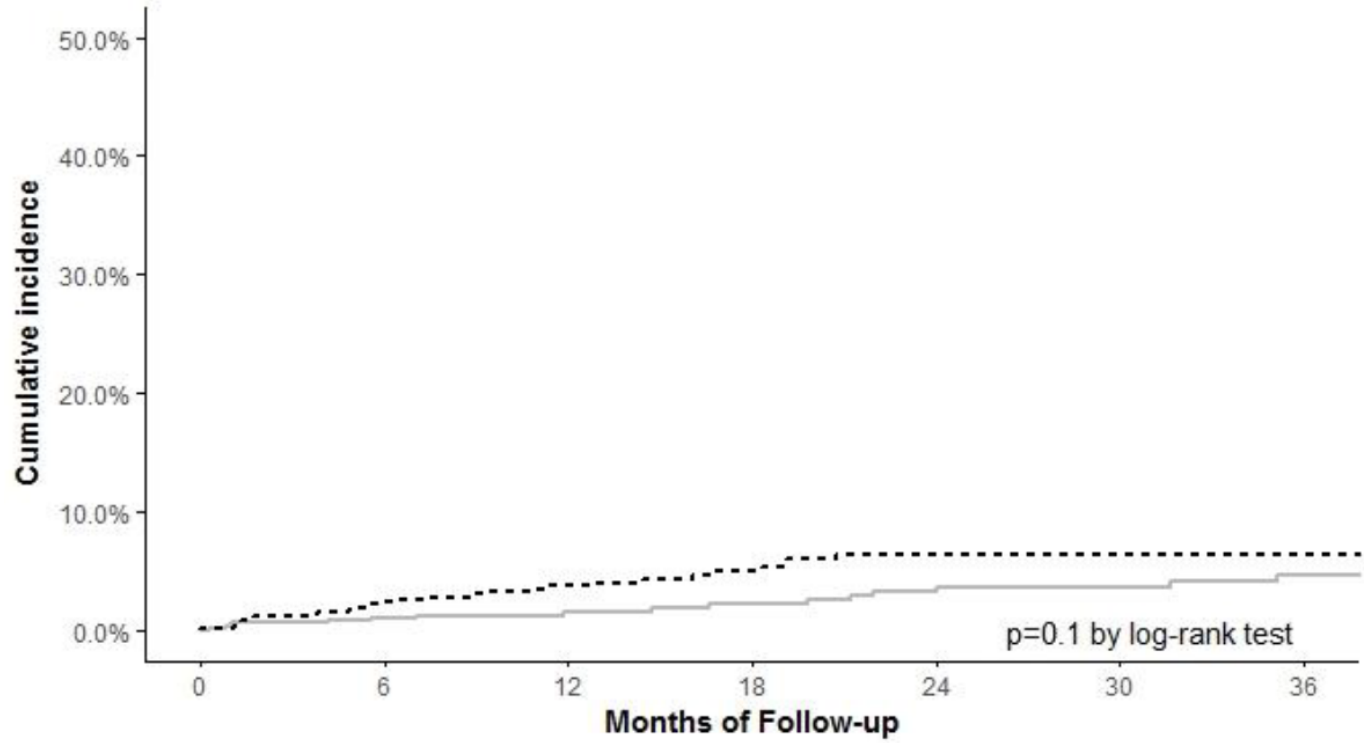
FUTURE

No Difference in Mortality Between FFR- and Angio-guidance



No. at Risk

Control	467	460	380	284	227	187	173
FFR	460	444	375	278	226	172	159

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FUTURE

Why didn't FFR-guided therapy outperform angio-guided therapy?

- This is a fairly complex patient population with relatively high SYNTAX score (19) and >50% with 3-vessel CAD.
- 127 lesions with FFR>0.80 received PCI anyway (27% of the FFR negative lesions).
- The study was underpowered with just 54% of the planned population enrolled.
- Finally, only 8% of patients received a different treatment.

FUTURE

Very little difference in ultimate treatment between two arms

	Control Group (n = 467)	FFR Group (n = 460)	*P* Value[a]
Revascularization strategy			0.002
Optimal medical treatment only	43 (9.0)	78 (17.0)	
CABG	55 (12.0)	54 (12.0)	
PCI	369 (79.0)	328 (71.0)	

Only 8% of patients (≈35-40) in the FFR-guided group received a different treatment (OMT instead of PCI) than in the Angio-guided group.

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FLOWER-MI

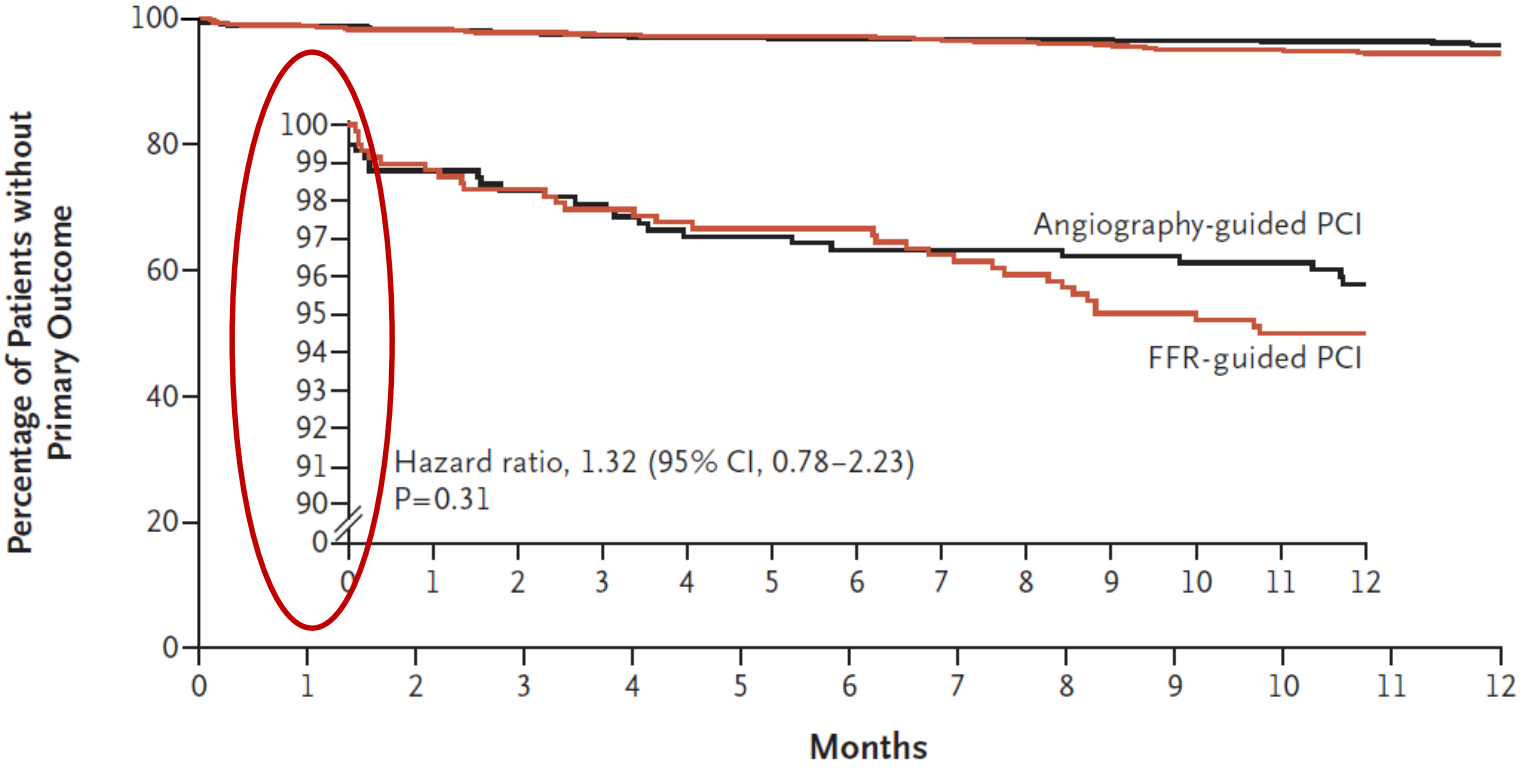
FFR-Guided PCI Trial in STEMI Patients with Multivessel CAD

- 1,163 patients with STEMI and successful primary PCI who had at least one other major vessel with ≥50% diameter stenosis
- Randomized to FFR-guided complete revascularization or angiography-guided complete revascularization
- Primary endpoint of death, MI or unplanned hospitalization with urgent revascularization at one year

Puymirat E, et al. N Engl J Med 2021; 385:297-308

FLOWER-MI

Death, MI or hospitalization with urgent revascularization at 1 year



No. at Risk

Angiography-guided PCI	577	570	567	565	560	560	557	555	555	554	552	548	371
FFR-guided PCI	586	577	573	570	567	566	566	562	559	553	553	549	385

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FLOWER-MI

Death, MI or hospitalization with urgent revascularization at 1 year

Outcomes	FFR-Guided Group (N = 586)	Angiography-Guided Group (N = 577)	Hazard Ratio or Difference (95% CI)†	P Value
Primary outcome				
Composite outcome — no. (%)‡	32 (5.5)	24 (4.2)	1.32 (0.78–2.23)	0.31
Death from any cause	9 (1.5)	10 (1.7)	0.89 (0.36–2.20)	
Nonfatal myocardial infarction§	18 (3.1)	10 (1.7)	1.77 (0.82–3.84)	
Unplanned hospitalization leading to urgent revascularization				
Patients with condition — no. (%)	15 (2.6)	11 (1.9)	1.34 (0.62–2.92)	
Treatment of target lesions in nonculprit artery by urgent revascularization — no./total no. (%)	8/15 (53.3)	3/11 (27.3)	—	

Procedural MI occurred in 7 patients in the FFR-guided arm and 2 patients in the angio-guided arm. Unclear why, when angio-guided groups had 260 more lesions treated with PCI.

Puymirat E, et al. N Engl J Med 2021; 385:297-308

FLOWER-MI

Other trial design considerations

- Ideally, randomization would have occurred after operators stated which non-culprit lesions would be treated.
- Instead, 980 lesions were identified in the FFR-guided arm vs 891 treated in the angio-guided arm.
- This explains why contrast usage and procedure time were similar between groups. Would have expected less with FFR.

FLOWER-MI

Other trial design considerations

- In addition, of the 980 lesions identified in the FFR-guided arm, the FFR value was missing in 154.
- There were 460 lesions with FFR ≤0.80, yet PCI was performed in 546 lesions in the FFR-guided arm.
- An average of 1.1 stents were placed in non-culprit lesions in the FFR-guided arm compared with 1.5 in the angio-guided arm.

FLOWER-MI

Other trial design considerations

- Ideally, FFR would have been measured in a blinded fashion in the angio-guided patients, allowing a comparison of PCI vs medical therapy for non-culprit lesions with FFR>0.80

FLOWER-MI

Was FLOWER-MI a negative trial for FFR?

- Should we have expected better outcomes with FFR in this STEMI population?
  - Both groups had a STEMI and underwent primary PCI. ***Expect similar outcome***
  - 66% of the FFR-guided patients underwent non-culprit PCI, 3% of angio-guided patients did not have non-culprit PCI. ***Expect similar outcome***
  - Only 198 patients in the FFR-guided arm did not have non-culprit PCI and could potentially contribute to a different outcome

FAME 3

FFR-guided PCI vs CABG in patients with 3-vessel CAD

- 1,500 patients with 3-vessel CAD (not involving the left main) randomized to FFR-guided PCI with current generation DES or to CABG.
- Primary endpoint was the rate of MACCE (death, MI, stroke, or repeat revascularization) at one year.
- Noninferiority design with margin set at a hazard ratio of 1.65.

New Engl J Med 2022;386:128-37.

FAME 3

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%

New Engl J Med 2022;386:128-37.

FAME 3

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%

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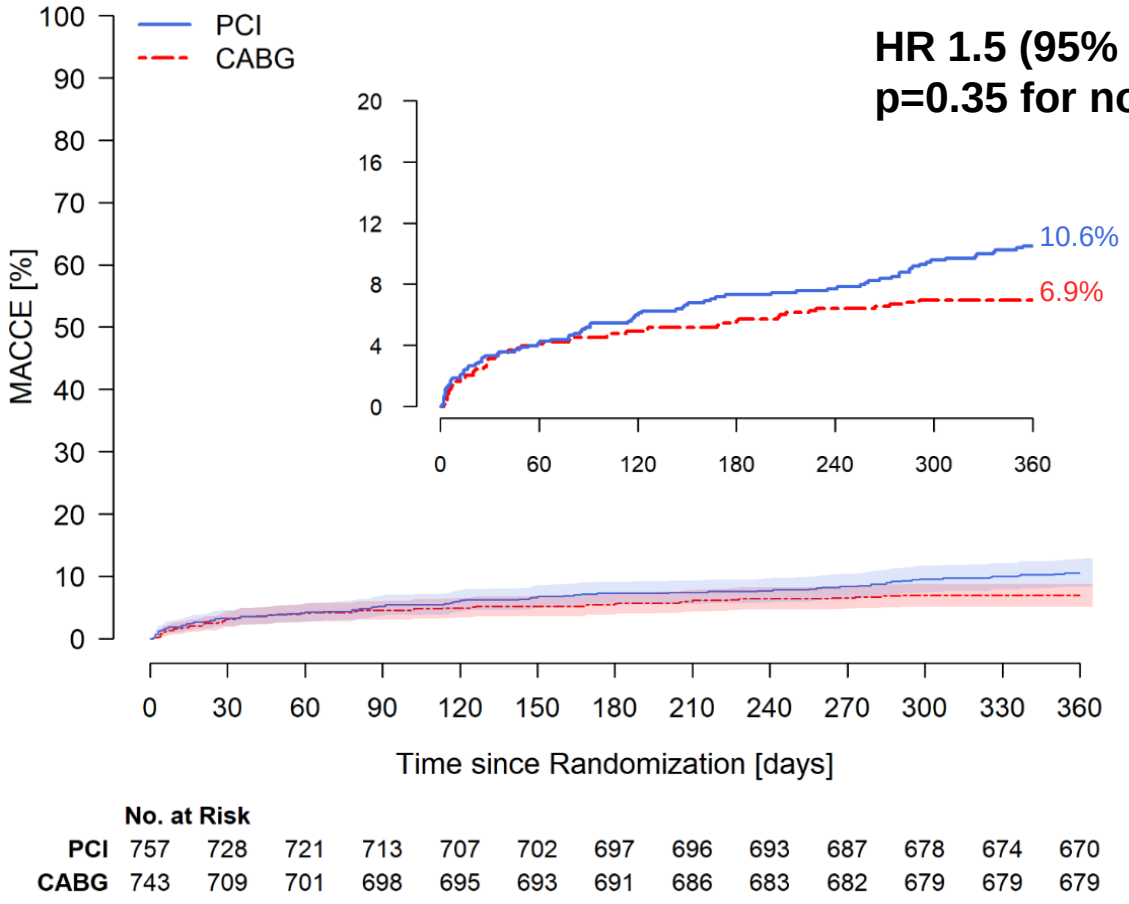
FAME 3

Primary Endpoint: MACCE at one year



HR 1.5 (95% CI: 1.1 – 2.2)
p=0.35 for noninferiority

New Engl J Med 2022;386:128-37.

FAME 3

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)

New Engl J Med 2022;386:128-37.

FAME 3

Secondary 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

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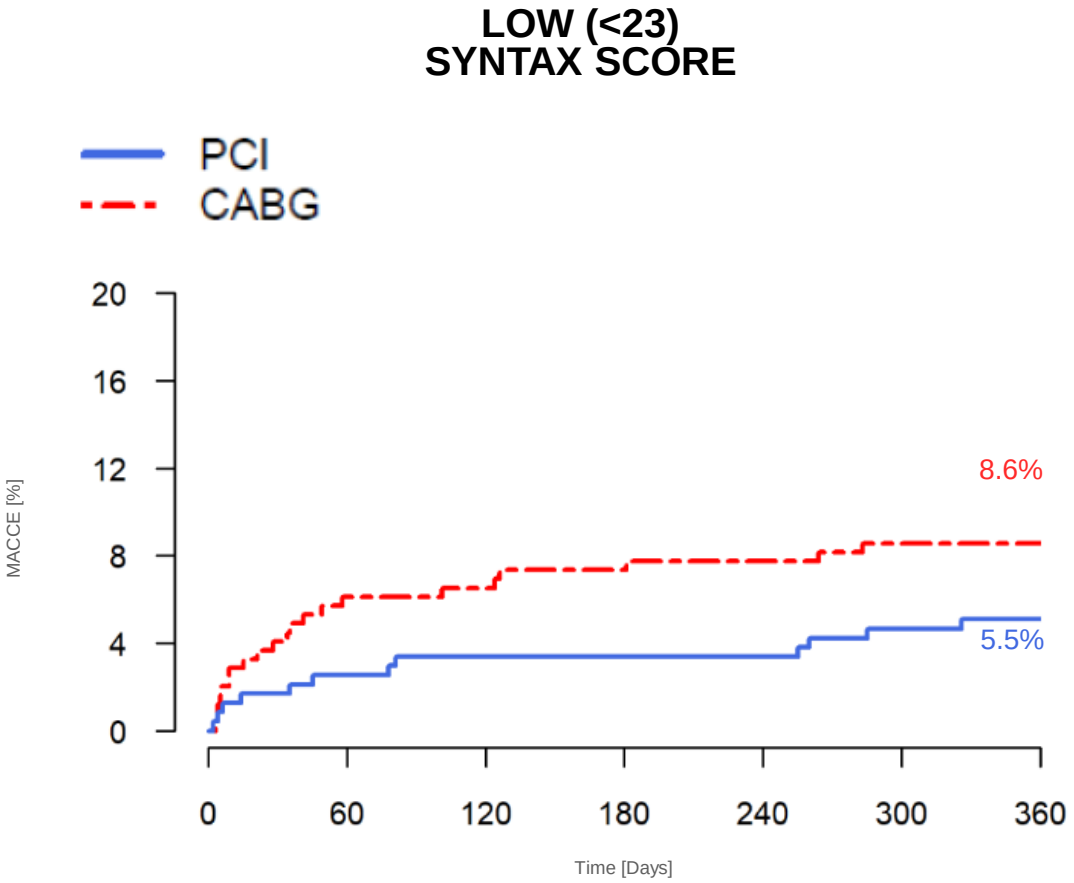
FAME 3

MACCE According to SYNTAX Score



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FAME 3

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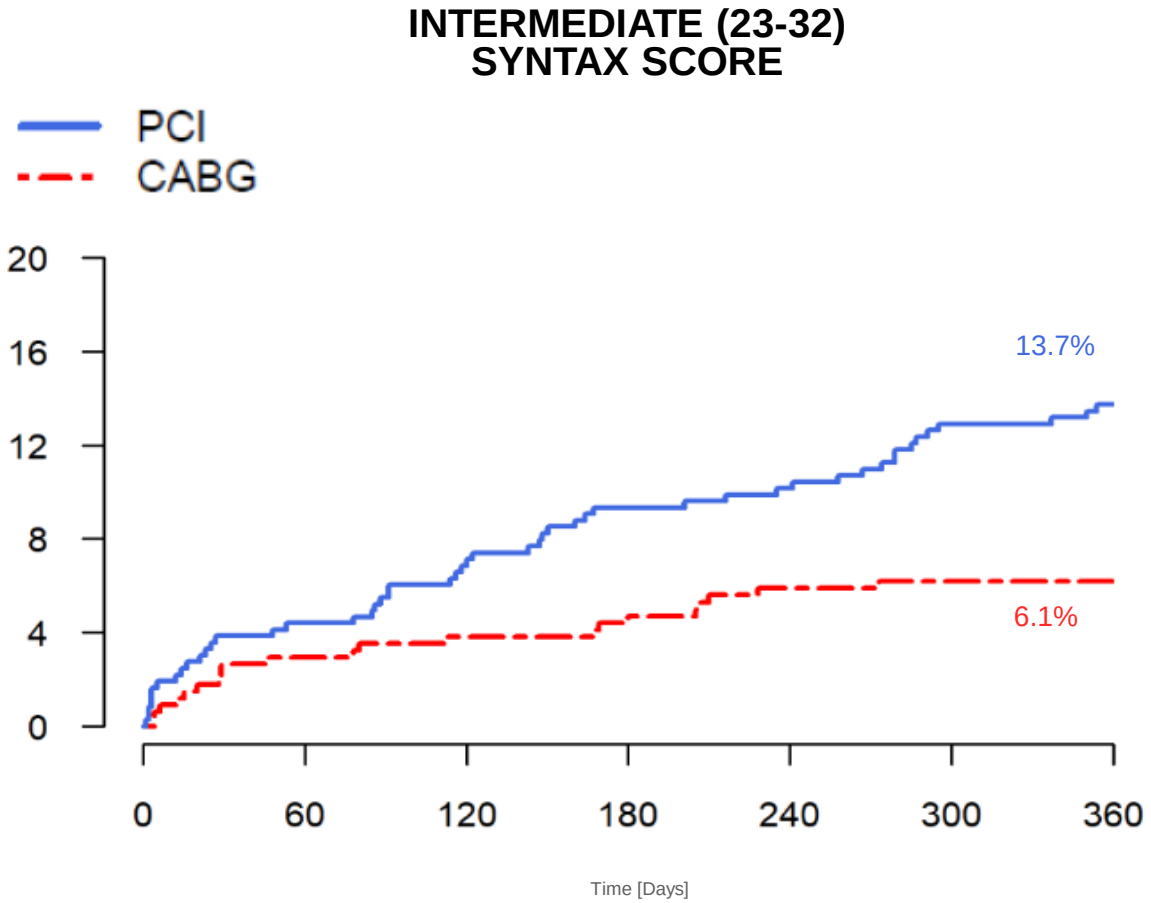

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FAME 3

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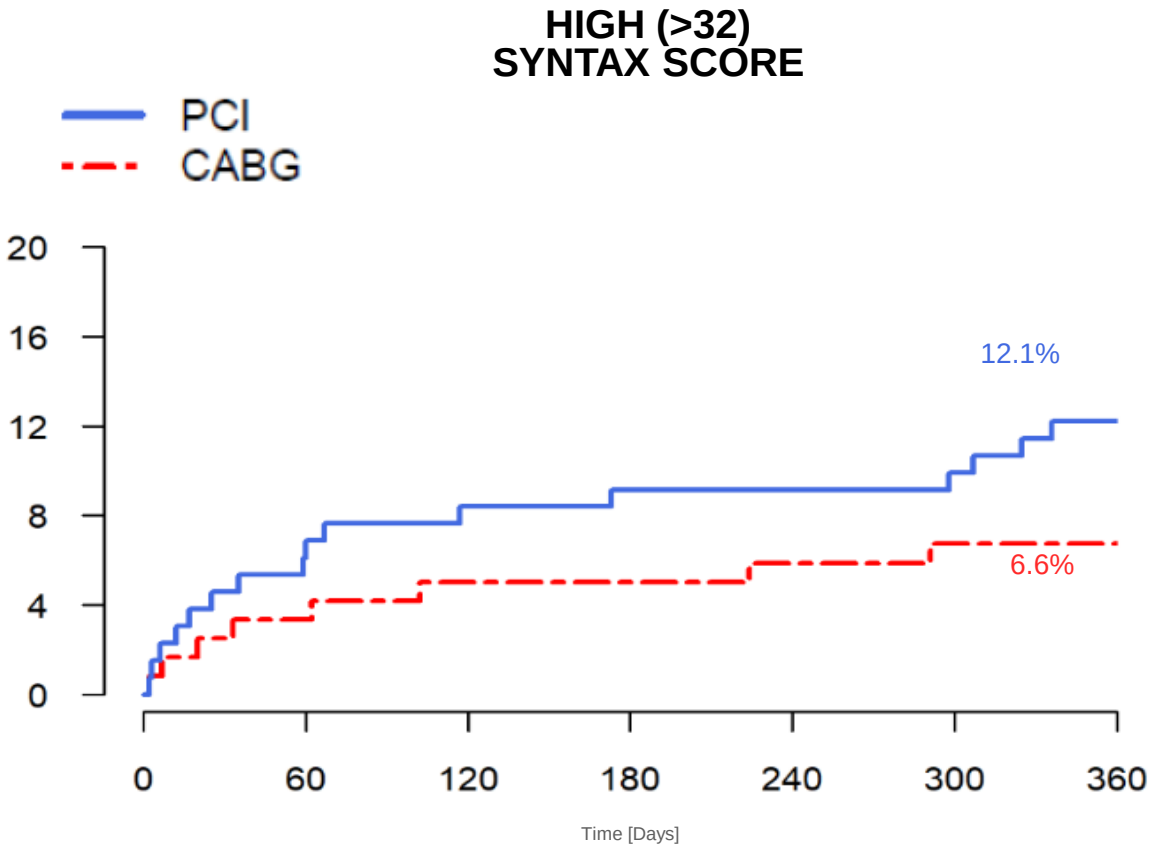

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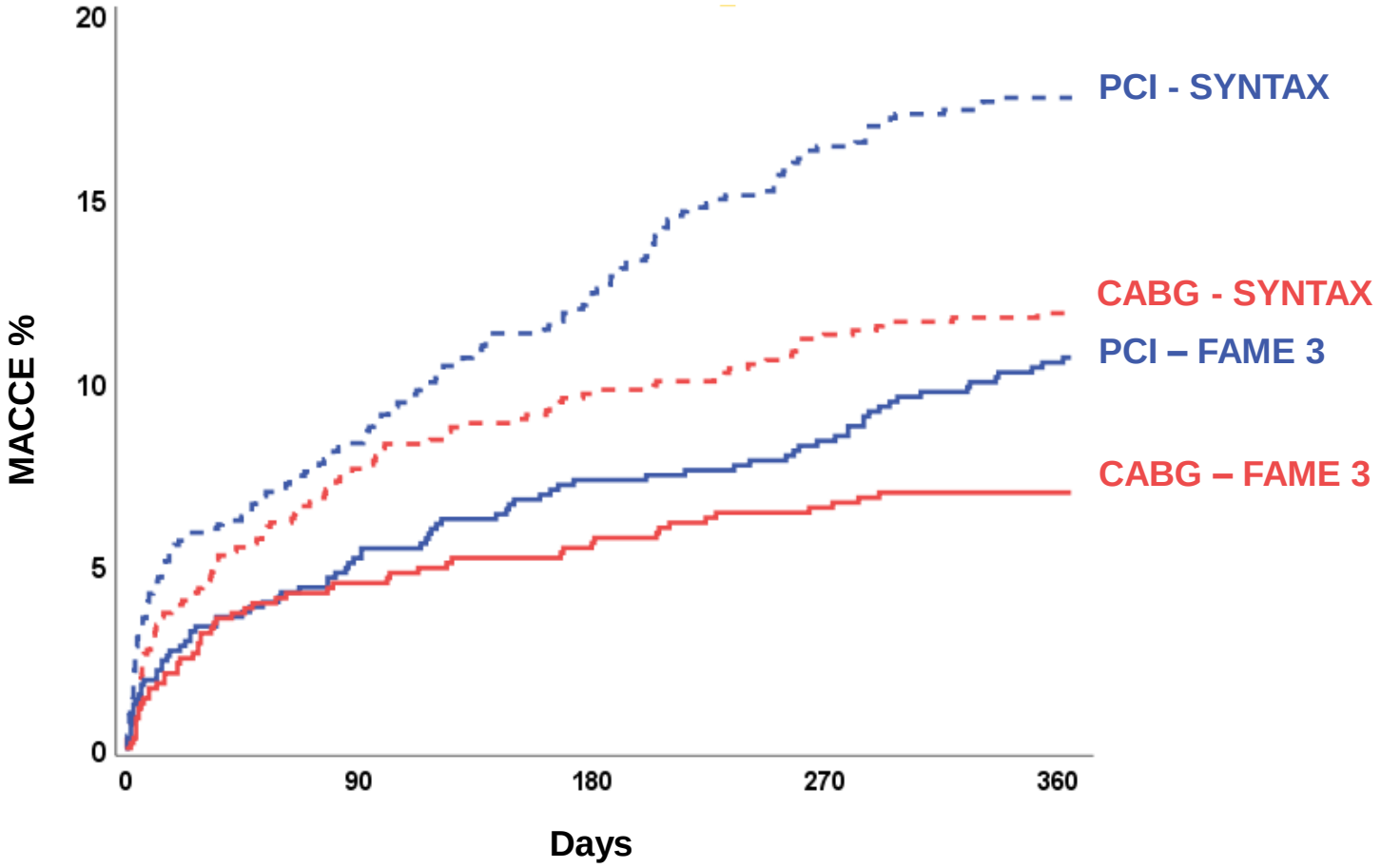
FAME 3

Was FAME 3 a negative trial for FFR?

- Only 24% of lesions in the FFR-guided patients had an FFR>0.80
- 21% of patients had a CTO
- Mean SYNTAX score was 26
- In patients with complex CAD, where FFR will be mostly positive, and where we know from previous studies, CABG outperforms PCI, FFR-guided PCI is less likely to have a benefit.

FAME 3

MACCE Outcomes in FAME 3 Compared with SYNTAX Trial



Observations

- What is the role of FFR-guided PCI in patients with multivessel CAD in 2022?
  - For any test to be useful, one must follow the results of the test; if the FFR is >0.80 then defer.
  - To optimize the benefit of FFR, apply it in cases where one is not certain about the significance of a lesion.
  - FUTURE, FLOWER-MI and FAME 3 all included patients with very low rates of negative FFRs.

Conclusion

- There is a wealth of data supporting the role of FFR in patients with multivessel CAD.

- FFR-guided PCI is still beneficial in patients with multivessel CAD, as long as it is applied in appropriate scenarios where it is likely to affect decision-making, and as long as its results are heeded.