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CLINICAL RESEARCH
Interventional cardiology

Fractional flow reserve in patients with reduced ejection fraction

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Aims Fractional flow reserve (FFR) has never been investigated in patients with reduced ejection fraction and associated coronary artery disease (CAD). We evaluated the impact of FFR on the management strategies of these patients and related outcomes.

Methods and results From 2002 to 2010, all consecutive patients with left ventricular ejection fraction (LVEF) ≤50% undergoing coronary angiography with ≥1 intermediate coronary stenosis [diameter stenosis (DS)% 50–70%] treated based on angiography (Angiography-guided group) or according to FFR (FFR-guided group) were screened for inclusion. In the FFR-guided group, 433 patients were matched with 866 contemporary patients of the Angiography-guided group. For outcome comparison, 617 control patients with LVEF >50% were included. After FFR, stenotic vessels per patient were significantly downgraded compared with the Angiography-guided group (1.43 ± 0.98 vs. 1.97 ± 0.84; $P < 0.001$). This was associated with lower revascularization rate (52% vs. 62%; $P < 0.001$) in the FFR-guided vs. the Angiography-guided group. All-cause death at 5 years of follow-up was significantly lower in the FFR-guided as compared with Angiography-guided group [22% vs. 31%. HR (95% CI) 0.64 (0.51–0.81); $P < 0.001$]. Similarly, rate of major adverse cardiovascular and cerebrovascular events (MACCE: composite of all-cause death, myocardial infarction, revascularization, and stroke) was significantly lower in the FFR-guided group [40% vs. 46% in the Angiography-guided group. HR (95% CI) 0.81 (0.67–0.97); $P = 0.019$]. Higher rates of death and MACCE were observed in patients with reduced LVEF compared with the control cohort.

Conclusions In patients with reduced LVEF and CAD, FFR-guided revascularization was associated with lower rates of death and MACCE at 5 years as compared with the Angiography-guided strategy. This beneficial impact was observed in parallel with less coronary artery bypass grafting and more patients deferred to percutaneous coronary intervention or medical therapy.

Keywords Fractional flow reserve • Coronary physiology • Heart failure • Clinical outcome

Introduction

In patients with reduced left ventricular ejection fraction (LVEF) and coronary artery disease (CAD), the indication to revascularization is often controversial. Myocardial stunning, hibernation, the presence and extent of myocardial scar and ischaemia all play a role in the pathogenesis of left ventricular systolic dysfunction, and each of these aspects can be evaluated by different imaging modalities. Yet,

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non-invasive stress imaging in patients with CAD and heart failure (HF) with reduced ejection fraction has a class IIb indication to indicate revascularization.[1]

Fractional flow reserve (FFR) invasively evaluates the ischaemic potential of coronary stenoses,[2] with consequent improved clinical outcomes in patients with preserved LVEF.[3–5] Moreover, FFR proved to be reliable even with elevated right filling pressures in a single-centre experience.[6] Nevertheless, there is no available data on the safety and on the long-term impact of an FFR-guided management strategy in patients with left ventricular systolic dysfunction. Therefore, we retrospectively evaluated the real-world impact of FFR on revascularization decisions and 5 years of clinical outcomes in patients with reduced LVEF and associated CAD.

Methods

Study cohort

From January 2002 to December 2010, we retrospectively identified 433 patients with reduced LVEF in whom at least one intermediate coronary stenosis was either revascularized with FFR ≤0.80 or deferred with FFR >0.8 (FFR-guided group). Then, from 2399 contemporary patients equally presenting with reduced LVEF and significant CAD in which the decision to revascularize was based on angiography only, we matched 866 as comparator (Angiography-guided group). All recruited patients were treated in the Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium.

Inclusion criteria were the presence of at least one intermediate stenosis by visual estimation [diameter stenosis (DS): 50–70%] of a major coronary artery at the time of angiography; LVEF ≤50%.

Patients with acute coronary syndromes, or with moderate/severe valvular heart disease requiring either surgical or percutaneous repair or replacement were not included in the study.

Left ventricular ejection fraction was assessed by angiography using the Simpson method with automatic edge detection and manual correction as appropriate. Coronary angiography was performed with 6 F diagnostic catheters. After the administration of 200–300 μg intracoronary isosorbide dinitrate, the angiogram was repeated in the projection allowing the best possible visualization of the stenosis. Experienced operators not involved in data analysis assessed LVEF and stenosis severity. Multivessel disease was defined as the presence of stenosis (≥50% in diameter) in ≥2 major coronaries.

Non-ischaemic cardiomyopathy was defined as patients with LVEF ≤40% and one vessel disease not involving a stenosis of the left anterior descending or the left main ≥75% DS.[7]

Fractional flow reserve was measured as previously described.[8] Revascularization procedures performed within 6 months from the diagnostic coronary angiography were referred to the index procedure if they were part of the initial treatment strategy.

An FFR-guided control cohort with preserved LVEF, including 617 patients, was built for outcome comparison. Patients treated with coronary artery bypass grafting (CABG) were extracted from a previous study comparing FFR-guided to Angiography-guided surgical revascularization,[9,10] whereas patients treated with percutaneous coronary intervention (PCI) or medical therapy were extracted from the FAME 2 trial.[5]

Clinical outcomes

The primary endpoint of this study was the rate of major adverse cardiovascular and cerebrovascular events (MACCE), defined as all-cause death, myocardial infarction (MI), revascularization, or stroke at 1 and 5 years of follow-up.

Secondary endpoints were all the individual endpoints included in the primary endpoint, HF hospitalization, and unplanned cardiac admission. The definition of clinical endpoints and data collection is reported in the Supplementary material online, *Appendix*.

Date of death was retrieved from Belgium national death registry. Informed consent as approved by the local Ethics Committee to the use of personal data was obtained from each patient.

Statistical analysis

All analyses were performed with SPSS 25.0 (IBM Inc., New York, NY, USA) and with Prism GraphPad 7.0 (GraphPad Software Inc., La Jolla, CA, USA).

Propensity score (PS) matching was used to reduce selection bias associated with revascularization strategy and potential confounding factors in the observational study, and to adjust significant differences in the patients' baseline characteristics. A detailed description of the statistical approach used for PS matching is reported in the Supplementary material online, *Appendix*.

Categorical variables are reported as frequencies and percentages. Normal distribution was tested with the Shapiro–Wilk test. Comparisons between continuous variables were performed with the Student's *t*-test or Mann–Whitney *U* test. Comparisons between categorical variables were evaluated with the Fisher's exact test or the Pearson's χ^2 test. The difference in survival was calculated by applying Kaplan–Meier curves and event rates are reported at 1 and 5 years. Cox-regression derived hazard ratios were used to compare the two groups. Landmark analyses were performed before and after the 1 year timepoint to analyse the peri-procedural and short-term effect of treatment strategies on clinical outcomes.

A multivariate Cox-regression analysis was used to compare clinical outcomes between the FFR-guided group and an FFR-guided control cohort with preserved LVEF.

Probability values were two-sided, and values of $P < 0.05$ were considered significant.

Results

Clinical, angiographic, and procedural characteristics

We included: (i) 433 patients with reduced LVEF and angiographically significant CAD in the FFR-guided group; (ii) 866 matched patients, in the Angiography-guided group. The two groups were similar with respect to most of the clinical and angiographic characteristics (*Table 1*). Left anterior descending artery was significantly more affected in the FFR-guided group. Patients with non-ischaemic cardiomyopathy were 27 (6%) in the FFR-guided and 44 (5%) in the Angiography-guided group ($P = 0.39$).

Fractional flow reserve was assessed in 597 stenoses. Mean FFR value was the lowest in the left anterior descending artery (0.78 ± 0.10) and the highest in the left circumflex (0.84 ± 0.11), whereas intermediate values were measured in the right coronary artery (0.81 ± 0.15) ($P < 0.001$).

There was no difference in FFR values across various strata of LVEF (Supplementary material online, *Appendix Figure S4*). After FFR, 18/59 (30%) angiographically mild stenoses (DS% 30–49%) were upgraded to physiologically significant, whereas 264/538 (49%)

Table 1 Clinical and angiographic characteristics of the propensity-matched population

	FFR-guided ($n = 433$)	Angio-guided ($n = 866$)	*P*-value
Age, years	66.3 ± 10.8	66.7 ± 10.6	0.51
Male sex	351 (81%)	691 (80%)	0.59
Smoking habit	242 (56%)	472 (54%)	0.63
PVD	46 (11%)	95 (11%)	0.92
Diabetes mellitus	111 (26%)	237 (27%)	0.51
IDDM	26 (6%)	56 (6%)	0.75
Hypertension	212 (49%)	419 (48%)	0.84
Hyperlipidaemia	249 (57%)	485 (56%)	0.61
Family history CAD	112 (26%)	216 (25%)	0.72
Previous CABG	45 (10%)	90 (10%)	1.00
Previous PCI	79 (18%)	158 (18%)	1.00
Atrial fibrillation	36 (8%)	75 (9%)	0.83
LVEF	39.4% ± 9%	39.1% ± 9%	0.51
LVEDVi, mL	106 ± 38	106 ± 40	0.54
LVESVi, mL	65 ± 29	65 ± 35	0.88
N° diseased vessels	2.00 ± 0.85	1.97 ± 0.84	0.54
1-vessel disease	154 (36%)	315 (36%)	0.92
2-vessel disease	124 (29%)	259 (30%)	
3-vessel disease	155 (36%)	292 (34%)	
Diameter stenosis	62% ± 23%	63% ± 20%	0.41
Stenosis location			
LMCA	43 (10%)	112 (13%)	0.11
LAD	348 (80%)	636 (74%)	0.007
LCX	240 (55%)	498 (58%)	0.43
RCA	237 (55%)	492 (57%)	0.45
FFR value			
Total	0.8 ± 0.12	N/A	<0.001*
LAD	0.78 ± 0.10		
LCX	0.84 ± 0.11		
RCA	0.81 ± 0.15		

CABG, coronary artery bypass grafting; CAD, coronary artery disease; FFR, fractional flow reserve; IDDM, insulin-dependent diabetes mellitus; LAD, left anterior descending; LCX, left circumflex; LMCA, left main coronary artery; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.
*P-value within the FFR-guided group.

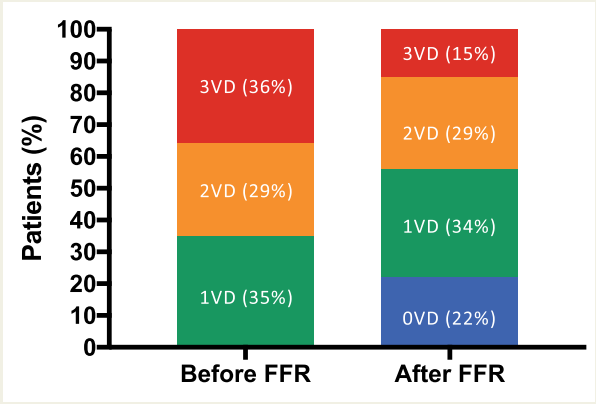


Figure 1 Downgrading in the number of diseased vessels after fractional flow reserve measurement. VD, vessel disease.

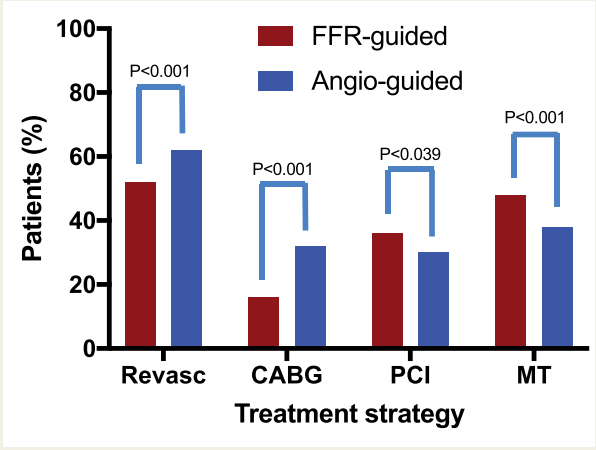


Figure 2 The difference in treatment strategies between fractional flow reserve- and Angiography-guided group. CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention; Revasc, revascularization.

angiographically significant stenoses (DS% 50–70%) were downgraded to physiologically non-significant (Supplementary material online, *Appendix Table S2*).

In the FFR-guided group, the number of diseased vessels per patient was significantly decreased (*Table 1* and *Figure 1*) with significantly lower revascularization vs. the Angiography-guided group [225 (52%) vs. 535 (62%); $P < 0.001$]. Percutaneous coronary intervention was more frequent in the FFR-guided group [155 (36%) vs. 261 (30%) of the Angiography-guided group; $P = 0.039$]; whereas CABG was more frequent in the Angiography-guided group [274 (32%) vs. 70 (16%) of the FFR-guided group, $P < 0.001$]. Patients in the FFR-guided group were more frequently deferred to medical therapy [208 (48%) vs. 331 (38%); $P < 0.001$] (*Figure 2*).

In CABG patients, significantly more off-pump, minimally invasive surgery, lower rate of venous grafts and anastomoses per patient were reported in the FFR-guided group (*Table 2*).

In PCI patients, no significant differences were found between the groups with regards to the angiographic and procedural characteristics, with the exception of the left main coronary artery more frequently revascularized in the FFR-guided group (*Table 3*).

Clinical, angiographic, and procedural characteristics of the FFR-guided control cohort with preserved ejection fraction are reported in Supplementary material online, *Appendix Tables S3–5*.

Clinical outcomes

Clinical follow-up was available for 1271 (98%) patients at a median of 5 (1.5–5) years (*Table 4*). At 1 year, there was a significantly lower rate of MACCE, all-cause death, and stroke in the FFR-guided group. At 5 years, the difference in the rate of MACCE and all-cause death

Table 2 Surgical procedural data

	FFR-guided (*n* = 70)	Angio-guided (*n* = 274)	*P*-value
On-pump CABG	44 (63%)	241 (88%)	<0.001
Off-pump CABG	26 (37%)	33 (12%)	<0.001
MIDCAB	4 (6%)	3 (1%)	0.015
Arterial graft/pt	1.53 ± 0.68	1.41 ± 0.79	0.28
Arterial anastomoses/pt	1.53 ± 0.68	1.43 ± 0.79	0.34
Venous graft/pt	1.02 ± 0.78	1.26 ± 0.70	0.023
Venous anastomoses/pt	1.16 ± 0.89	1.54 ± 0.97	0.007

CABG, coronary artery bypass grafting; MIDCAB, minimally invasive direct coronary artery bypass.

was confirmed, whereas no difference between the two groups was observed in other endpoints. Clinical outcomes at 5 years in the control cohort are shown in Supplementary material online, *Appendix Table S6*.

Landmark analysis

One year landmark analysis showed that the difference in MACCE and all-cause death between the two groups accrued up to 1 year and was no longer present between 1 and 5 years (*Take home figure*). Clinical outcomes between 1 and 5 years are reported in Supplementary material online, *Appendix Table S7*.

Clinical outcomes according to left ventricular ejection fraction strata

When stratifying according to LVEF, the clinical benefit of the FFR-guided strategy in all-cause death was confirmed both in patients with LVEF ≤35% (*n* = 419) [HR (95% CI) 0.48 (0.31–0.75)] and with LVEF >35% (*n* = 852) [HR (95% CI) 0.74 (0.56–0.98)]. An FFR-guided strategy was also associated with improved MACCE in patients with LVEF ≤35% [HR (95% CI) 0.67 (0.47–0.94)], whereas there was only a trend in patients with LVEF between 36% and 50% [HR (95% CI) 0.87 (0.71–1.08)] (*Figure 3*).

Clinical outcomes stratified by treatment

Patients treated with CABG showed higher MACCE rate with respect to patients treated with PCI or medical therapy. In the FFR-guided group, patients treated with medical therapy had significantly less events than those treated by PCI, whereas the outcomes were similar for patients treated with medical therapy or PCI in the Angiography-guided group (*Figure 4*).

The number of stenotic vessels in both groups according to clinical management, before and after FFR measurement is reported in Supplementary material online, *Appendix Table S8*.

Discussion

In patients with reduced LVEF and CAD, FFR assessment is significantly associated with lower rates of death and MACCE. This is obtained by either reducing functionally inappropriate revascularizations or by decreasing the invasiveness of the procedures performed. In patients with regional wall motion abnormalities, left ventricular systolic dysfunction can be caused by stunned or hibernating myocardium and may be reversed by revascularization. The target for revascularization (i.e. ischaemic or viable myocardium) can be assessed by several non-invasive stress tests. Nevertheless, convincing association between ischaemia or viability at non-invasive tests with consistent benefit from revascularization has not yet been shown.[11–13] Therefore, these tests have only a weak indication in guiding revascularization.[1] Previous studies have shown that FFR is able to distinguish patients with positive from patients with negative SPECT imaging after a MI and that for similar degree of stenosis, the value of FFR depends on the mass of viable myocardium.[14,15] Moreover, FFR was shown to be reliable in patients with reduced left ventricular function even in the presence of elevated right atrial pressure.[6]

Table 3 Angiographic and procedural characteristics of patients treated with PCI

	FFR-guided (*n* = 155)	Angio-guided (*n* = 261)	*P*-value
DS%	60.7 ± 16.9	60.4 ± 15.7	0.85
RVD, mm	2.93 ± 0.78	2.96 ± 0.74	0.69
MLD, mm	1.15 ± 0.45	1.17 ± 0.38	0.63
post-PCI DS%	8.21 ± 7.99	9.33 ± 9.12	0.21
post-PCI RVD, mm	3.11 ± 0.65	3.08 ± 0.61	0.63
post-PCI MLD, mm	2.87 ± 0.62	2.80 ± 0.58	0.24
N° treated vessel			0.53
1	72 (46%)	136 (52%)	
2	73 (47%)	109 (42%)	
3	10 (7%)	16 (6%)	
Type of vessel treated			
LMCA	16 (10%)	12 (4%)	0.024
LAD	138 (89%)	224 (86%)	0.88
LCX	33 (21%)	69 (26%)	0.24
RCA	61 (39%)	97 (37%)	0.65
N° stents implanted	1.55 ± 0.81	1.47 ± 0.86	0.35
Drug-eluting stent	64 (41%)	119 (46%)	0.39
Stent min diameter, mm	3.04 ± 0.46	3.11 ± 0.45	0.13
Stent max diameter, mm	3.23 ± 0.43	3.29 ± 0.47	0.19
Stent length, mm	29.0 ± 15.9	29.7 ± 16.9	0.67

DS, diameter stenosis; LAD, left anterior descending; LCX, left circumflex artery; LMCA, left main coronary artery; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RCA, right coronary artery; RVD, reference vessel diameter.

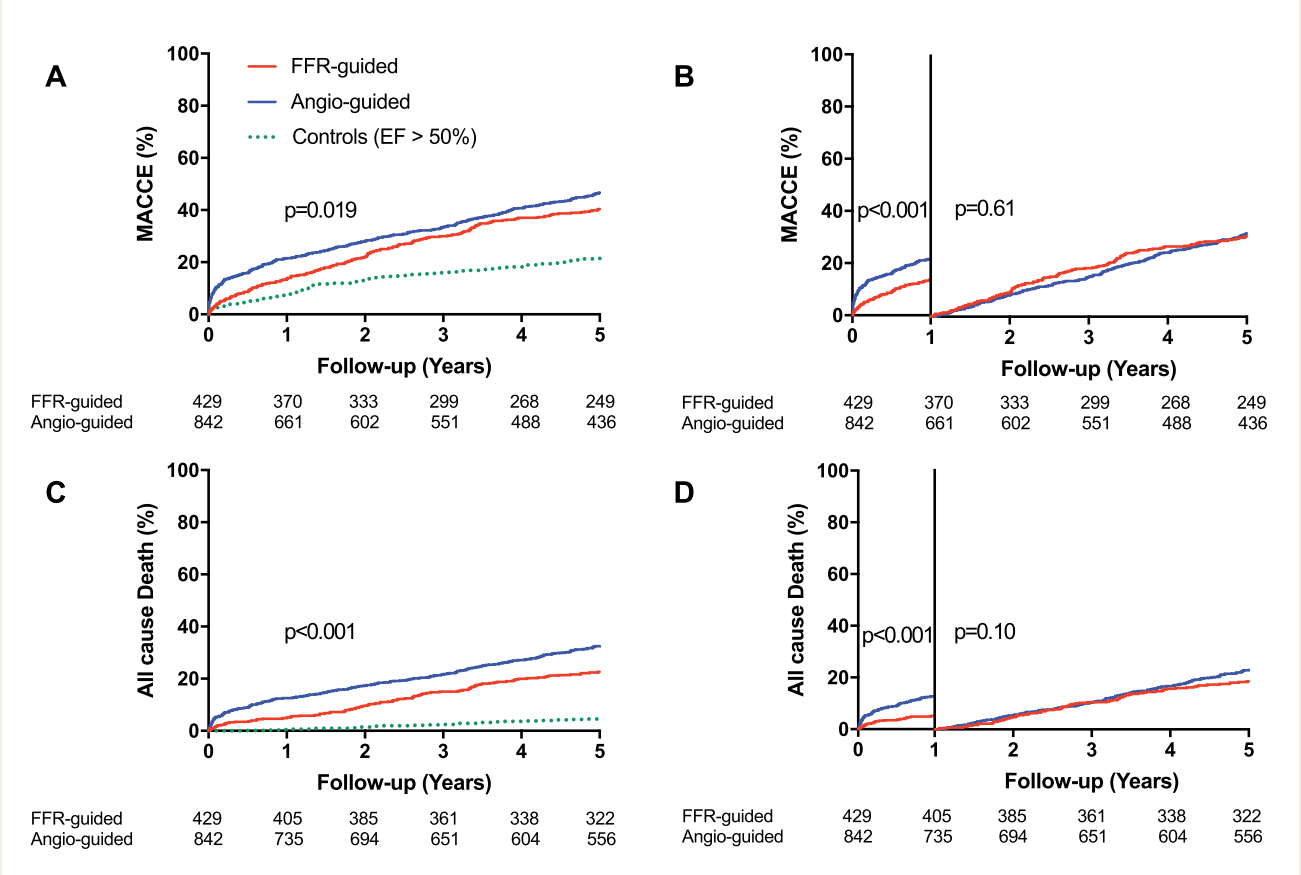
Impact of fractional flow reserve on clinical management and revascularization strategy

Fractional flow reserve measurements were associated with significant downgrading in the angiographic severity of CAD, in agreement with previous reports.[16,17] Interestingly, in 22% of the patients with angiographically significant CAD, FFR suggested that none of the epicardial stenoses was able to induce reversible ischaemia. In addition, the rate

Table 4 Clinical outcomes at 1 and 5 years

Endpoint	1 year		HR (95% CI)	*P*-value	5 years		HR (95% CI)	*P*-value
	FFR-guided, *n* (%)	Angio-guided, *n* (%)			FFR-guided, *n* (%)	Angio-guided, *n* (%)		
MACCE	59 (14)	181 (21)	0.60 (0.45–0.80)	0.001	172 (40)	389 (46)	0.81 (0.67–0.97)	0.019
All-cause death	24 (6)	107 (13)	0.42 (0.27–0.66)	<0.001	96 (22)	272 (31)	0.64 (0.51–0.81)	<0.001
MI	8 (2)	30 (3)	0.52 (0.221.22)	0.13	22 (5)	54 (6)	0.73 (0.43–1.25)	0.25
Revascularization	36 (8)	71 (8)	0.91 (0.61–1.38)	0.54	77 (18)	126 (15)	1.13 (0.85–1.50)	0.40
Stroke	1 (0)	12 (2)	0.84 (0.62–0.96)	0.03	11 (3)	28 (3)	0.68 (0.37–1.65)	0.51
HF hospitalization	15 (3)	45 (5)	0.64 (0.34–1.21)	0.16	42 (10)	106 (13)	0.75 (0.51–1.10)	0.15
Unplanned cardiac hospitalization	30 (7)	85 (10)	0.65 (0.41–1.03)	0.065	87 (20)	200 (24)	0.81 (0.62–1.05)	0.11

HF, heart failure; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.



Take home figure Cumulative incidences and landmark analysis for MACCE and all-cause death. cumulative incidence of MACCE (*A*) and all-cause death (*C*); landmark analysis before and after 1 year timepoint for MACCE (*B*) and all-cause death (*D*). The dotted green line represents the control cohort with preserved LVEF, for visual comparison. *P*-values are referred to the fractional flow reserve-guided and the Angiography-guided groups.

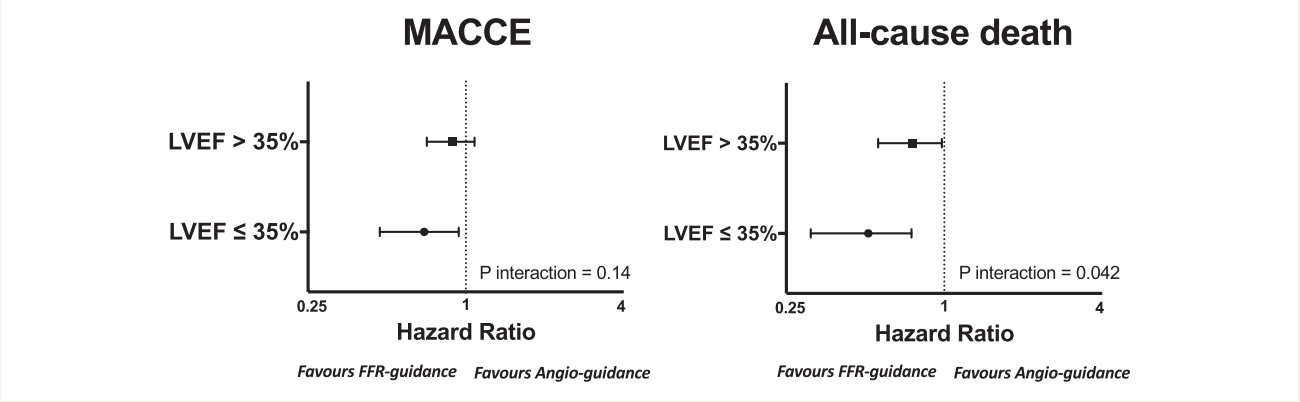


Figure 3 Impact of fractional flow reserve on MACCE and all-cause death in patients with LVEF ≤35% and with LVEF 36–50%.

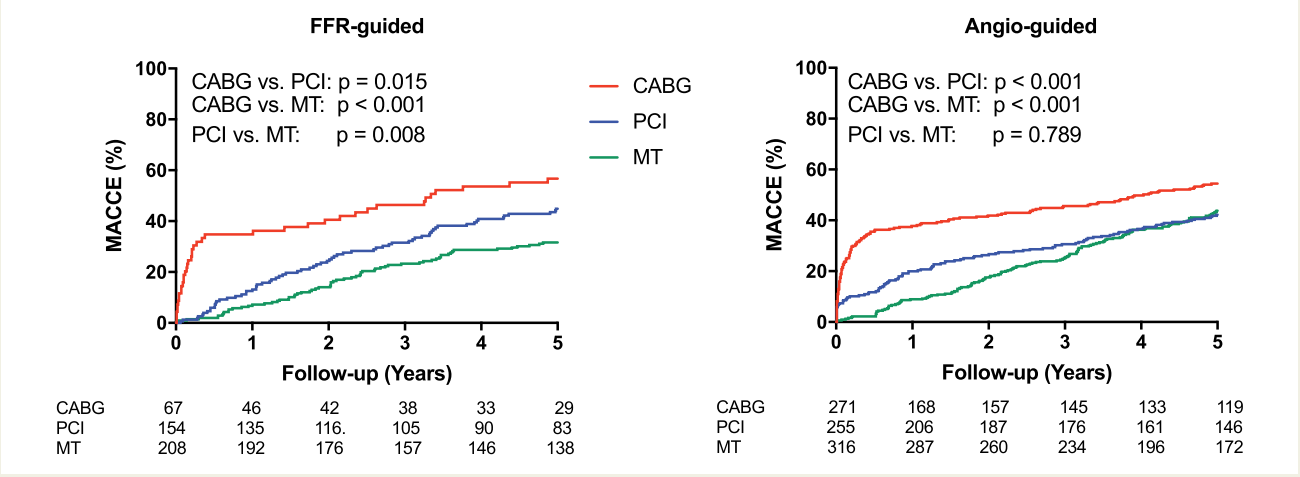


Figure 4 Cumulative incidence at 5 years MACCE in the fractional flow reserve-guided (left) and in the Angiography-guided (right) group according to treatment strategy. CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention.

of patients with three-vessel disease decreased from 36% to 15% after FFR. This reclassification was associated with an increased number of patients treated medically and with less patients treated with CABG in the FFR-guided as compared with the Angiography-guided group.

In keeping with previous studies,[9,10,18,19] the surgical procedures performed in our patients with reduced LVEF were much simplified in the FFR-guided group: e.g. 'off-pump' more often performed, mini-invasive CABG, and less venous graft and anastomoses implanted.

Since our study included mainly patients with ischaemic cardiomyopathy, various degrees of microvascular impairment were certainly present across the population. Regardless of the status of the microvascular function, FFR quantifies the extent to which the epicardial stenosis contributes to reduced myocardial perfusion and the potential benefit expected from revascularization.[20]

Impact of the fractional flow reserve-guided strategy on clinical outcome

An FFR-guided revascularization strategy has been proven to be beneficial on clinical outcomes in patients with preserved systolic function.[3–5] To date, this is the first study to investigate clinical outcomes associated with an FFR-guided revascularization strategy in a population of patients with reduced ejection fraction. The very high rates of MACCE and all-cause death reported in our study are in line with previous reports.[21–22] At 1 and 5 years of follow-up, we observed less MACCE and all-cause death in patients treated with an FFR-guided strategy. The benefits in MACCE and in mortality were driven from events occurring during the 1st year, including higher rate of stroke in the Angiography-guided group. Of note, 8 out of 12 strokes occurring during the 1st year in the Angiography-guided group were observed in patients receiving CABG, whereas the stroke in the FFR-guided group occurred in a patient treated with PCI. No difference in stroke beyond 1 year was observed between the groups, confirming that the risk profile for stroke was similar between the two groups. These findings suggested higher peri-procedural and short-term risk, possibly associated with more aggressive treatments in the Angiography-guided group. Clinical outcomes stratified by treatment confirmed this hypothesis. Both in FFR- and Angiography-guided group, patients with the highest

coronary burden treated surgically had the worst outcome, with the great majority of adverse events occurring within a few months after enrolment.

In the STITCH trial, less death was reported at 10 years when patients with severe CAD and LVEF <35% were treated with CABG compared with medical therapy. This benefit started to accrue only after 2 years, whereas for the 1st month after randomization the risk of death with CABG was three times higher than with medical therapy alone.[23] Our study complements the results of this trial, which did not explore the possibility to treat patients with severe anatomical CAD based on a strategy directed by the invasive functional significance of the coronary stenoses. The latter in fact translated into less aggressive treatment, i.e. more PCI performed, that exposes patients to a lower peri-procedural risk as compared with CABG. This is further corroborated by the fact that in our study the highest improvement in clinical outcome was observed in patients with severely reduced LVEF. Notably, in the STITCH trial, the benefit of CABG over medical therapy in the subgroup with one or two vessel disease was less clear and non-statistically significant.

In our study, we observed only a trend towards less cardiac admissions at both 1 and 5 years of follow-up. However, most of the benefit associated with an FFR-guided strategy was gained during the very 1st month after the index procedure and often during the index hospitalization.

We did not find differences in the rates of MI or revascularization. There are a few possible explanations. As previously reported, the most common cause of cardiovascular death at 36 months in patients with ischaemic cardiomyopathy was HF (32.2%), followed by sudden death (16%); MI was the cause of death only in 8.3% of the patients, whereas in 7.7% of patients the cause of death was unknown.[22] Our patients of the Angiography-guided group received more frequently a complete anatomical revascularization. On the other hand, patients in the FFR-guided group were more often treated with PCI. This disproportion might be responsible for the non-significant difference in revascularizations at follow-up. In fact, it has been shown that comparing repeat revascularization between CABG and PCI is heavily biased against PCI.[24]

In patients with left ventricular dysfunction and CAD, current guidelines recommend myocardial revascularization.[1] Our study provides additional data on the clinical benefits potentially deriving by implementing a functional reclassification of the patients presenting with angiographic multivessel disease. By correctly identifying stenoses able to induce reversible ischaemia, FFR has the ability to discriminate patients who will derive most of the benefit from surgical revascularization, whereas safely deferring other patients to less invasive and aggressive treatment, therefore preventing or reducing unnecessary procedure-related risk. Thus, alongside clinical judgement, FFR might represent an important risk stratification tool for proper treatment allocation.

Implementing FFR in clinical decision-making seems to be even more impactful in patients with more severe ventricular dysfunction (LVEF $\leq$ 35), suggesting that performing less interventions in these more fragile patients might portend better clinical outcomes.

Limitations

This is an observational study limited by its retrospective design. Although we tried to reduce bias by propensity matching, we cannot exclude potential confounders deriving both from patients' and operators' decision. Capturing some of these characteristics remains difficult. Factors including patient frailty, vessel tortuosity and calcification, total coronary atherosclerotic burden (e.g. SYNTAX score), problems of vascular or surgical access, and chronic kidney disease are frequent residual confounders that were not taken into account by our analysis.

Although the majority of patients were diagnosed with ischaemic cardiomyopathy, we cannot exclude overlapping conditions such as dilated or hypertrophic cardiomyopathy, amyloidosis, pulmonary hypertension, or other diseases as the primary cause of reduced LVEF in some patients.

Patients with mild coronary stenoses only were not included in the study. Especially in arteries supplying large myocardial territories, such stenoses might be functionally significant and their treatment might portend prognostic implications.[25,26]

Coronary stenosis severity was not assessed by an independent angiographic core laboratory. In patients undergoing PCI, quantitative coronary angiography (QCA) analysis was performed at the time of PCI by attending cathlab physicians unaware of the study design and outcomes. In all patients, DS was assessed through visual estimation. However, in the absence of a core laboratory, visual estimation has been shown to predict physiology better than QCA.[27]

We did not systematically collect and therefore do not report information on medical therapy and on non-invasive ischaemia/viability tests.

Conclusion

In patients with reduced LVEF and CAD, an FFR-guided revascularization strategy was associated with lower rates of death and MACCE at 5 years of follow-up as compared with the Angiography-guided strategy. This beneficial impact was observed in parallel with less CABG and more patients deferred to PCI or medical therapy. Future prospective studies are necessary to confirm these findings and to clarify the role of physiological assessment in patients with reduced LVEF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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