Significance of Intermediate Values of Fractional Flow Reserve in Patients With Coronary Artery Disease

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Background—The fractional flow reserve (FFR) value of 0.75 has been validated against ischemic testing, whereas the FFR value of 0.80 has been widely accepted to guide clinical decision making. However, revascularization when FFR is 0.76 to 0.80, within the so-called gray zone, is still debatable.

Methods and Results—From February 1997 to June 2013, all patients with single-segment disease and an FFR value within the gray zone or within the 2 neighboring FFR strata (0.70–0.75 and 0.81–0.85) were included. Study end points consisted of major adverse cardiovascular events (death, myocardial infarction, and any revascularization) up to 5 years. Of 17 380 FFR measurements, 1459 patients were included. Of them, 449 patients were treated with revascularization and 1010 patients were treated with medical therapy. In the gray zone, the major adverse cardiovascular events rate was similar (37 [13.9%] versus 21 [11.2%], respectively; *P*=0.3) between medical therapy and revascularization, whereas a strong trend toward a higher rate of death or myocardial infarction (25 [9.4] versus 9 [4.8], *P*=0.06) and overall death (20 [7.5] versus 6 [3.2], *P*=0.059) was observed in the medical therapy group. Among medical therapy patients, a significant step-up increase in major adverse cardiovascular events rate was observed across the 3 FFR strata, especially with proximal lesion location. In revascularization patients, the major adverse cardiovascular events rate was not different across the 3 FFR strata.

Conclusions—FFR in and around the gray zone bears a major prognostic value, especially in proximal lesions. These data confirm that FFR≤0.80 is valid to guide clinical decision making. **(*Circulation*. 2016;133:502-508. DOI: 10.1161/CIRCULATIONAHA.115.018747.)**

Key Words: coronary artery disease ■ fractional flow reserve ■ mortality ■ myocardial revascularization ■ patient outcome assessment

The fractional flow reserve (FFR) represents the standard of reference for invasive functional evaluation of the ischemic potential of coronary stenosis and is a valuable tool to guide percutaneous revascularization.[1–3] An FFR value ≤0.75 is almost uniformly associated with signs of ischemia,[4–9] whereas an FFR >0.80 is usually associated with the absence of ischemia. Based on numerous randomized trials[2–5] and registries in most subsets of lesions and patients, the threshold value of 0.80 has been widely accepted to guide clinical decision making.[6–11]

Clinical Perspective on p 508

Accordingly, in the latest European guidelines, revascularization in patients with stable ischemic heart disease in a wide range of coronary stenosis severity (50%–90%) has been recommended under FFR guidance in the absence of an objective demonstration of ischemia at noninvasive functional evaluation (Level I, evidence A).[12] Current US guidelines have recommended the use of FFR to guide revascularization in patients with stable ischemic heart disease when FFR is ≤0.80 (Level IIa, evidence A).[13]

The best treatment strategy for intermediate stenosis with FFR in the narrow gray zone of values, that is, between 0.76 and 0.80, has been questioned. Therefore, we analyzed the long-term clinical outcome of patients with an isolated stenosis within the gray zone (0.76–0.80) or immediately next to the gray zone (0.70–0.75 and 0.81–0.85).

Methods

Patient Population

From February 1997 to June 2013, we retrospectively considered for inclusion patients presenting at the Cardiovascular Center Aalst

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From Cardiovascular Research Center Aalst OLV Clinic, Aalst, Belgium (J.A., B.D.B., V.F., G.D.G., A.F., M.P., G.G.T., J.B., M.V., G.R.H., W.W., E.B.); Division of Cardiology, Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy (G.D.G., M.P., E.B.); and University Heart Centre Graz, Medical University Graz, Austria (G.G.T.).

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(Belgium) with an isolated stenosis and an FFR value within the gray zone of 0.76 to 0.80, irrespective of the angiographic severity and lesion location. To serve as controls, we also considered for inclusion patients presenting with an isolated stenosis and an FFR value in the adjacent FFR strata of 0.70 to 0.75 and 0.81 to 0.85. We excluded patients with multivessel and multiple-segment disease, previous coronary artery bypass grafting (CABG), in-stent restenosis, myocardial bridging, and previous heart transplantation.

Coronary Angiogram

Coronary angiography was performed by a standard percutaneous radial or femoral approach using a 6F or 7F diagnostic or guiding catheters. After the administration of 200 mg of intracoronary isosorbide dinitrate, the angiogram was performed in the projection allowing the best possible visualization of the stenosis and avoiding, as far as possible, foreshortening or overlap of other arterial segments.

Quantitative coronary angiography was performed using one of the following software: Siemens Healthcare Axiom Artis VB35D110803 (Siemens Medical Solutions, Siemens AG; Forcheim, Germany), Siemens Healthcare ACOM.PC 5.01 System (Siemens Medical Solutions, Siemens AG), or General Electric AW VolumeShare 6E (General Electric Inc., Fairfield, OH). All measurements were obtained by an experienced technician unaware of the FFR results. Data were saved on a different page of the local database. The contrast-filled catheter was used for calibration. From an end-diastolic still frame, the reference diameter, minimum luminal diameter, and percent diameter stenosis were calculated.

Intracoronary Pressure Measurements

A 0.014-inch pressure guide wire (Pressure Wire, St. Jude Medical, St. Paul, MN) was placed distally to the coronary artery lesion. Maximal hyperemia was induced either by intracoronary (bolus of 100–200 μg) or intravenous infusion (at a rate of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of adenosine.[14,15] Simultaneous recording of aortic and distal coronary pressure was performed. FFR was calculated as the ratio of hyperemic mean distal coronary pressure to mean aortic pressure.

Metrics and Clinical End Points

Data were analyzed by lesion location (proximal versus distal), treatment (medical therapy versus revascularization), and FFR stratum (0.70–0.75, 0.76–0.80, and 0.81–0.85). The lesion location was defined as coronary arterial segments, according to the American Heart Association, as modified for the Arterial Revascularization Therapies Study (ARTS) and Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) studies.[16,17] Lesions were grouped either in proximal (referred as to segments 1, 2, 5, 6, 7, 11, and 12) or distal (referred as to segments 3, 4, 8, 9, 10, 12a, 12b, 13, 14, 15, and 16) segments. As to the treatment adopted, patients were grouped either in the revascularization group, in which they were treated by percutaneous coronary intervention (PCI) or CABG within 3 months from FFR measurements, or medical therapy group, where they were deferred to medical therapy after FFR measurements.

The clinical end points were major adverse cardiac events (MACE), the composite of overall death or myocardial infarction (MI), overall death, cardiovascular death, MI, and target vessel revascularization up to 5 years follow-up. MACE was defined as the composite of overall death, myocardial infarction, and target vessel revascularization. Myocardial infarctions were either spontaneous or related to the revascularization performed. Spontaneous myocardial infarction (type I) was defined according to the third universal definition of MI.[18] Revascularization-related myocardial infarction (both types 4A and 5) was defined according to the Society for Cardiovascular Angiography and Interventions definition of clinically relevant MI.[19] Follow-up was obtained on patient medical records and telephone calls. All subjects gave written informed consent to the use of anonymized clinical data for research purposes. The local Ethics Committee approved the informed consent.

Statistical Analysis

Comparisons between groups were performed by an unpaired *t* test, Mann-Whitney test, or 1-way analysis of variance for continuous variables where appropriate, and the χ^2 test or Fisher exact test for categorical data according to the samples size. A Cox proportional hazards model was used to estimate the hazard ratios with 95% confidence intervals of the clinical end points (MACE, composite of death or MI, overall and cardiovascular death, MI and TVR) between medical therapy and revascularization groups within the FFR gray zone, within medical therapy (each FFR stratum versus reference FFR 0.81–0.85 stratum, and according to proximal or distal lesion location) and revascularization group (across the 3 FFR strata). In case of $P<0.05$, multivariable analysis was adjusted for minimum luminal diameter and FFR values for comparisons between the medical therapy (MT) and revascularization (REV) groups within the gray zone; sex and percent diameter stenosis for comparisons within the MT group; and reference diameter for comparisons within the REV group. Kaplan-Meier curves were compared by the log-rank test and were generated to highlight the cumulative rate of MACE and death or MI in the gray-zone patients and MACE-free survival rate within the MT group across the 3 FFR strata. *P* values were considered statistically significant if <0.05. Statistical analysis was performed by using SPSS version 21.0 (SPSS, Inc).

Results

During the study period, 17 380 FFR measurements were performed (Figure 1). Of all these FFR measurements, we considered 8170 values (47%) corresponding to 2602 (15%) within the gray zone, 1951 (11%) within the 0.70 to 0.75 strata, and 3617 (21%) within the 0.81 to 0.85 strata. We then excluded 6711 measurements because of the presence of multivessel disease, multiple-segment disease, previous CABG, in-stent restenosis, myocardial bridging, or previous heart transplantation. The remaining 1459 patients with single-segment disease were included in our study.

Among these patients, 1010 (70%) received MT and 449 (30%) underwent REV. In the REV group, 344 (77%) patients were treated with PCI and 105 (23%) were treated with CABG. The reasons to perform CABG in these patients, despite their having single-vessel disease, were attributed to the lesion location (left main or ostial left anterior descending artery in 61 patients), to a concomitant valve disease (in 40 patients), or to diffuse coronary left anterior descending artery disease (in 4 patients). Revascularization was performed in 200 patients (45%) with an FFR value between 0.70 and 0.75, in 187 patients (42%) with FFR within the gray zone, and in 62 patients (14%) with an FFR value between 0.81 and 0.85.

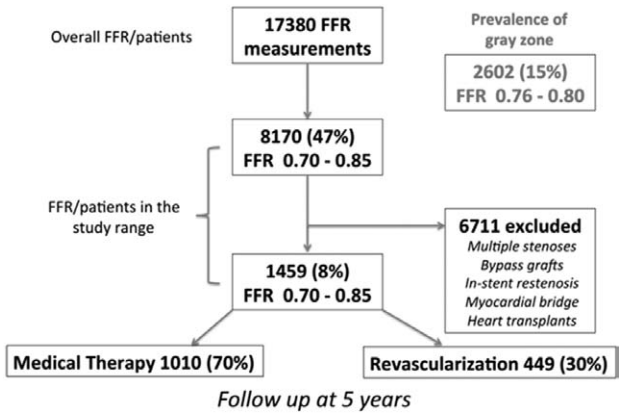

Figure 1. Study flow diagram. FFR indicates fractional flow reserve.

Table 1. Clinical and Angiographic Characteristics of REV and MT Groups Within the FFR Gray Zone (0.76–0.80)

Clinical Characteristics	REV Group (n=187)	MT Group (n=266)	*P* Value
Age, y	64±10	64±11	0.09
Male sex, n (%)	137 (73)	184 (69)	0.4
BMI	28±5	27±4	0.16
Diabetes mellitus, n (%)	49 (26)	64 (24)	0.7
Hypertension, n (%)	100 (53)	145 (54)	0.8
Hyperlipidemia, n (%)	114 (61)	152 (57)	0.4
Current smoker, n (%)	71 (38)	87 (33)	0.3
Asymptomatic/silent ischemia, n (%)	31 (17)	49 (18)	0.7
Stable angina, n (%)	110 (59)	147 (56)	0.4
Acute coronary syndromes, n (%)	46 (24)	70 (26)	0.8
Stenotic vessel, n (%)			0.17
LM	15 (8)	13 (5)	
LAD	131 (70)	210 (79)	
LCx	13 (7)	12 (4)	
RCA	28 (15)	31 (12)	
Proximal lesion location, n (%)	162 (87)	232 (87)	0.9
DS, %	53±13	44±12	<0.001
RD, mm	2.7±0.7	2.6±0.6	0.6
MLD, mm	1.4±0.5	1.5±0.4	0.017
FFR	0.78±0.01	0.79±0.01	<0.001
LVEF, %	62±17	68±17	0.058

BMI indicates body mass index; DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MLD, minimum lumen diameter; MT, medical therapy; RCA, right coronary artery; RD, reference diameter; and REV, revascularization.

Clinical and Angiographic Characteristics

Clinical and angiographic characteristics of the patients within the FFR gray zone according to treatment strategy are summarized in Table 1. In comparison with patients undergoing REV, patients treated with MT presented less angiographically severe coronary stenoses (as suggested by lower percent diameter stenosis and higher minimal lumen diameter) and slightly higher FFR values.

Clinical and angiographic characteristics of the MT and REV group according to FFR strata are summarized in Table I in the online-only Data Supplement. Within the group of patients treated with MT only, there were differences in terms of male sex and percent diameter stenosis across the 3 FFR strata. Irrespective of the FFR stratum, the lesions were mostly located in proximal coronary segments. Coronary stenoses were angiographically more severe in the FFR stratum 0.70 to 0.75 and did not present any difference in terms of lesion complexity in comparison with stenosis in the FFR stratum 0.70 to 0.75 treated with REV (Table II in the online-only Data Supplement).

Within the group of patients treated with REV, there were differences in terms of percent diameter stenosis and the reference diameter of the vessel across the 3 FFR strata.

Table 2. Clinical End Points in REV Versus MT Group Within the FFR Gray Zone (0.76–0.80)

End Points	REV Group	MT Group	HR (95% CI)	*P* Value
MACE, n (%)	21 (11.2)	37 (13.9)	1.31 (0.77–2.24)	0.3
Death or MI, n (%)	9 (4.8)	25 (9.4)	2.07 (0.97–4.44)	0.06
Overall death, n (%)	6 (3.2)	20 (7.5)	2.41 (0.97–6.01)	0.059
CV death, n (%)	1 (0.5)	6 (2.3)	4.24 (0.51–35.26)	0.18
MI, n (%)	3 (1.6)	6 (2.3)	1.46 (0.36–5.83)	0.6
TVR, n (%)	14 (7.5)	23 (8.6)	1.22 (0.63–2.38)	0.5

CI indicates confidence interval; CV, cardiovascular; FFR, fractional flow reserve; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; MT, medical therapy; REV, revascularization; and TVR, target vessel revascularization.

Among the patients undergoing percutaneous REV (n=344), 180 (52%) underwent drug-eluting stent implantation and 164 (48%) underwent bare metal stent implantation. The rate of drug-eluting stent/bare metal stent was similar in patients undergoing PCI within the gray zone (81 [54%]/69 [46%]). Irrespective of the FFR stratum, the lesions were mostly located in proximal coronary segments.

Clinical Outcome

Median follow-up was 25 (6–48) months in the MT group and 26 (13–47) months in the REV group (P=0.3). At the Cox regression analysis (Table 2), the patients of the MT group presented a strong trend toward a higher rate of death or myocardial infarction and overall death in comparison with the REV group. Cumulative rate of MACE was not significantly different, whereas the rate of death or MI tended to be higher in the MT than in the REV group up to 5 years (Figure 2).

Within the group of patients treated with MT only, a progressive significant decrease in MACE rate and a significant increase of MACE-free survival were observed with increasing FFR stratum (Table 3, Figure 3). A significant increase of death or MI, overall death, and cardiovascular death was exclusively observed in the gray zone group of patients in comparison with the FFR 0.81 to 0.85 stratum. In addition, the rate of target vessel revascularization was significantly higher in the FFR 0.70 to 0.75 stratum in comparison with the FFR 0.81 to 0.85 stratum. In patients with proximal location of the coronary stenoses, MACE rate significantly increased with decreasing FFR stratum (Figure 4). This association remained significant after adjusting for sex and diameter stenosis (hazard ratio, 0.49; 95% confidence interval, 0.34–0.72; P<0.001). At the variance, this association was not observed in patients with distal location of the coronary stenoses (hazard ratio, 0.58; 95% confidence interval, 0.23–1.43; P=0.2).

In the REV group, there was no difference in any of the clinical end points across the 3 FFR strata after REV (Table III in the online-only Data Supplement).

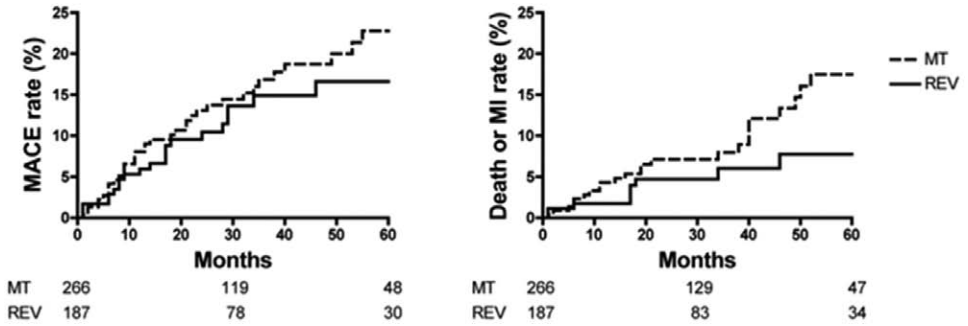

Figure 2. Cumulative rate (%) of MACE (log-rank, 0.87; *P*=0.3) and death or MI (log-rank, 2.96; *P*=0.08) in the gray-zone patients treated with medical therapy or revascularization. MACE indicates major adverse cardiovascular event; MI, myocardial infarction; MT, medical therapy; and REV, revascularization.

Discussion

The present study focused on treatment strategies and related outcomes of patients presenting with an isolated coronary stenosis and FFR value within the gray zone of 0.76 to 0.80. The main findings can be summarized as follows. (1) Patients with single-vessel disease and a coronary stenosis with FFR within the gray zone more frequently underwent REV if presenting with angiographically more severe lesions; (2) these patients, when treated with MT only, had a trend toward higher risk of combined death or myocardial infarction and overall death in comparison with patients presenting also with coronary stenosis and FFR within the gray zone but treated with combined MT and REV; (3) among patients treated with MT only, the risk of MACE progressively and independently decreased with increasing FFR stratum, suggesting an incremental risk of the gray zone patients in comparison with patients with coronary stenosis and FFR >0.80; (4) this increased risk was only observed in patients with proximal location of the coronary stenoses.

FFR Gray Zone

FFR was initially validated against composite information from sequentially performed noninvasive tests.[20–22] It was shown that, below the value of 0.75, epicardial stenoses were associated with 100% positive predictive value for stress-inducible myocardial ischemia, whereas an FFR value >0.80 has a negative predictive value of >95%.[20] The DEFER trial indicated that PCI of coronary stenoses with FFR values >0.75 did not improve clinical outcome in comparison with patients deferred to MT.[1] In a minority of patients, an FFR value between 0.75 and 0.80 was found to be associated with typical exercise-induced angina and reversible flow maldistributions.[23] Therefore, in the era of drug-eluting stents, the threshold of 0.80 was adopted in subsequent studies[2,3] and in clinical practice, as well. In addition, similar results have been obtained in multiple registries and real-world practices accounting for >10 000 patients.[24] FFR values between 0.75 and 0.80 have been referred to as the FFR gray zone, alluding to some uncertainty regarding the degree of ischemia present related to the stenosis being interrogated.

FFR Risk Continuum

Our study provides novel data in a large data set of carefully selected patients with single-vessel and single-segment disease. In patients undergoing MT, a progressive increase in MACE rate was observed when going from the highest FFR stratum of 0.81 to 0.85 to the lowest FFR stratum of 0.70 to 0.75. These data are in line with the recent meta-analysis of Johnson et al[25] indicating a linear relationship between FFR values and clinical outcome. The present data extend this concept to lesions within the narrow range of 0.70 to 0.85. Even within this range of values, the lower the FFR value, the higher the event rate. This finding is clinically relevant, because almost half of all FFR measurements fall within this range. Moreover, these lesions are often associated with atypical symptoms and dubious results of noninvasive testing. One could argue that in these patients left under MT, the awareness by the patient and his physician of the presence of a hemodynamically and angiographically significant stenosis might have lowered the threshold of REV. However, the present data

Table 3. Clinical End Points in Patients of the Medical Therapy Group

End Points	0.81–0.85 (Ref)	0.76–0.80	0.70–0.75	HR (95% CI) 0.76–0.80 vs Ref	*P* Value	HR (95% CI) 0.70–0.75 vs Ref	*P* Value
MACE, n (%)	59 (8.5)	37 (13.9)	12 (22.6)	1.71 (0.97–3.02)	0.06	3.78 (1.72–8.31)	0.001
Death or MI, n (%)	32 (4.6)	25 (9.4)	2 (3.8)	2.08 (1.09–3.98)	0.027	0.91 (0.21–3.97)	0.9
Overall death, n (%)	20 (2.9)	20 (7.5)	1 (1.9)	2.54 (1.18–5.44)	0.017	0.64 (0.08–5.02)	0.7
CV death, n (%)	2 (0.3)	6 (2.3)	0	10.08 (1.03–98.43)	0.047	0.93 (0.91–0.95)	0.9
MI, n (%)	14 (2)	6 (2.3)	1 (1.9)	1.13 (0.35–3.63)	0.8	1.26 (0.15–10.42)	0.8
TVR (%)	63 (9.1)	23 (8.6)	10 (18.9)	0.73 (0.38–1.43)	0.4	2.29 (1.04–5.07)	0.039

CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; and TVR, target vessel revascularization.

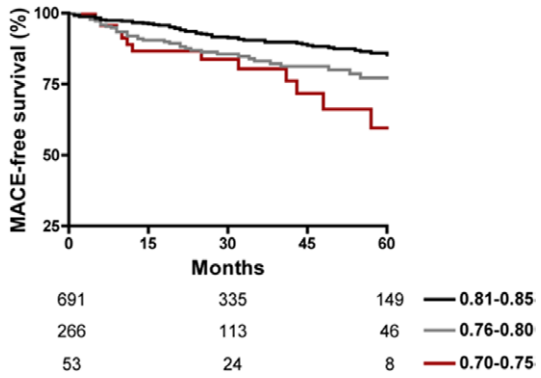

Figure 3. MACE-free survival (%) in patients of the medical therapy group stratified by FFR strata (log-rank, 15; $P<0.001$). FFR indicates fractional flow reserve; and MACE, major adverse cardiovascular event.

show that the difference in MACE is not just driven by REV, but also by a trend toward higher risk of combined death or myocardial infarction, overall and cardiovascular death. Of interest, we did not observe a step-up increase of these later end points with decreasing FFR stratum. One possible explanation of this finding might be that, in the group of patients treated medically, those with FFR in the range of 0.70 to 0.75 received target vessel revascularization twice as much the patients with FFR in the range 0.76 to 0.80 (18.9% versus 8.6%). This higher REV rate within the 0.70 to 0.75 group probably contributed to a significant dilution of the risk of coronary events in comparison with patients within the gray zone. Alternatively, we cannot exclude that this result was attributable to the play of chance.

A similar FFR risk continuum was not observed in the group of patients who underwent REV. Stated another way, regardless of the actual FFR value, the risk of MACE remained similar after REV (Table III in the online-only Data Supplement). This is in line with the results of the Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease (FAME 2) trial, in which patients with at least 1 hemodynamically significant stenosis and randomly assigned to PCI had the same MACE rates as patients with no hemodynamically significant

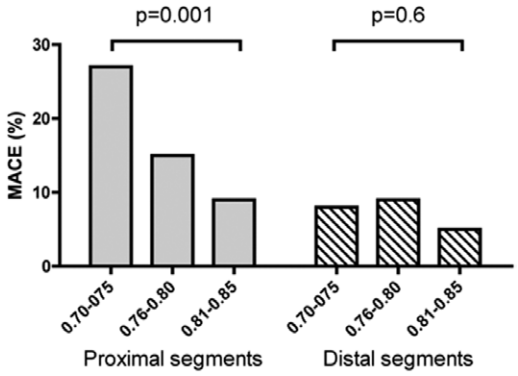

Figure 4. MACE rate (%) in patients receiving medical therapy, stratified according to the FFR strata, and grouped according to the location of the lesions (proximal vs distal). FFR indicates fractional flow reserve; and MACE, major adverse cardiovascular event.

stenosis and treated with MT. This suggests that one of the main determinants of outcome is the ischemic potential of the stenosis.

Medical Therapy Versus Revascularization in the Gray Zone

Confirming previous data, the present study indicates that, below the threshold of 0.80, clinical outcomes tend to be better after REV with associated MT than under MT alone.[3,5] This finding not only confirms the value of the 0.80 threshold, but also narrows the gray zone for clinical decision making: stenoses with an FFR <0.80 deserve REV, whereas stenoses with an FFR >0.80 are better treated with MT, even though this dichotomy should obviously be nuanced by the morphological characteristics of the stenosis and the clinical context of the patient.

Proximal Versus Distal Location of the Stenosis

In our study, we included patients who have single-vessel disease with a single lesion mostly located in proximal coronary segments. We found that the interaction between FFR strata and MACE was significant in patients with stenoses located in proximal coronary segments, unlike in patients with stenoses located in distal coronary segments. This finding is not unexpected and underscores the clinical impact of hemodynamically significant proximal in comparison with distal coronary stenoses, because of the larger extent of the myocardium at risk.[26,27]

Limitations

The present study is retrospective, and REV was left to the operator's discretion. Hence, a selection bias cannot be excluded. It is likely that lesion or patient's features not accounted for in the baseline characteristics influenced the therapeutic decision. It should therefore be emphasized that, especially in the gray zone, the clinical context remains critically important. Along the same line, the small number of patients in the FFR strata 0.70 to 0.75 receiving MT has to be acknowledged. This reflects the current attitude to revascularize hemodynamically significant lesions, especially in patients with isolated stenosis in a proximal segment. Third, the present conclusions were drawn in selected patients with a single lesion and might therefore not necessarily be extrapolated to more complex disease. Yet, this selection was done on purpose to minimize confounding factors and to render less elusive the mechanistic link between the stenosis and patient outcome. Fourth, our study included lesions mostly located on the left anterior descending artery. Fifth, the overall rate of myocardial infarction (both periprocedural or spontaneous) reported in our study is low. This might be attributable either to the definitions adopted or to underreporting. Sixth, the lack of a prospective and independent Clinical Event Committee adjudication of the patients' events, and of an independent core-laboratory evaluation of the coronary stenoses investigated, as well, represent limitations of our study.

Conclusion

Patients with an isolated stenosis located in a proximal coronary segment and FFR within the gray zone of 0.76 to 0.80

demonstrate a clinical outcome that is suboptimal when deferred to MT alone. These data confirm the value of the 0.80 FFR threshold, and favor a REV strategy of coronary stenoses with FFR ≤0.80.

Disclosures

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CLINICAL PERSPECTIVE

A fractional flow reserve (FFR) value ≤0.75 is almost uniformly associated with signs of ischemia, whereas an FFR >0.80 is usually associated with the absence of ischemia. Based on numerous randomized trials and registries, the threshold value of 0.80 has been widely accepted and recommended to guide clinical decision making. Yet, the best treatment strategy for intermediate stenosis with FFR in the narrow gray zone of values between 0.76 and 0.80 has been questioned. Our study focused on treatment strategies and related outcomes of patients presenting with an isolated coronary stenosis and FFR value within the gray zone of 0.76 to 0.80. The main findings of the study are: (1) Patients with single-vessel disease and a coronary stenosis with FFR within the gray zone have a numeric trend toward twice as much risk of combined death or myocardial infarction and overall death if treated with medical therapy only. (2) In these latter patients, the risk of a major adverse cardiovascular event progressively and independently decreased with increasing FFR stratum, suggesting an incremental risk of the gray-zone patients in comparison with patients with coronary stenosis and FFR >0.80. (3) This increased risk was only observed in patients with proximal location of the coronary stenoses. These data confirm the value of the 0.80 FFR threshold, and favor a revascularization strategy of coronary stenoses with FFR ≤0.80.

Significance of Intermediate Values of Fractional Flow Reserve in Patients With Coronary Artery Disease

Julien Adjedj, Bernard De Bruyne, Vincent Floré, Giuseppe Di Gioia, Angela Ferrara, Mariano Pellicano, Gabor G. Toth, Jozef Bartunek, Marc Vanderheyden, Guy R. Heyndrickx, William Wijns and Emanuele Barbato

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Supplemental Material

Supplemental table 1: Clinical and angiographic characteristics of the patients treated with Medical Therapy (MT) or Revascularization (Rev) in the 3 FFR strata

Clinical characteristics	Rev group				MT group			
	0.70-0.75 (n=200)	0.76-0.80 (n=187)	0.81-0.85 (n=62)	P value	0.70-0.75 (n=63)	0.76-0.80 (n=266)	0.81-0.85 (n=691)	P value
Age (years)	66±11	64±10	64±11	0.2	66±9	64±11	66±10	0.9
Male gender (%)	146 (73)	137 (73)	40 (64)	0.4	41 (65)	184 (69)	416 (60)	0.03
BMI	28±6	28±5	27±5	0.6	28±5	27±4	28±14	0.8
Diabetes (%)	49 (24)	49 (26)	12 (19)	0.5	11 (17)	64 (24)	161 (23)	0.5
Hypertension (%)	98 (49)	100 (53)	26 (42)	0.3	29 (46)	145 (54)	340 (49)	0.3
Hyperlipidemia (%)	113 (56)	114 (61)	30 (48)	0.2	32 (51)	152 (57)	399 (58)	0.9
Current smoker (%)	69 (34)	71 (38)	18 (29)	0.4	14 (22)	87 (33)	222 (32)	0.7
Asymptomatic/ silent ischemia (%)	36 (18)	31 (17)	10 (16)	0.9	13 (21)	49 (19)	135 (19)	0.8
Stable angina (%)	117 (59)	110 (59)	37 (60)	0.9	35 (55)	147 (55)	378 (55)	0.9
Acute coronary syndromes (%)	47 (23)	46 (24)	15 (24)	0.9	15 (24)	70 (26)	178 (26)	0.9
Stenotic vessel				0.7				0.9
LM (%)	22 (11)	15 (8)	9 (15)		4 (6)	13 (5)	34 (5)	
LAD (%)	144 (72)	131 (70)	40 (64)		49 (78)	210 (79)	531 (77)	
LCx (%)	12 (6)	13 (7)	4 (6)		3 (5)	12 (4)	42 (6)	
RCA (%)	22 (11)	28 (15)	9 (15)		7 (11)	31 (12)	84 (12)	
Proximal lesion location (%)	181 (90)	162 (87)	52 (84)	0.3	41 (77)	232 (87)	602 (87)	0.12
DS (%)	55±13	53±13	47±16	0.009	47±13	44±12	41±12	0.002
RD (mm)	2.6±0.6	2.7±0.7	3.5±1.6	<0.001	2.7±0.5	2.6±0.6	2.8±0.7	0.2

MLD (mm)	1.4±0.4	1.4±0.5	1.6±0.6	0.6	1.5±0.3	1.5±0.4	1.8±0.3	0.6
FFR	0.73±0.02	0.78±0.01	0.82±0.01	<0.001	0.73±0.02	0.79±0,01	0.83±0.01	<0.001
LVEF (%)	66±17	62±17	63±13	0.3	74±14	68±17	66±17	0.15

BMI: body mass index; DS: diameter stenosis; RD: reference diameter; MLD: minimum lumen diameter; FFR: fractional flow reserve; LVEF: left ventricular ejection fraction; LM: left main coronary artery; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

Supplemental table 2: Angiographic features of the stenoses with FFR <0.75 in the Medical Therapy (MT) or Revascularization (Rev) group

	FFR<0.75 (MT group, n=53)	FFR<0.75 (Rev group, n=200)	P value
Lesion Type A (%)	11 (21)	42 (21)	0.9
Lesion Type B1 (%)	16 (30)	52 (26)	0.5
Lesion Type B2 (%)	18 (34)	70 (35)	0.9
Lesion Type C (%)	8 (15)	36 (18)	0.6
Proximal location (%)	16 (30)	64 (32)	0.8

Supplemental table 3: Clinical outcome of patients within the Revascularization group

Endpoints	Revascularization group (Rev)				H.R. (95% C.I)	p value
	Overall (n=449)	0.70-0.75 (n=200)	0.76-0.80 (n=187)	0.81-0.85 (n=62)		
MACE (%)	57 (12.7)	27 (13.5)	21 (11.2)	9 (14.5)	0.94 (0.65-1.39)	0.7
Death or MI (%)	24 (5.3)	11 (5.5)	9 (4.8)	4 (6.5)	0.99 (0.57-1.73)	0.9
Overall Death (%)	20 (4.5)	11 (5.5)	6 (3.2)	3 (4.8)	0.79 (0.42-1.49)	0.5
CV death (%)	4 (0.9)	2 (1)	1 (0.5)	1 (1.6)	1.05 (0.28-3.99)	0.9
MI (%)	4 (0.9)	0	3 (1.6)	1 (1,6)	2.70 (0.70-10.51)	0.15
TVR (%)	41 (9.1)	21 (10.5)	14 (7.5)	6 (9.7)	0.85 (0.55-1.32)	0.5

MACE is major adverse cardiovascular events; MI is myocardial infarction; CV death is cardiovascular death; TVR is target vessel revascularization.

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Supplemental table 1: Clinical and angiographic characteristics of the patients treated with Medical Therapy (MT) or Revascularization (Rev) in the 3 FFR strata

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