Journal of the American Heart Association

ORIGINAL RESEARCH

Deferral of Coronary Revascularization in Patients With Reduced Ejection Fraction Based on Physiological Assessment: Impact on Long-Term Survival

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BACKGROUND: Deferring revascularization in patients with nonsignificant stenoses based on fractional flow reserve (FFR) is associated with favorable clinical outcomes up to 15 years. Whether this holds true in patients with reduced left ventricular ejection fraction is unclear. We aimed to investigate whether FFR provides adjunctive clinical benefit compared with coronary angiography in deferring revascularization of patients with intermediate coronary stenoses and reduced left ventricular ejection fraction.

METHODS AND RESULTS: Consecutive patients with reduced left ventricular ejection fraction (≤50%) undergoing coronary angiography between 2002 and 2010 were screened. We included patients with at least 1 intermediate coronary stenosis (diameter stenosis ≥40%) in whom revascularization was deferred based either on angiography plus FFR (FFR guided) or angiography alone (angiography guided). The primary end point was the cumulative incidence of all-cause death at 10 years. The secondary end point (incidence of major adverse cardiovascular and cerebrovascular events) was a composite of all-cause death, myocardial infarction, any revascularization, and stroke. A total of 840 patients were included (206 in the FFR-guided group and 634 in the angiography-guided group). Median follow-up was 7 years (interquartile range, 3.22–11.08 years). After 1:1 propensity-score matching, baseline characteristics between the 2 groups were similar. All-cause death was significantly lower in the FFR-guided group compared with the angiography-guided group (94 [45.6%] versus 119 [57.8%]; hazard ratio [HR], 0.65 [95% CI, 0.49–0.85]; $P<0.01$). The rate of major adverse cardiovascular and cerebrovascular events was lower in the FFR-guided group (123 [59.7%] versus 139 [67.5%]; HR, 0.75 [95% CI, 0.59–0.95]; $P=0.02$).

CONCLUSIONS: In patients with reduced left ventricular ejection fraction, deferring revascularization of intermediate coronary stenoses based on FFR is associated with a lower incidence of death and major adverse cardiovascular and cerebrovascular events at 10 years.

Key Words: coronary angiography ■ coronary artery disease ■ fractional flow reserve, myocardial ■ myocardial infarction ■ myocardial revascularization

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Presented in part at the 82nd SIC National Congress 2021 in Rome, Italy, December 9 to 12, 2021, and published in abstract form (*Eur Heart J Suppl*. 2021;23[suppl_G]:suab140.025; https://doi.org/10.1093/eurheartj/suab140.025).

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026656

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is a retrospective study assessing whether fractional flow reserve (FFR) provides adjunctive clinical benefit compared with coronary angiography in deferring revascularization of patients with intermediate coronary stenoses and reduced left ventricular ejection fraction.
- We found that deferring revascularization based on angiography plus invasive functional assessment with FFR is associated with lower rate of death and major adverse cardiovascular and cerebrovascular events at 10 years of follow-up, compared with angiographic assessment.
- When the end points between the FFR-guided versus the angiography-guided group were compared in relation to the left ventricular ejection fraction continuum, the benefit of deferring revascularization based on FFR is clearly more pronounced when the ejection fraction is >25%, whereas under this value, the benefit of FFR tends to decrease.

What Are the Clinical Implications?

- In patients with reduced left ventricular ejection fraction, an undetected functionally significant stenosis might compromise the potential recruitment of hibernated segments.
- Moreover, a selective revascularization strategy limited only to those target vessels/patients with hemodynamically significant stenoses might avoid exposing patients with reduced left ventricular ejection fraction, who are generally more fragile and affected by comorbidities, to the excessive risk potentially associated with extensive (surgical or percutaneous) interventions.
- In these patients, an FFR-guided strategy of deferring revascularization, compared with coronary angiography alone, is associated with a lower rate of end points most likely because it does not leave behind undisclosed hemodynamically significant stenoses; however, larger perspective studies are needed to confirm these results.

Nonstandard Abbreviations and Acronyms

FFR	fractional flow reserve
IPTW	inverse probability of treatment weighting
MACCE	major adverse cardiovascular and cerebrovascular event

The most common cause of heart failure is ischemic cardiomyopathy, and the presence of more extensive underlying coronary artery disease is associated with shorter survival.[1,2] Coronary revascularization of patients with heart failure is likely to result in significant clinical benefit. The STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that surgical revascularization on top of medical therapy in patients with heart failure and severely reduced left ventricular ejection fraction (LVEF) improved long-term survival.[3,4] Thus, revascularizing or deferring intermediate coronary stenoses potentially associated with reversible myocardial ischemia might prove to be clinically impactful, particularly in patients with more compromised left ventricular function. This concept is supported by a subanalysis of the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), where patients with left ventricular dysfunction assigned to an initial invasive strategy had better outcomes when compared with a conservative strategy.[5]

Fractional flow reserve (FFR) invasively assesses the hemodynamic significance (a surrogate of the ischemic burden) of coronary stenoses; FFR to guide revascularization of intermediate lesions in patients with preserved LVEF is associated with improved clinical outcomes compared with angiographic guidance alone.[6–8] However, data on the impact of FFR in patients with heart failure are still limited. FFR has shown to be an effective tool in detecting hemodynamically significant coronary stenosis even in case of elevated filling pressures,[9,10] and performing revascularization based on FFR guidance has been associated with better outcomes compared with angiographic guidance.[11] Yet, the role of FFR in deferring revascularization of patients with reduced LVEF has never been investigated.

In the present study, we aimed to compare long-term clinical outcomes after deferring revascularization in patients with reduced LVEF based on either angiography or FFR.

METHODS

Study Population

Between 2002 and 2010, consecutive patients undergoing coronary angiography for chronic coronary syndrome were included if LVEF was ≤50% and at least 1 intermediate stenosis by visual estimation (diameter stenosis ≥40%) was present.[12,13] Then, we selected patients in whom the revascularization was deferred on the basis of either FFR or angiography. Patients who underwent any revascularization at the time of the baseline angiography or in whom a revascularization was planned on the basis of the index examination were excluded. Likewise, patients presenting with acute coronary syndromes or with concomitant severe

valvular disease requiring either surgical or percutaneous intervention were excluded. Patients with a history of heart transplantation or active neoplasia were also excluded. Lesions located in secondary or distal branches were considered as exclusion criteria.

Left ventricular ejection fraction was assessed by angiography using the Simpson method with automatic edge detection and manual correction. This latter method is standard of care in our center, being systematically performed during coronary angiograms and left-right heart catheterization. A value of ejection fraction (EF) >50% calculated from the mean between 2 orthogonal projections is considered as normal. Coronary angiography was performed with 6F diagnostic catheters. After the administration of 0.2 mg 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. FFR was measured after coronary angiography with a commercially available pressure wire, as previously described.[14] After the administration of intracoronary nitrates, the pressure wire was positioned in the distal part of the coronary to be evaluated. Maximum hyperemia was induced by intravenous infusion of adenosine (140–180 μg/kg per minute) via the forearm or femoral vein, or by an intracoronary injection of adenosine (100–200 μg).

Clinical Outcomes

Clinical outcomes were defined according to the uniform definitions for cardiovascular and stroke outcomes developed by the Standardized Data Collection for Cardiovascular Trials Initiative and the US Food and Drug Administration.[15] The primary end point of our study was death from any cause up to 10 years, with the date of death retrieved from the Belgian national death registry. The secondary end point of major adverse cardiovascular and cerebrovascular events (MACCE) at 10 years was defined as a composite of all-cause death, myocardial infarction (MI), any revascularization, and stroke. Any revascularization performed within 3 months from the diagnostic coronary angiogram was considered staged and therefore referred to the index procedure only if it was clearly declared at the initial treatment strategy. Informed consent, as approved by the local Ethics Committee to the use of personal data, was obtained from each patient. The investigation conforms with the principles outlined in the Declaration of Helsinki. The authors declare that all supporting data are available within the article and its supplemental files.

Statistical Analysis

Baseline characteristics are presented as numbers (percentages) for categorical variables and as means±SDs for continuous variables. Differences between groups were analyzed using the Student *t*-test or the Mann-Whitney U-test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables, as appropriate. Standardized mean difference and propensity score matching were used to reduce selection bias associated with potential confounding covariates in the observational study, and to adjust for significant differences in the patients' baseline characteristics. The propensity score was computed by a logistic regression model, and the matching was performed using the nearest neighbor method with a 1:1 ratio. Matching criteria were age, sex, smoking habits, peripheral artery disease, diabetes, hypertension, dyslipidemia, atrial fibrillation, LVEF, history of previous percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), and number of diseased vessels. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. Cox proportional hazards regression models were fit for each outcome, and results are presented as hazard ratio (HR) (95% CI) and *P* value. Models were fit for both unmatched and matched cohort. Additional adjustments were made with weighted Cox proportional hazard regression models with inverse probability of treatment weighting (IPTW). Predicted probability of death across continuous EF values was calculated on the basis of the Cox proportional hazard regression model, where the covariate LVEF was included as restricted cubic spline in a cubic polynomial regression model. Analyses were performed with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

RESULTS

Clinical and Procedural Characteristics

Consecutive patients (n=4577) with reduced LVEF (≤50%) undergoing coronary angiography between 2002 and 2010 were screened. We eventually included patients with at least 1 intermediate coronary stenosis (diameter stenosis ≥40%) in whom revascularization was deferred on the basis of either angiography plus FFR (FFR guided; n=206) or angiography alone (angiography guided; n=634). Patients in the angiography-guided group were older (70.65±9.14 versus 67.14±10.53 years; $P<0.001$), with higher prevalence of diabetes (205 [32.3%] versus 50 [24.3%]; $P=0.029$), previous CABG (288 [45.4%] versus 25 [12.1%]; $P<0.001$), and multivessel disease (438 [69.1%] versus 113 [54.9%]; $P<0.001$), and lower LVEF (36.5±10.1% versus 40.0±9.1%; $P<0.001$).

From the angiography-guided group, 206 patients were matched in a 1:1 ratio with those of the FFR-guided group. No differences were observed across baseline characteristics of the matched population

Table 1. Baseline Characteristics in the Matched Cohort

Characteristic	Angiography-guided group (N=206)	FFR-guided group (N=206)	Total (N=412)	*P* value
Age, y	67.95±10.4	67.14±10.5	67.54±10.4	0.430
Male sex	167 (81.1)	166 (80.6)	333 (80.8)	0.900
Smoking	115 (55.8)	109 (52.9)	224 (54.4)	0.553
PAD	28 (13.6)	28 (13.6)	56 (13.6)	1.000
Diabetes	43 (20.9)	50 (24.3)	93 (22.6)	0.409
IDDM	6 (2.9)	7 (3.4)	13 (3.2)	0.778
Hypertension	131 (63.6)	127 (61.7)	258 (62.6)	0.684
Dyslipidemia	127 (61.7)	136 (66.0)	263 (63.8)	0.356
AF	32 (15.5)	36 (17.5)	68 (16.5)	0.596
Previous PCI	65 (31.6)	72 (35.0)	137 (33.3)	0.464
Previous CABG	22 (10.7)	25 (12.1)	47 (11.4)	0.642
ICD	33 (16.0)	31 (15.0)	64 (15.5)	0.786
GFR, mL/min				0.160
>60	152 (73.7)	139 (67.5)	291 (70.6)	
<60	54 (26.3)	67 (32.5)	121 (29.4)	
LVEF, %	39.48±9.12	40.04±9.09	39.76±9.10	0.532
LVEF strata, %				0.767
>45	75 (36.4)	82 (39.8)	157 (38.1)	
35–45	79 (38.3)	76 (36.9)	155 (37.6)	
≤35	52 (25.2)	48 (23.3)	100 (24.3)	
No. of diseased vessels				0.922
1	97 (47.1)	93 (45.1)	190 (46.1)	
2	67 (32.5)	70 (34.0)	137 (33.3)	
3	42 (20.4)	43 (20.9)	85 (20.6)	
LVEDVI, mL/m^2	109.89±41.92	105.22±34.87	107.56±38.59	0.221
LVESVI, mL/m^2	67.53±34.11	63.94±27.18	65.74±30.87	0.240
LVESP, mm Hg	138.73±28.01	137.42±26.47	138.08±27.24	0.633
LVEDP, mm Hg	18.11±7.70	18.18±7.70	18.14±7.69	0.930
Stenosis location				
LM	4 (1.9)	2 (1.0)	6 (1.5)	0.411
LAD	144 (69.9)	177 (85.9)	321 (77.9)	<0.001
LCX	103 (50.2)	119 (57.8)	222 (54.0)	0.126
RCA	138 (67.0)	131 (63.6)	269 (65.3)	0.469
FFR				<0.001*
LAD	NA	0.86 (0.05)	0.86 (0.05)	
LCX	NA	0.90 (0.06)	0.90 (0.06)	
RCA	NA	0.92 (0.05)	0.92 (0.05)	
%DS LAD				0.063
40–70	100 (69.4)	139 (78.5)	239 (74.5)	
>70	44 (30.6)	38 (21.5)	82 (25.5)	
%DS LCX				0.051
40–70	67 (65.7)	90 (77.6)	157 (72.0)	
>70	35 (34.3)	26 (22.4)	61 (28.0)	
%DS RCA				0.050
40–70	72 (54.5)	87 (66.4)	159 (60.5)	
>70	60 (45.5)	44 (33.6)	104 (39.5)	

Data are presented as mean±SD or number (percentage). AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; DS, diameter stenosis; FFR, fractional flow reserve; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IDDM, insulin dependent diabetes mellitus; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESP, left ventricular end-systolic pressure; LVESVI, left ventricular end-systolic volume indexed; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

**P* value within FFR-guided group.

(Table 1). Mean LVEF in the overall matched cohort was 39.76±9.10% without differences between the 2 groups. Left ventricular end-diastolic and end-systolic volumes and pressures were similar between the 2 groups. In the FFR-guided group, left anterior descending artery was more frequently stenotic than in the angiography-guided group. Percentage diameter stenosis assessed by visual estimation was similar in both groups. Median follow-up in the overall population was 7.05 years (interquartile range, 3.22–11.08 years). Details of the propensity score matching are reported in Figures S1 and S2. Baseline characteristics of the unmatched cohort are in Table S1.

Clinical Outcomes in the Matched Population

The design and the main results of the study are summarized in the Graphical Abstract. Outcome rates and survival curves in the matched cohort are presented in Table 2 and Figure 1.

At 10 years, the rate of death was significantly lower in the FFR-guided group compared with the angiography-guided group (94 [45.6%] versus 119 [57.8%]; HR, 0.65 [95% CI, 0.49–0.85]; *P*<0.01) (Figure 1A). Likewise, the risk of MACCE was significantly lower in the FFR-guided group (123 [59.7%] versus 139 [67.5%]; HR, 0.75 [95% CI, 0.59–0.95]; *P*=0.02) (Figure 1B). No significant differences were observed between the 2 groups in terms of stroke (4 [1.9%] versus 10 [4.8%]; HR, 0.34 [95% CI, 0.11–1.08]; *P*=0.07) (Figure 1C), any revascularization (39 [18.9%] versus 28 [13.6%]; HR, 1.20 [95% CI, 0.74–1.95]; *P*=0.46) (Figure 1D), and MI (9 [4.4%] for both groups; HR, 0.85 [95% CI, 0.34–2.16]; *P*=0.74) (Figure S3A). HRs of the unmatched and matched cohort are presented in Figure 2. One-year landmark analysis performed in the matched cohort showed that the statistically significant difference in death and MACCEs was present up to 1 year and beyond 1 year (Figure 3).

Clinical Outcomes in the Overall Population

In the overall population of 840 patients, clinical outcomes were compared between the 2 groups as crude data and after IPTW adjustment. At 10 years of follow-up, death occurred in 510 (60.7%) patients, 94 (45.6%) from the FFR-guided group and 416 (65.6%) from the angiography-guided group (HR, 0.55 [95% CI, 0.44–0.69]; *P*<0.001). The incidence of MACCEs was lower in the FFR-guided group (123 [59.7%] versus 479 [75.5%]; HR, 0.64 [95% CI, 0.52–0.78]; *P*<0.001). Cox regression model adjusted for IPTW confirmed the advantage of the FFR-guided over the angiography-guided strategy: that is, the incidence of death (HR, 0.75 [95% CI, 0.58–0.97]; *P*=0.02) and MACCEs (HR, 0.78 [95% CI, 0.62–0.98]; *P*=0.03) was lower in the FFR-guided group. The incidence of MI, similar between the 2 groups in the unadjusted analysis, was lower in the FFR-guided group when the HR was corrected for the IPTW (9 [4.4%] versus 40 [6.3%]; unadjusted HR, 0.57 [95% CI, 0.28–0.18]; *P*=0.1; adjusted HR, 0.43 [95% CI, 0.19–0.95]; *P*=0.04). The rate of revascularization was similar between the 2 groups in both unadjusted and adjusted analysis (39 [18.9%] versus 92 [14.5%]; adjusted HR, 0.96 [95% CI, 0.63–1.46]; *P*=0.96). The lower incidence of stroke in the FFR-guided group turned out to be nonsignificant when the HR was corrected for IPTW (4 [1.9%] versus 32 [5.0%]; unadjusted HR, 0.31 [95% CI, 0.11–0.87]; *P*=0.03; adjusted HR, 0.44 [95% CI, 0.14–1.30]; *P*=0.06). The rates of clinical end points in the overall population are summarized in Table S2, whereas the unadjusted HRs are reported in Figure 2. Kaplan-Meier curves of the overall populations are reported in Figure S4.

Clinical Outcomes According to LVEF

The impact of deferring revascularization based on FFR was assessed as continuum of LVEF. Interestingly, when an FFR-guided strategy was compared with an angiography-guided strategy by using LVEF as continuous variable, the FFR-guided group showed lower probability of death, especially for LVEF higher (Figure 4), whereas for lower values, the impact of an FFR-based strategy seemed to be neglectable. This was supported by the regression analysis performed in the LVEF subgroups (≥45%, 35%–45%, and <35%). An FFR-based strategy of deferral revascularization was shown to be a predictor of lower probability

Table 2. Clinical Outcomes in the Matched Cohort

Outcome	No. (%) of events		HR (95% CI)	*P* value
	Angiographically-guided group (N=206)	FFR-guided group (N=206)		
Death	119 (57.8)	94 (45.6)	0.65 (0.49–0.85)	0.002
MACCEs	139 (67.5)	123 (59.7)	0.75 (0.58–0.95)	0.02
MI	9 (4.4)	9 (4.4)	0.85 (0.34–2.16)	0.74
Any revascularization	28 (13.6)	39 (18.9)	1.19 (0.75–1.95)	0.46
Stroke	10 (4.8)	4 (1.9)	0.34 (0.11–1.08)	0.07

FFR indicates fractional flow reserve; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; and MI, myocardial infarction.

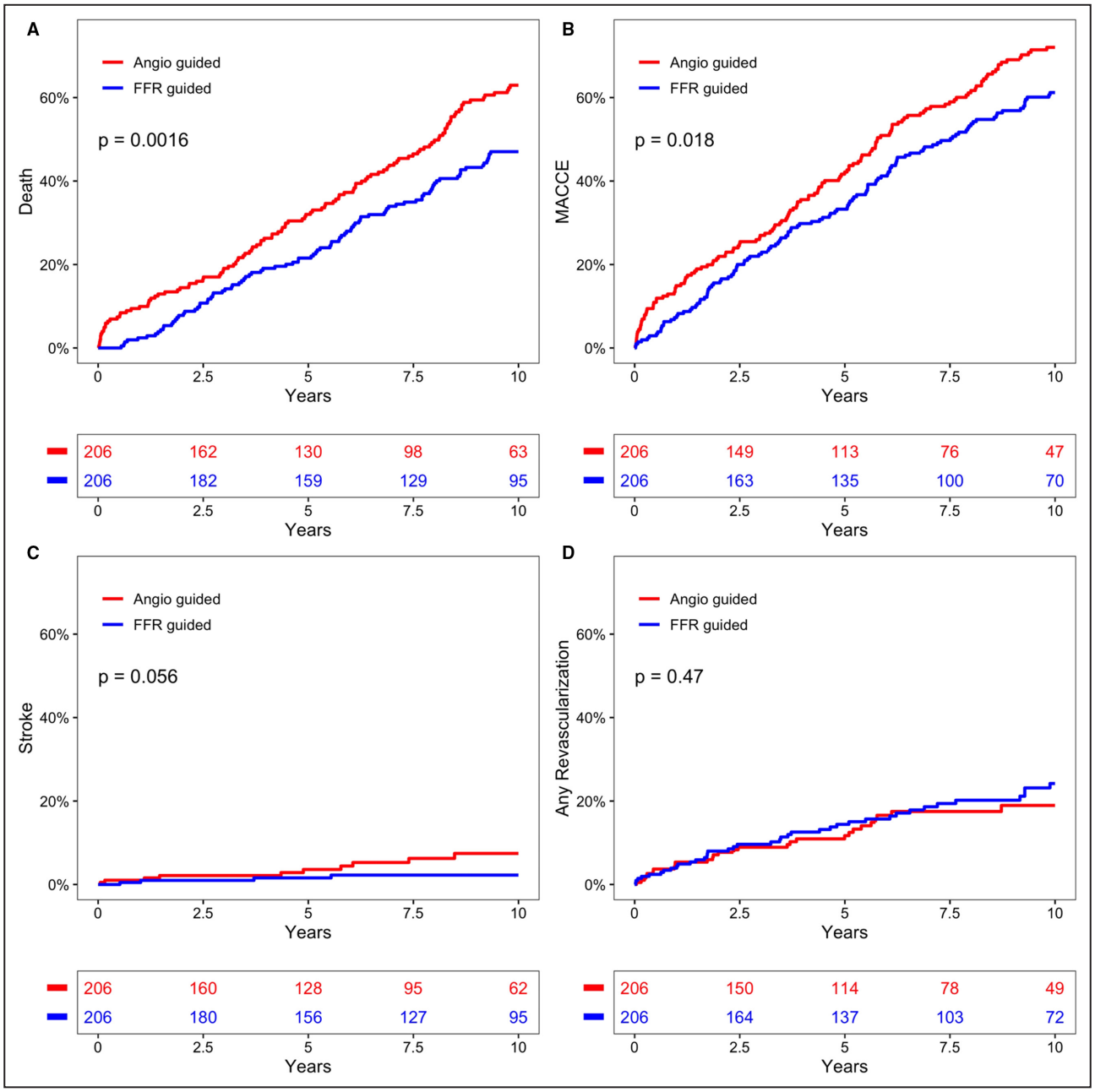

Figure 1. Kaplan-Meier event curves for clinical outcomes in the matched cohort.
All-cause death (**A**); major adverse cardiovascular and cerebrovascular events (MACCEs) (**B**); stroke (**C**); and any revascularization (**D**). Angio indicates angiography; and FFR, fractional flow reserve.

of death for LVEF values ≥35% (coefficient, −0.133 [*P*<0.001] for LVEF ≥45%; coefficient, −0.139 [*P*=0.006] for LVEF 35%–45%), whereas the benefit of FFR in terms of death was neglectable when LVEF was <35% (*P*=0.461) (Table S3).

DISCUSSION

The main results of our retrospective study are as follows: (1) the rate of death and MACCEs up to 10 years of follow-up was significantly lower in the FFR-guided group; (2) the difference in rates of MI, stroke, and revascularization between the 2 groups was not statistically significant; and (3) the advantage of FFR over conventional angiographic guidance in deferring revascularization is higher when LVEF is >35%.

In patients with preserved LVEF, the DEFER trial demonstrated that deferring revascularization of angiographically severe but functionally nonsignificant stenoses is safe up to 15 years of follow-up.[16] Moreover, a

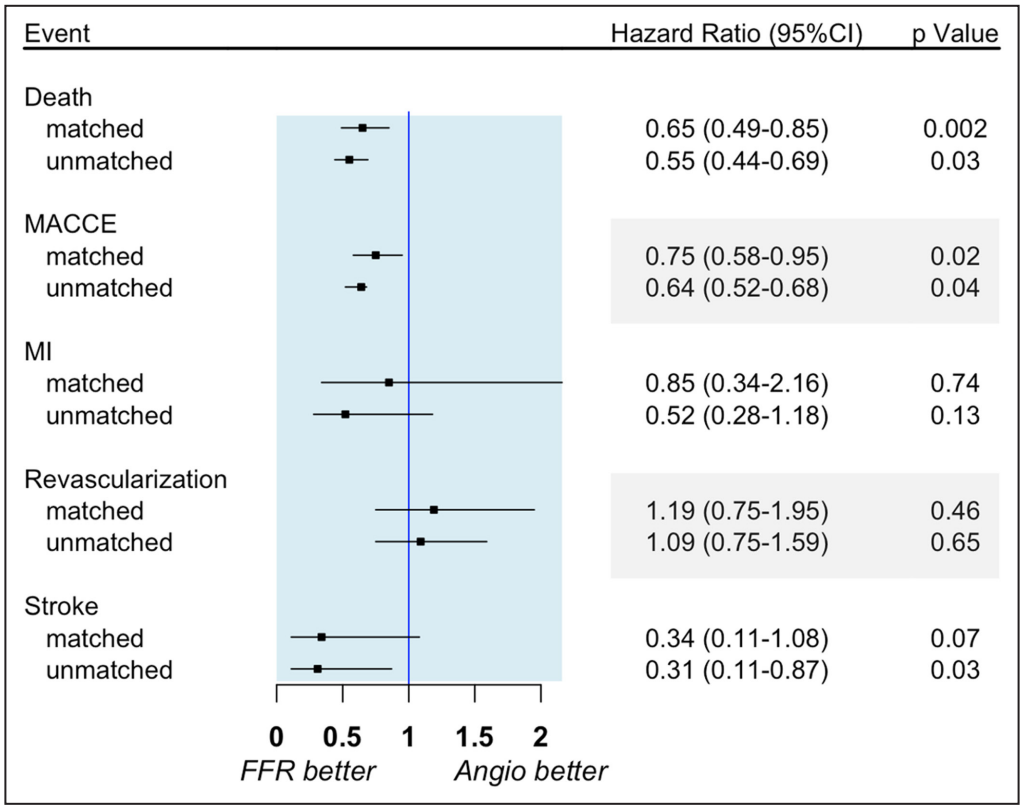

Figure 2. Clinical end points after deferring revascularization in the matched and unmatched populations.
Angio indicates angiography; FFR, fractional flow reserve; MACCE, major adverse cardiovascular and cerebrovascular event; and MI, myocardial infarction.

subanalysis of the FAME2 (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) trial has shown that patients with intermediate coronary stenoses but FFR <0.80 had worse outcomes compared with patients with angiographically severe but functionally nonsignificant stenoses, thus demonstrating that functional severity by FFR overrules angiographic severity in predicting the natural history of stable coronary artery disease (CAD).[13]

In patients with reduced LVEF, deferring revascularization of underlying CAD is challenging, given the demonstrated benefit of revascularization over medical treatment alone in this clinical setting (especially for CABG, given the lack of evidence about the benefit of PCI in these patients).[17] A meta-analysis of 16 191 patients with reduced EF (<40%) showed a reduction in mortality when either CABG or PCI was compared with medical therapy (CABG: HR, 0.66 [95% CI, 0.61–0.72]; *P*<0.001; PCI: HR, 0.73 [95% CI, 0.62–0.85]; *P*<0.001).[18] The BARI2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) Trial found no differences in terms of death and major cardiovascular events among patients with type 2 diabetes and CAD randomized to either prompt revascularization (PCI or CABG) or medical therapy.[19] However, in patients with LVEF <50% and extensive CAD, CABG significantly reduced the rate of death, MI, or stroke at 5 years.[20] In the STICH trial, CABG compared with medical therapy was associated with a lower rate of death at 10 years in patients with severely reduced EF (<35%)[4]; however, the absence or presence of myocardial viability was not associated with any beneficial effect of CABG over medical therapy, thus suggesting the potential limitation of noninvasive functional testing in the clinical decision making of these patients.[21]

In our study, we demonstrated that deferring revascularization on the basis of invasive physiologic assessment in patients with reduced LVEF is not just safe, but it is also significantly associated with lower incidence of death and MACCEs. There are several pathophysiologic reasons that might explain these findings. First, FFR is superior to angiography in detecting hemodynamically significant stenosis (eg, it has been shown that ≈17% of patients with nonangiographically severe coronary lesions [<50% diameter stenosis] have abnormal FFR).[22] Second, when myocardial ischemia is the underlying mechanism of wall motion abnormalities, deferring revascularization of an undetected

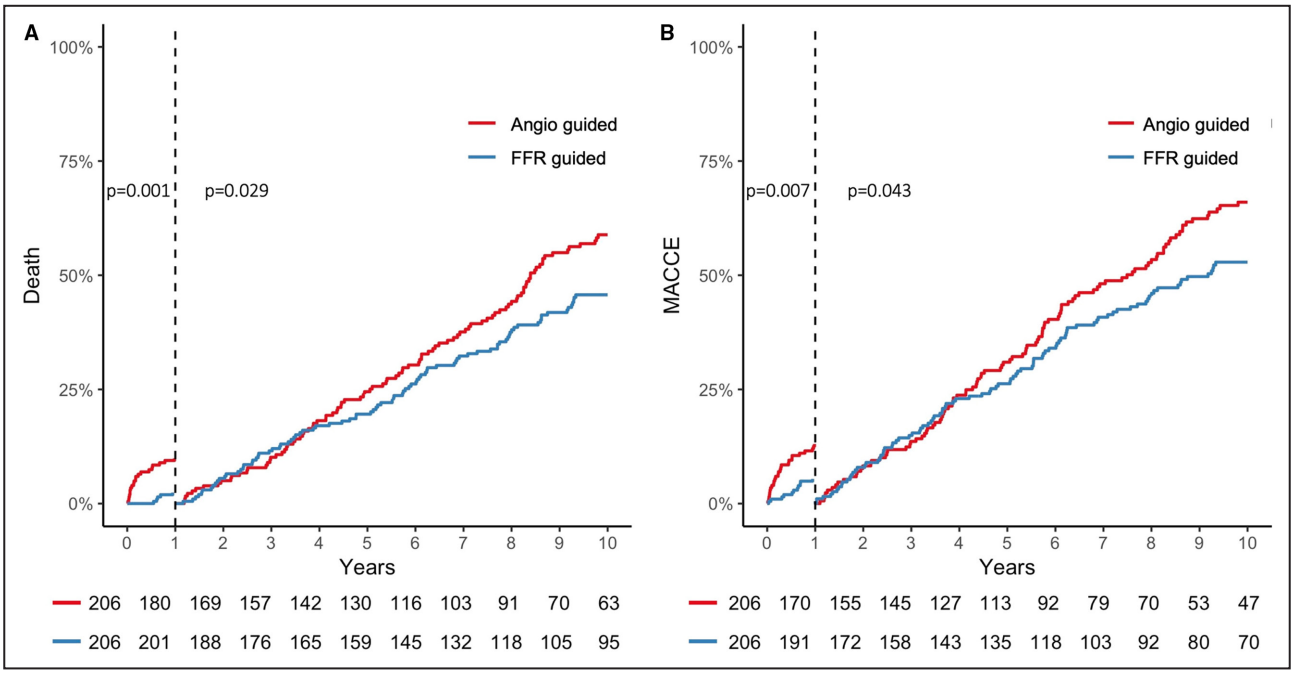

Figure 3. Landmark analysis before and after 1-year time point for cumulative incidence of death (A) and major adverse cardiovascular and cerebrovascular events (MACCEs) (B).
Angio indicates angiography; and FFR, fractional flow reserve.

functionally significant stenosis might compromise the potential recruitment of hibernated segments.[23,24] Our results suggest that in patients with reduced EF and CAD, deferring revascularization based on FFR is safe and effective in ruling out functionally significant intermediate coronary stenoses. Recent insights from the ISCHEMIA showed that patients with a history of left ventricular dysfunction treated with an initial invasive strategy had better event-free survival compared with those treated conservatively.[5] These results suggest that a more aggressive strategy in patients with reduced EF may provide incremental benefit, because CAD is the only therapeutic target to improve cardiac reserve. In addition, our results complement those of the ISCHEMIA[5,25] (ie, even when deferring the revascularization of an intermediate stenosis in patients with reduced EF, invasive physiologic assessment, in addition to coronary angiography, provides incremental benefits in terms of survival and major adverse events).

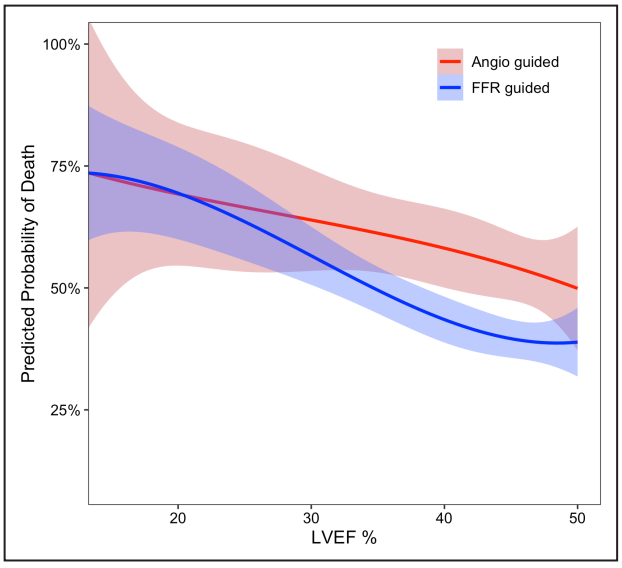

Figure 4. Predicted probability of death per group in the matched cohort, according to the left ventricular ejection fraction (LVEF), presented as a continuous variable.
Angio indicates angiography; and FFR, fractional flow reserve.

When the end points between the FFR-guided versus the angiography-guided group were compared in relation to the LVEF continuum, the benefit of deferring revascularization based on FFR is clearly more pronounced when the EF is >35%, whereas under this value, the benefit of FFR tends to decrease. The latter can be explained by the fact that the clinical impact of deferring intermediate coronary stenoses is likely to be limited with more dysfunctional left ventricular myocardium.

The difference in terms of MI rates between the 2 matched populations was not significant, whereas in the overall population, we observed a lower incidence of MI in the FFR group after IPTW correction. Although a risk of underreporting for this end point cannot be excluded, the explanation of this trend can be that FFR is a better predictor of outcomes compared with conventional angiography. A complete functional evaluation of the atherosclerotic burden (known as "global FFR" [ie, the sum of FFR in all the 3

vessels]) has shown to predict the incidence of MACE (Major Adverse Cardiovascular Events) and MI better than a global angiographic evaluation of the atherosclerotic burden.[26]

The risk of ischemic stroke in patients with chronic heart failure is 2 to 3 times higher than in patients without.[27] Herein, the most frequently recognized cause of stroke is thrombus formation, secondary to atrial fibrillation and/or left ventricular dysfunction. In 2 large studies, the risk of stroke was inversely related to EF, especially for values <25%.[28] In our study, we observed, in the angiography-guided group, a significantly higher incidence of stroke, but only in the unmatched population. This finding might be related to differences in baseline clinical characteristics between the 2 groups, with the angiography-guided group having a significantly lower ejection fraction and higher ventricular volumes.

Our study may have important clinical implications. Available data and guideline recommendations support extensive revascularization in patients with reduced ejection fraction and associated severe coronary artery disease.[29] Yet, a selective revascularization strategy limited only to those target vessels/patients with hemodynamically significant stenoses might avoid exposing these patients, who are generally more fragile and affected by comorbidities, to the excessive risk potentially associated with extensive (surgical or percutaneous) interventions. Our findings support the safety of deferring revascularization on hemodynamic grounds by FFR compared with angiographic guidance alone. We can speculate, in fact, that the lower rate of end points observed in the FFR-guided group was most likely the consequence of a selective revascularization strategy that did not leave behind undisclosed hemodynamically significant stenoses compared with the angiography-guided group.

Limitations

This is a retrospective observational study. Although we tried to reduce selection bias by using propensity score matching and IPTW, we cannot exclude potential confounders deriving from patients' or operators' decisions. Because of the retrospective study design, end points (eg, cardiac death and target vessel revascularization) subject to underreporting were not included in our analysis.

Although it would have been interesting to assess clinical outcomes also in patients with reduced LVEF and FFR <0.80, we do not dispose of such a cohort because these patients are routinely revascularized in our center.

Other elements related to coronary anatomy and/or atherosclerotic burden (such as vessel tortuosity, calcification, and synergy between PCI with taxus and cardiac surgery score) have not been taken into account in our study. Coronary stenosis severity by visual estimation was not assessed by an independent core laboratory. Yet, visually estimated stenosis severity has been demonstrated to predict physiologic significance of coronary lesions better than quantitative coronary angiography.[30]

CONCLUSIONS

In patients with reduced LVEF and CAD, deferring revascularization based on angiography plus invasive functional assessment with FFR is associated with lower rate of death and MACCEs at 10 years of follow-up, compared with angiographic assessment. The advantage is greater for higher values of LVEF, whereas it tends to be neglectable when the EF is severely reduced. Larger prospective studies are necessary to confirm these findings.

ARTICLE INFORMATION

Received May 9, 2022; accepted August 18, 2022.

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Sources of Funding

Drs Paolisso, Di Gioia, Esposito, Fabbricatore, and Berolone are supported by a research grant from the CardioPaTh PhD Program. Dr Di Gioia is financially supported by UniNAand Compagnia di San Paolo in the frame of program Sostegno Territoriale alle Attività di Ricerca. Dr Collet reports receiving research grants from Biosensor, Coroventis Research, GE Healthcare, Medis Medical Imaging, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc, and Abbott Vascular; and consultancy fees from HeartFlow Inc, Opsens, Pie Medical Imaging, Abbott Vascular, and Philips Volcano. Dr De Bruyne has a consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, and Coroventis Research; receives research grants from Abbott Vascular, Coroventis Research, Cathworks, and Boston Scientific; and holds minor equities in Philips Volcano, Siemens, GE Healthcare, Edwards Life Sciences, HeartFlow, Opsens, and Celiad. Dr Barbato declares speaker's fees from Abbott Vascular, Boston Scientific, and GE.

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of the unmatched groups

	Angio-guided (N = 634)	FFR-guided (N = 206)	Total (N = 840)	p value
Age (y)	70.65 (9.14)	67.14 (10.53)	69.79 (9.61)	< 0.001
Sex Male	511 (80.6%)	166 (80.6%)	677 (80.6%)	0.996
Smoking	343 (54.1%)	109 (52.9%)	452 (53.8%)	0.766
PAD	103 (16.2%)	28 (13.6%)	131 (15.6%)	0.362
Diabetes	205 (32.3%)	50 (24.3%)	255 (30.4%)	0.029
IDDM	48 (7.6%)	7 (3.4%)	55 (6.5%)	0.035
Hypertension	432 (68.1%)	127 (61.7%)	559 (66.5%)	0.086
Dyslipidemia	440 (69.4%)	136 (66.0%)	576 (68.6%)	0.364
LVEF (%)	36.47 (10.12)	40.04 (9.09)	37.35 (9.99)	< 0.001
AF	76 (12.0%)	36 (17.5%)	112 (13.3%)	0.044
Previous PCI	178 (28.1%)	72 (35.0%)	250 (29.8%)	0.061
Previous CABG	288 (45.4%)	25 (12.1%)	313 (37.3%)	< 0.001
ICD	148 (23.3%)	31 (15.0%)	179 (21.3%)	0.012
EF				< 0.001
>45%	175 (27.6%)	82 (39.8%)	257 (30.6%)	
35-45 %	207 (32.6%)	76 (36.9%)	283 (33.7%)	
≤35%	252 (39.7%)	48 (23.3%)	300 (35.7%)	
N. of vessel disease				< 0.001
- 1	196 (30.9%)	93 (45.1%)	289 (34.4%)	
- 2	200 (31.5%)	70 (34.0%)	270 (32.1%)	
- 3	212 (33.4%)	43 (20.9%)	255 (30.4%)	
- 4	26 (4.1%)	0 (0.0%)	26 (3.1%)	
LVEDVI (mL/m^2)	120.12 (74.61)	105.22 (34.87)	116.47 (67.38)	0.006
LVESVI (mL/m^2)	77.12 (42.12)	63.94 (27.18)	73.90 (39.40)	< 0.001
LVESP (mmHg)	138.99 (27.78)	137.42 (26.47)	138.61 (27.46)	0.485
LVEDP (mmHg)	18.85 (8.14)	18.18 (7.70)	18.69 (8.03)	0.302
Stenosis Location				
LM	78 (12.3%)	2 (1.0%)	80 (9.5%)	< 0.001
LAD	479 (75.6%)	177 (85.9%)	656 (78.1%)	0.002
LCX	392 (62.1%)	119 (57.8%)	511 (61.1%)	0.266
RCA	471 (74.3%)	131 (63.6%)	602 (71.7%)	0.003
FFR				NA
LAD	NA	0.86 (0.05)	0.86 (0.05)	
LCX	NA	0.90 (0.06)	0.90 (0.06)	
RCA	NA	0.92 (0.05)	0.92 (0.05)	
DS LAD				<0.001
40-70%	193 (40.5)	139 (78.5)	332 (50.8%)	
>70%	284 (59.5)	38 (21.5)	322 (49.2%)	
DS LCX				<0.001
40-70%	174 (44.3)	90 (77.6)	264 (51.9)	
>70%	219 (55.7)	26 (22.4)	245 (48.1)	
DS RCA				<0.001
40-70%	142 (30.2)	87 (66.4)	229 (38.1)	
>70%	328 (69.8)	44 (33.6)	372 (61.9)	

Data are presented as mean ±SD or n (%). PAD = Peripheral artery disease; IDDM = Insulin Dependent Diabetes Mellitus; LVEF = Left Ventricular Ejection Fraction; AF = Atrial Fibrillation; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; ICD = Implantable Cardioverter Defibrillator; EF = Ejection Fraction; LVEDVI = Left Ventricular End-Diastolic Volume Indexed; LVEDSI = Left Ventricular End-Systolic Volume Indexed; LVESP = Left Ventricular End-Systolic Pressure; LVEDP = Left Ventricular End-Diastolic Pressure; LM = Left Main; LAD = Left Anterior Descending Artery; LCX = Left Circumflex Artery; RCA = Right Coronary Artery; FFR = Fractional Flow Reserve; DS = Diameter Stenosis (%).

Table S2. Event rate and Hazard Ratios in the overall population

Outcome	Unmatched Cohort (N = 840)					
	N. of events (%)		uHR (95% CI)	p	aHR (95%CI)	p
	Angio (N = 634)	FFR (N = 206)				
Death	416 (65.6)	94 (45.6)	0.55 (0.44-0.69)	<0.001	0.75 (0.58-0.98)	0.03
MACCE	479 (75.5)	123 (59.7)	0.64 (0.52-0.68)	<0.001	0.78 (0.62-0.98)	0.04
MI	40 (6.3)	9 (4.4)	0.52 (0.28-1.18)	0.13	0.43 (0.19-0.95)	0.04
Any Revascularization	92 (14.5)	39 (18.9)	1.09 (0.75-1.59)	0.65	0.96 (0.63-1.46)	0.85
Stroke	32 (5.0)	4 (1.9)	0.31 (0.11-0.87)	0.03	0.44 (0.14-1.30)	0.14

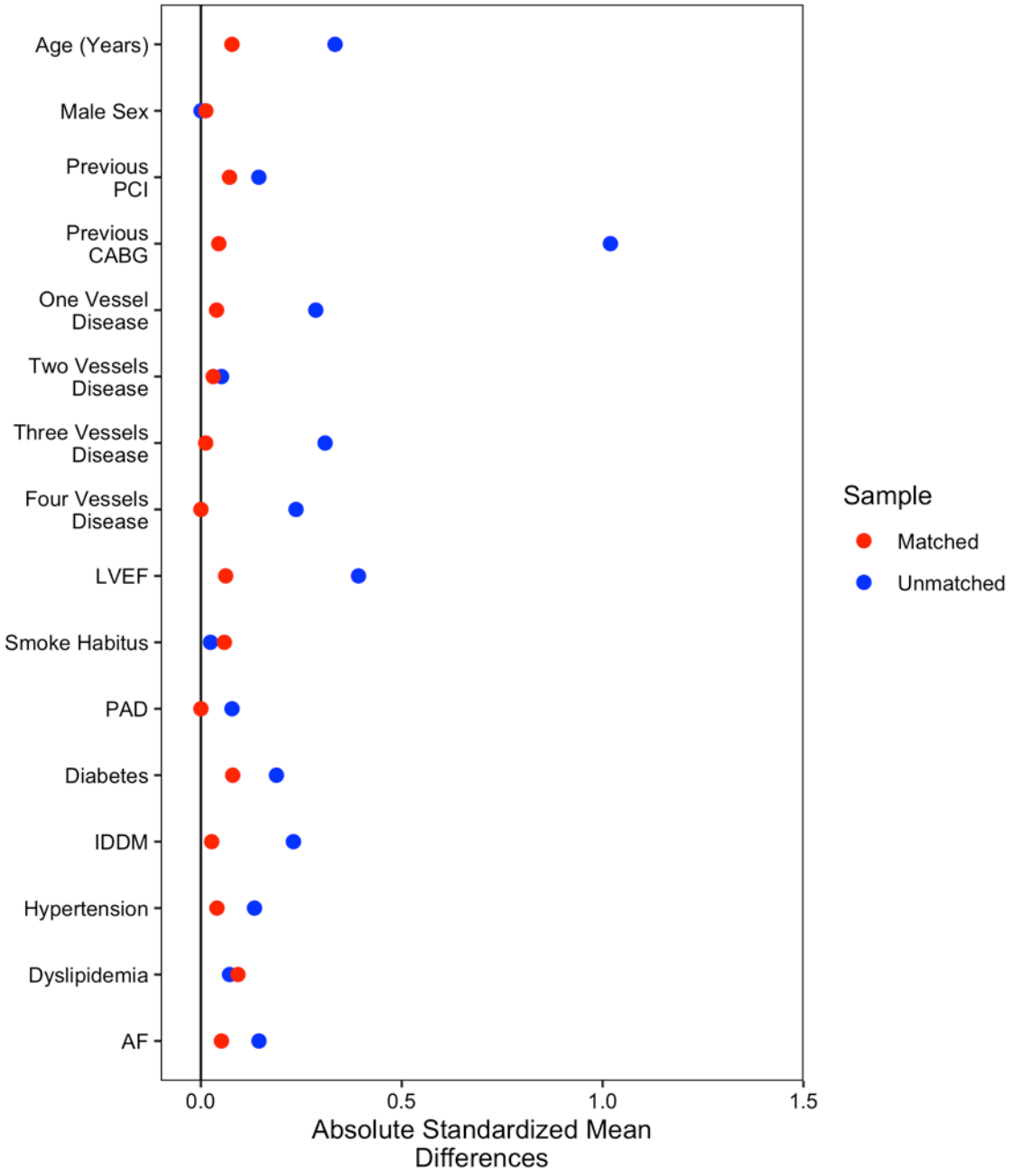
Hazard Ratios are presented as crude (unadjusted, uHR) and adjusted for the IPTW (aHR). FFR= Fractional Flow reserve-guided group; HR = Hazard Ratio; MACCE = Major Adverse Cardiovascular and Cerebrovascular Events; MI = Myocardial Infarction.

Table S3. Predicted probability of death according to FFR based strategy (by univariate analysis) for LVEF strata

	Coeff	Std Error	T value	P value	R sqr	F-stat
LVEF≥45%						
Intercept	0.529	0.276	19.18	<0.001	0.073	12.25
FFR	-0.133	0.038	-3.50	**<0.001**		
LVEF 35-45%						
Intercept	0.571	0.035	16.27	<0.01	0.312	7.74
FFR	-0.139	0.050	-2.783	**0.006**		
LVEF <35%						
Intercept	0.657	0.054	12.03	<0.01	0.005	0.548
FFR	-0.058	0.079	-0.74	0.461		

Coeff=β coefficient; Std Error: standard error; FFR: Fractional flow reserve based strategy; LVEF: Left Ventricular Ejection Fraction.

Figure S1. Love plot presenting absolute standardized mean differences before and after matching



PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; LVEF = Left Ventricular Ejection Fraction; PAD = Peripheral artery disease; IDDM = Insulin Dependent Diabetes Mellitus; AF = Atrial Fibrillation

Figure S2. Distribution of the propensity scores in the unmatched and matched cohort

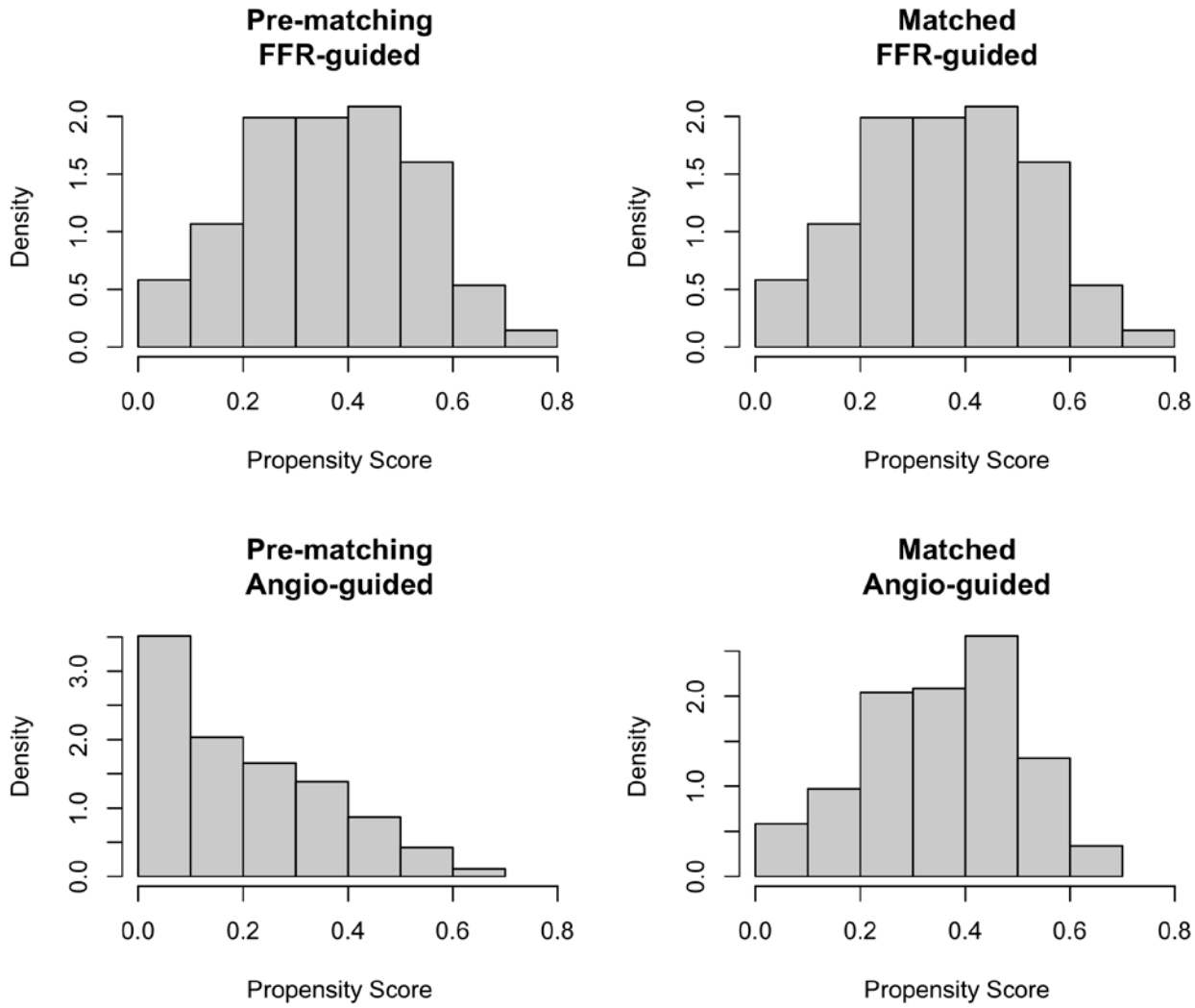
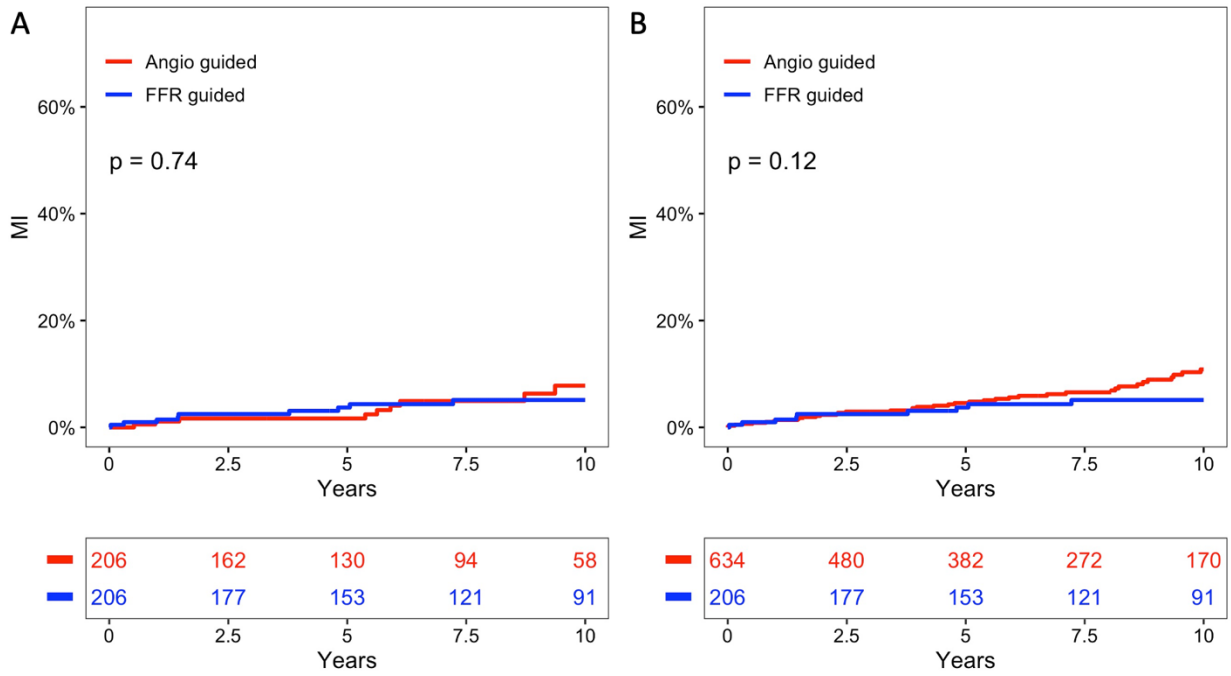


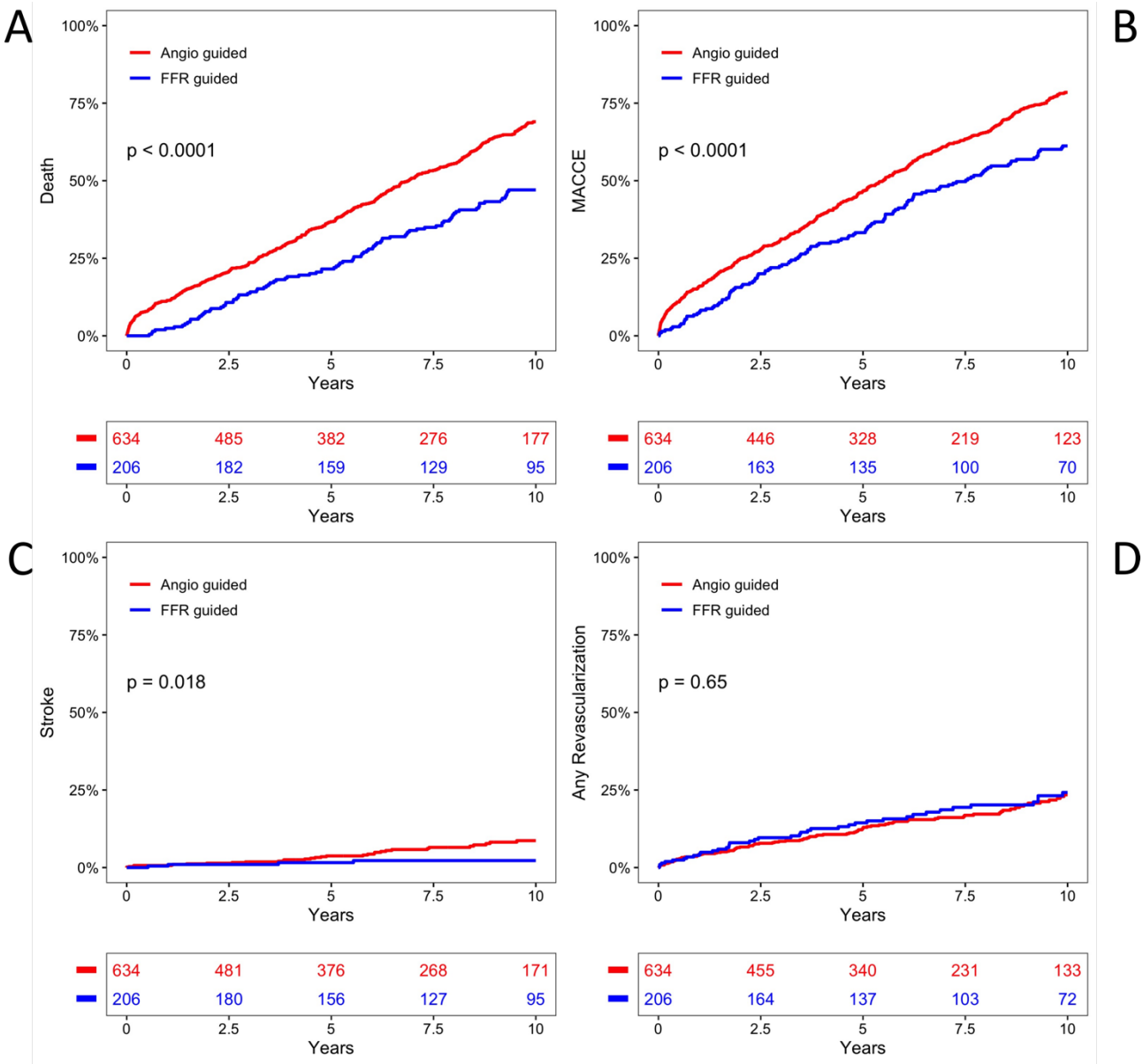
Figure S3. Kaplan–Meier events curves for Myocardial Infarction



(A) Matched cohort (B)overall population.

MI = Myocardial Infarction

Figure S4. Kaplan–Meier event curves for clinical outcomes in the overall population



(A) All-cause death; (B) Major Adverse Cardiovascular and Cerebrovascular Events; (C) Stroke; (D) Any revascularization.

MACCE= Major Adverse Cardiovascular and Cerebrovascular Events