The utility of high-sensitivity C-reactive protein levels in patients with moderate coronary lesions and gray-zone fractional flow reserve

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Abstract

Objective: It remains controversial whether patients with fractional flow reserve (FFR) values of 0.75–0.80 (gray-zone) should be treated with percutaneous coronary intervention (PCI). This study aimed to evaluate the prediction of high-sensitivity C-reactive protein (hs-CRP) levels to guide treatment selection in gray-zone patients.

Methods: This prospective interventional trial was conducted between January 2015 and March 2016. A total of 785 patients with stable angina and single-vessel stenosis with moderate coronary lesions were admitted to hospital in this period. After measurement of hs-CRP levels, coronary angiography, and FFR, gray-zone patients (n=308) were included in the study and were divided into four groups on the basis of a cutoff hs-CRP level of 3 mg/L and then on the basis of whether they underwent PCI or not. Patients in groups I (≥3 mg/L, n=70) and III (<3 mg/L, n=84) underwent PCI, whereas those in groups II (≥3 mg/L, n=70) and IV (<3 mg/L, n=84) were administered only drugs. Major adverse clinical events (MACEs) included cardiac death, nonfatal myocardial infarction (MI), target vessel revascularization (TVR), and PCI or coronary artery bypass grafting (CABG). These parameters were also evaluated during follow-up.

Results: The total Kaplan-Meier curves showed macrodistribution differences among the four groups ($p<0.05$). There was a significantly increased MACE incidence in group II compared with group I or IV ($p=0.039$ or 0.006, respectively), and an increased incidence in group I compared with group III ($p=0.028$). However, there were no differences in MACE incidence between groups III and IV ($p=0.095$) despite the fact that these patients received different treatments.

Conclusion: Among FFR gray-zone patients, hs-CRP level was a predictor of MACE and risk stratification could guide treatment selection. Increased hs-CRP levels (≥3 mg/L) are an indication for urgent PCI whereas normal levels (<3 mg/L) are an indication for delayed PCI treatment. Patients with identical FFR values could require different treatment. *(Anatol J Cardiol 2018; 20: 143-51)*

Keywords: fractional flow reserve, gray-zone, high-sensitivity C-reactive protein (hs-CRP), major adverse cardiac events

Introduction

A large number of studies from several heart disease centers worldwide have shown that fractional flow reserve (FFR) is a reliable physiological index for determining the functional significance of coronary stenosis, and this new "gold standard" approach for diagnosing coronary artery disease (CAD) makes treatment with percutaneous coronary intervention (PCI) more rational. Specifically, an FFR value <0.75 is associated with inducible myocardial ischemia, and an FFR value >0.80 indicates the absence of inducible myocardial ischemia with a high diagnostic accuracy (1, 2). However, whether revascularization should be performed in patients in the gray-zone, defined as an FFR value between 0.75 and 0.80, remains debatable. We sought to further study relatively high-risk patients in the gray-zone subjected to PCI treatment.

Atherosclerosis remains the leading cause of CAD, and inflammation is an inherent part of the atherosclerotic process. C-reactive protein, an inflammatory marker, directly interacts with atherosclerotic vessels by activating of the complement system, thereby promoting inflammation and thrombosis (3). In addition to its role in triggering immunity in plaque deposition, *in vitro* studies have indicated associations among CRP levels, inhibition of endothelial nitric oxide synthase, and impaired vasoreactivity (4). Shah et al. (5) considered hs-CRP a predictor of future major adverse cardiac events. However, it remains unclear whether

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hs-CRP levels could guide treatment selection in FFR gray-zone patients. This study aimed to evaluate the prediction of hs-CRP levels and to guide treatment selection in such patients.

Methods

Patients

This study was a prospective interventional trial. The study population was selected from patients who consulted from the Department of Cardiology in our hospital. We selected stress-test–positive hospitalized stable angina patients and single-vessel stenosis with moderate coronary lesions (40%–70% by means of visual estimation). Stable angina pectoris was defined as no change in the frequency, duration, or intensity of symptoms within 4 weeks. Exclusion criteria were as follows: (1) active infections; (2) autoimmune diseases; (3) severe hepatic or renal dysfunction; (4) contraindication for anticoagulation or excessive risk of bleeding; (5) history of myocardial infarction (MI), target vessel PCI, or coronary artery bypass graft; (6) left ventricular EF <40%; (7) left main coronary stenosis, branch distal lesion or multiple stenosis; (8) acute coronary syndrome; or (9) life expectancy of <1 year. The study protocol was approved by the Ethics Committee of our institution. All enrolled patients provided written informed consent for participation before coronary angiography.

Between January 2015 and March 2016, 1255 consecutive patients were admitted to our hospital. On the basis of the inclusion and exclusion criteria, hs-CRP levels were evaluated in a total of 785 stress-test–positive hospitalized patients with stable angina and single-vessel stenosis with moderate coronary lesions (40%–70% by means of visual estimation) after an 8-h fast. hs-CRP levels were checked twice to confirm a stable value despite individual fluctuations, and the average value of the two examinations was recorded and saved before the intervention. Serum hs-CRP levels were measured using immune scatter turbidimetric analysis (Germany, SIEMENS BN-II) on the basis of manufacturer's instructions. Two patients lost to follow-up within 1 year were excluded. Thus, following coronary angiography and FFR measurement, a total of 308 patients fulfilled the FFR gray-zone criteria and were included in the present study. There were186 males and 122 females with a mean ± standard deviation of 61.2±5.7 (range, 54.5-67.6 years).

Coronary angiography

After disinfection and local anesthesia, coronary angiography was performed using a 6-F guiding catheter via the transradial approach. To avoid vasospasm and achieve maximal epicardial vasodilatation, intracoronary injection of 200 μg nitroglycerin before coronary angiography. The imaging time was ≥3-8 cardiac cycles. Quantitative coronary angiography (QCA) was performed using standard techniques with an automated edge-detection algorithm (CASS-5; Pie Medical, Maastricht, Netherlands) (6). The reference vessel diameter (RVD), minimum lumen diameter (MLD), diameter stenosis (DS), and lesion length were calculated by two experienced observers who were blinded to the FFR value and to the patient's clinical characteristics.

FFR measurement

A 0.014-inch pressure wire (St. Jude Medical, St. Paul, MN, USA) was calibrated and advanced into the coronary artery while ensuring coaxial alignment with the coronary ostium to prevent dampening of the arterial pressure waveform. After the intracoronary administration of 100-200 μg of nitroglycerine, FFR was measured at maximal hyperemia induced by intravenous continuous infusion of adenosine 5′-triphosphate (140 mg/kg/min) (7). The dose was increased to achieve maximal hyperemia and a stable state. The pressure wire was then placed at the distal portion of the coronary artery, ensuring that the pressure sensor was positioned beyond the coronary lesion of interest. The mean distal coronary pressure (Pd) was recorded and simultaneously adjusted, and zeroed guiding catheters recorded mean aortic coronary pressures (Pa) according to the ratio FFR=Pd/Pa (7). After this process, a total of 310 patients showed single-vessel stenosis of moderate coronary lesions (40%-70%) and simultaneously fulfilled the criterion of FFR value of 0.75–0.80. These patients were included in the present study and were clinically followed up for 1 year. Among these gray-zone patients, 22 patients (7%) showed 40%–49% stenosis,77 patients (25%) showed 50%–59% stenosis, and 209 patients (68%) showed 60%–69% stenosis, Of the 140 patients with serum hs-CRP value of >3 mg/L, there were eight patients (6%), 31 patients (22%), and 101 patients (72%), respectively, in the stenosis subgroups described above.

Grouping and treatment

The cutoff points of serum hs-CRP levels were defined as normal level (mean <3.0 mg/L) and increased levels (mean ≥3.0 mg/L). A value of 3 mg/L was chosen as the optimum cutoff point because hs-CRP levels >3 mg/L were associated with high cardiovascular risk (8). Among the 310 patients, 140 fulfilling the increased level criterion were randomly divided into groups I and II (n=70, each). Meanwhile 170 patients who fulfilled the normal criterion were also evenly divided into groups III and IV (n=85, each). PCIs were performed in groups I and III via the transradial approach using a standard technique, and everolimus-eluting stents were employed in the target lesions. Patients in groups II and IV received conservative treatment with pharmacotherapy appropriate for maintaining a blood pressure of 130/80 mm Hg, low-density-lipoprotein cholesterol (LDL-C) ≤1.8 mmol/L and fasting blood glucose of ≤6 mmol/L as goal values.

Clinical follow-up

General clinical data and the coronary angiography and QCA parameters in the four groups were recorded and analyzed. A total of 310 patients were subsequently tracked via telephone calls and outpatient visits. Patients in groups I and III also received pharmacotherapy to achieve therapeutic goals similar to those

Table 1. Patient basic and clinical characteristics

	Group I	Group II	Group III	Group IV	*P* value
Age	61.4±5.2	61.2±6.4	60.3±5.8	61.1±5.4	0.591
Gender (male)	45 (64)	42 (60)	49 (58)	50 (60)	0.513
Hypertension	37 (53)	39 (56)	46 (55)	45 (54)	0.734
Diabetes	40 (57)	38 (54)	39 (46)	41 (49)	0.158
Current smokers	36 (51)	37 (53)	43 (51)	40 (48)	0.865
Dyslipidemia	38 (54)	33 (47)	32 (39)	30 (37)	0.081
BMI (kg/m^2)	22.1±1.8	22.0±1.5	21.6±1.6	21.8±1.8	0.312
LVEF	47.7±4.7	48.1±4.4	48.4±4.0	49.4±4.9	0.294
Family history of CAD	27 (39)	29 (41)	35 (42)	38 (45)	0.642
b-Blocker	40 (57)	39 (56)	47 (56)	51 (69)	0.103
ACE-I/ARB	32 (46)	29 (41)	38 (45)	45 (54)	0.278
Antiplatelet drug	53 (76)	50 (71)	57 (68)	55 (66)	0.433
Statin	63 (90)	60 (85)	68 (81)	70 (83)	0.084
Organic nitrate drugs	35 (50)	31 (44)	41 (49)	37 (44)	0.487

BMI - body mass index; CAD - coronary artery disease; Data are provided as n (%) or (Mean±SD)

of groups II and IV (LDL-C, blood pressure, and fasting blood glucose). The endpoint of this study was MACE (MACE), defined as cardiac death, nonfatal MI, and target vessel revascularization (TVR), including PCI or coronary artery bypass grafting (CABG) within 12 months. These parameters were observed and recorded during follow-up. MI was defined as (two out of three criteria) prolonged chest pain >20 min; serum creatine kinase (or the MB fraction) or troponin levels greater than two-fold above the upper limit of normal, and a new or presumed new left-bundle-branch block (LBBB), ST-T segment changes, or new Q waves on serial electrocardiograms indicative of myocardial damage, a new wall-motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy (9). All deaths were considered to be cardiac origin unless an obvious noncardiac cause can be identified. TVR, including PCI or CABG, was defined as any clinically driven revascularization of the target vessel, and unstable angina was the reason for TVR that was used to apply the Canadian Cardiovascular Society classification of symptom severity. Events were related to the lesion and were proven by coronary angiography to be related to the same lesion by comparing the previously evaluated coronary angiographic imaging.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (Chicago, IL, USA). Descriptive statistics [frequencies, percentages, means, and standard deviations (SD)] were first calculated. Subsequently, Kolmogorov–Smirnov tests were used to examine normality, and Box's M tests were used to examine the homogeneity of variance. Analyses of variances (ANOVAs) were used to evaluate differences in continuous variables when the data were normally distributed and in accordance with assumptions regarding the homogeneity of variance; otherwise, Kruskal–Wallis (K-W) H tests were used. If p values of ANOVAs or K-W H tests were <0.05, post hoc tests were conducted. A p value of <0.05 was considered statistically significant.

Results

Basic and clinical characteristics of the patients

Among the 310 patients who met the inclusion criteria (FFR value 0.75–0.80), two patients (0.6%; one from group III, one from group IV) were lost to follow-up and were excluded. Thus, 308 patients were included in the final analysis. There were a total of 70 cases in group I, 70 cases in group II, 84 cases in group III, and 84 cases in group IV. The baseline and clinical characteristics of the patients are summarized in Table 1. There were no significant differences in terms of age, sex, hypertension, diabetes, dyslipidemia LVEF, family history of CAD, means and standard deviations of body mass index (BMI) or optimal medical therapy [including b-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACE-I/ARB), statin medicines, antiplatelet drugs, and organic nitrate drugs] among the four groups (p>0.05).

Angiographic and FFR findings

The angiographic and FFR findings are summarized in Table 2. In total, 308 patients underwent a successful angiographic and FFR measurement. Quantitative data were analyzed with a computer according to a validated edge-detection algorithm using

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Table 2. Angiographic and FFR findings

	Group I	Group II	Group III	Group IV	*P* value
Target vessels					
RCA	30 (43)	33 (47)	37 (44)	35 (42)	0.382
LAD	28 (40)	24 (35)	30 (36)	34 (40)	0.130
LCX	12 (17)	13 (17)	17 (20)	15 (18)	0.224
Lesion location					
Proximal	30 (43)	28 (40)	35 (42)	33 (39)	0.486
Mid	21 (30)	25 (36)	27 (32)	25 (30)	0.334
Distal	19 (27)	17 (24)	22 (26)	26 (31)	0.401
ACC/AHA lesion type (%)					
A	8 (11)	10 (14)	26 (31)	29 (35)	▾0.614/▴0.622
B1	19 (27)	14 (20)	28 (35)	31 (37)	•0.004/••0.001
B2	18 (26)	27 (39)	19 (23)	12 (14)	*0.002/**0.003
C	25 (36)	19 (27)	11 (13)	12 (14)	0.312
					▾0.103/▴0.164
					•0.654/••0.080
					*0.031/**0.001
					▾0.275/▴0.822
					•0.001/••0.002
					*0.028/**0.051
QCA					
RVD (mm)	2.7±0.4	2.6±0.3	2.7±0.3	2.6±0.4	0.323
MLD (mm)	1.0±0.2	1.1±0.3	1.2±0.2	1.1±0.2	0.081
DS (%)	63.5±6.0	62.0±5.3	61.6±6.1	62.5±5.9	0.564
Lesion length (mm)	16.7±2.9	16.5±2.6	13.9±2.3	13.6±1.9	▾1.000/▴1.000
					•P<0.001/••P<0.001
					*P<0.001/**P<0.001
Hs-CRP value	5.6±1.3	5.7±1.5	1.6±0.7	1.8±0.6	▾1.000/▴1.000
					•P<0.001/••P<0.001
					*P<0.001/**P<0.001

ACC - American College of Cardiology; AHA - American Heart Association; RCA - right coronary artery; LAD - left anterior descending artery; LCX - left circumflex; MI - myocardial infarction; QCA - quantitative coronary angiography, RVD - reference vessel diameter; MLD - minimum lumen diameter; DS - diameter stenosis.
I versus II: ▾P, III versus IV; ▴P.
I versus III: •P, I versus IV; ••P.
II versus III: *P, II versus IV; **P

the guiding catheter as a reference. No differences were noted in the target vessels, the location of the target lesion, or the QCA parameters, including the reference vessel diameter, minimal lumen diameter, and percent DS among the four groups. The lesions in group I were longer than those in group III or IV (16.7±2.9 vs. 13.9±2.3 or 13.6±1.9, p<0.001, p<0.001), and lesions in group II were longer than those in group III or IV (16.5±2.6 vs. 13.9±2.3 or 13.6±1.9, p<0.001, p<0.001). The proportion of ACC/AHA lesion type A in groups I or II was less than in group III or IV (p=0.004, p=0.001, p=0.002, p=0.003), By contrast, the proportion of lesion type B2 in group II was more than in group IV (p=0.001), and the proportion of lesion type C in group I was more than in group III or IV (p=0.001, p=0.002). Thus, increased hs-CRP levels in patients with an FFR value of 0.75–0.80 were associated with complex lesions.

Clinical follow-up and patient outcomes

We investigated clinical events during the 12-month follow-up period. All follow-up data were obtained by telephone and outpatient visits. There were no differences in terms of medication use, including antiplatelet therapy, b-blockers, ACE-I/

Table 3. Case summary of TVR

	Age/gender	Target Vessel	DS (%)	Baseline FFR	Revascularization FFR	Hs-CRP (mg/L)	MACE Month	Reason for revascularization
1	64/M	LCX	64	0.76	0.73	5.5	4.0	ECG (+)
2	63/M	LAD	60	0.75	0.66	3.9	10.0	Serum marker (+)
3	62/F	LAD	69	0.77	0.72	4.1	9.0	ECG (+)
4	58/M	RCA	62	0.75	0.63	7.2	3.0	Serum marker (+)
5	57/F	LAD	65	0.76	0.59	4.6	8.0	ECG (+)
6	51/M	LCX	61	0.75	0.69	3.4	11.0	ECG (+)
	Group II							
1	63/M	RCA	58	0.77	0.71	7.9	2.0	ECG (+)
2	58/F	LAD	59	0.76	0.64	4.3	5.0	Serum marker (+)
3	60/F	LCX	67	0.79	0.72	5.6	4.0	ECG (+)
4	68/M	RCA	67	0.78	0.70	4.1	5.0	ECG (+)
5	64/F	LAD	68	0.76	0.72	4.8	6.0	ECG (+)
6	55/F	LCX	68	0.75	0.62	6.9	3.0	Serum marker (+)
7	62/M	LAD	65	0.77	0.70	5.8	4.0	Serum marker (+)
8	62/F	RCA	59	0.78	0.73	3.4	8.0	ECG (+)
9	58/F	LAD	61	0.75	0.70	5.2	6.0	ECG (+)
10	71/M	LAD	66	0.76	----	7.8	7.0	Cardiac death (+)
11	58/M	LCX	62	0.77	----	4.2	5.0	Cardiac death (+)
12	59/F	LCX	66	0.76	0.65	6.9	2.0	ECG (+)
13	59/M	RCA	66	0.75	0.58	5.1	6.0	Serum marker (+)
14	72/M	LCX	63	0.75	0.67	7.3	3.0	ECG (+)
	Group III							
1	55/M	RCA	62	0.77	0.73	2.3	11.0	ECG(+)
	Group IV							
1	68/F	LAD	70	0.75	0.72	2.2	10.0	ECG (+)
2	61/F	RCA	55	0.77	0.73	2.8	6.0	ECG (+)
3	55/M	LCX	55	0.76	0.61	2.3	7.0	Serum marker (+)
4	63/ M	RCA	55	0.75	0.62	1.8	11.0	Serum marker (+)
5	67/ M	RCA	55	0.78	0.73	2.0	11.0	ECG (+)

FFR - fractional flow reserve; Hs-CRP - high-sensitivity C-reactive protein; MACE - major adverse cardiac events; ---, cardiac death; other abbreviation are noted in Table 2

ARB, and antiangina agents, at follow-up compared with drug treatment before the intervention. As the endpoint of this study, MACE values were recorded for all patients (six cases in group I; 14 cases in group II; one case in group III, and five cases in group IV). Case summaries of TVR are presented in Table 3. There were two patients with acute MI and four patients with unstable angina in group I (8.6%); four patients with acute MI, eight patients with unstable angina, and two patients with cardiac death in group II (20.0%); there was one patient with unstable angina in group III (1.9%); there were two patients with acute MI and three patients with unstable angina in group IV (6.0%). The Kaplan–Meier curves for MACEs are presented in Figures 1-5. Kaplan–Meier curves in Figure 1 indicated a significantly increased MACE incidence in group II compared to group I (p=0.039). There was no difference in MACE incidence between group III and IV (p=0.095) despite the fact that these patients received different treatments (Fig. 2). The total Kaplan–Meier curves in Figure 3 show macrodistribution differences among the four groups (p<0.05). Figures 4 and 5 show significantly greater incidence in group II than in group IV (p=0.006), and greater incidence in group I than in group III (p=0.028). These results suggest that hs-CRP levels are a predictor for MACE, and risk stratification could guide treatment selection in gray-zone patients. An increased hs-CRP level and drug administration alone were associated with a worse prognosis. PCI treatment could

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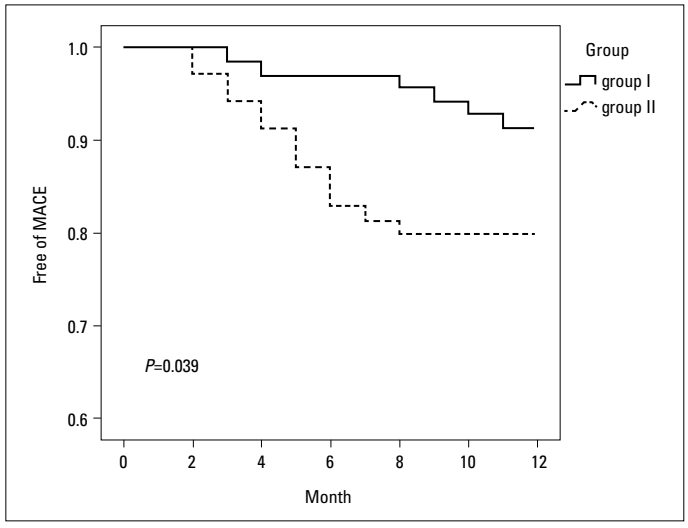

Figure 1. Kaplan–Meier major adverse cardiac event in group II compared with group I
Legends: The MACE curve showed that MACE incidence increased significantly in group II compared with group I (*P*=0.039)

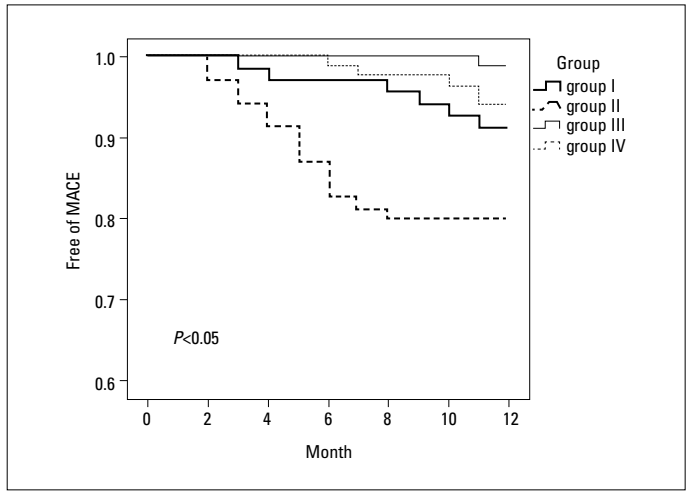

Figure 3. Total Kaplan–Meier major adverse cardiac event
Legends: The total MACE curve showed that the incidence of MACE macrodistribution difference among four groups (*P*<0.05).
MACE: cardiac death, target vessel-related myocardial infarction, revascularization

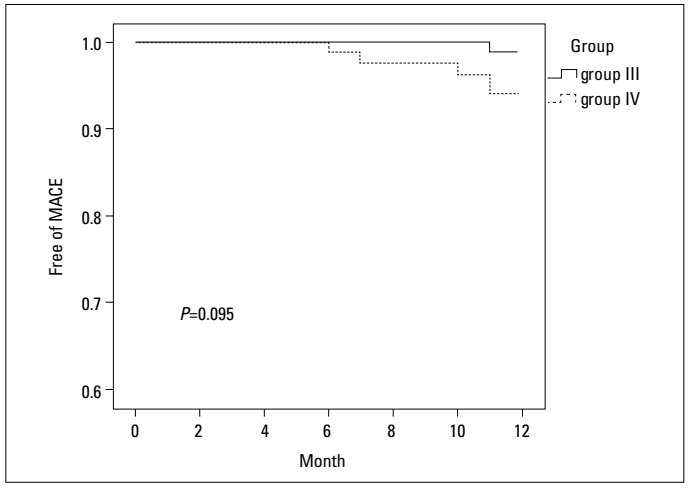

Figure 2. Kaplan–Meier major adverse cardiac event in group III compared with group IV
Legends: The MACE curve showed that no difference in MACE incidence between group III and IV (*P*=0.095)

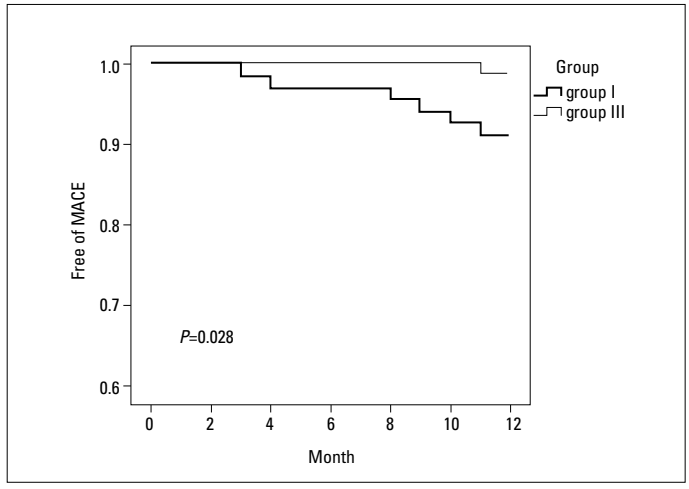

Figure 4. Kaplan–Meier major adverse cardiac event in group I compared with group III
Legends: The MACE curve showed that the incidence of MACE increased significantly in group I compared with group III (*P*=0.028)

improve the prognosis. There were no differences in outcomes between PCI and delayed PCI treatment in gray-zone patients with normal CRP levels. This finding raises the question of whether these normal hs-CRP patients should undergo PCI treatment. Risk stratification of the hs-CRP level could guide treatment selection and serve as a predictor for gray-zone patients. Increased levels indicated PCI, and normal levels indicated delayed PCI treatment.

Discussion

The highlight of the present study was the finding that hs-CRP levels identified before coronary angiography were a predictor of whether patients in the FFR gray-zone (0.75–0.80) should receive PCI treatment. This study was conducted in the Department of Cardiology between January 2015 and March 2016, and the interventional procedures, including coronary angiography, FFR, and PCIs, were performed in the cardiology interventional treatment center at our hospital. The application of PCI and FFR has led to debate concerning the treatment of gray-zone patients (FFR, 0.75–0.80). Although hs-CRP is known to be an important risk factor for long-term cardiovascular events, few have applied CRP in the study of gray-zone patients. Indeed, after 12 months of follow-up, our results suggested that gray-zone patients should undergo personalized treatment according to risk stratification by hs-CRP levels. Patients with increased levels are recommended to undergo PCI whereas normal levels suggest delayed PCI treatment despite the fact that these patients had identical FFR values.

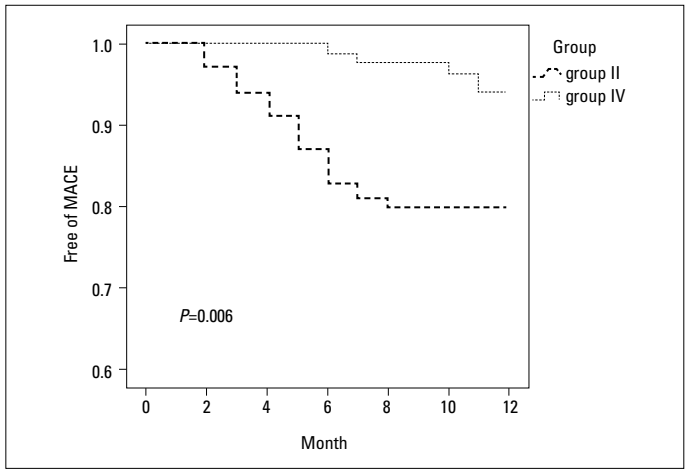

Figure 5. Kaplan–Meier major adverse cardiac event in group II compared with group IV
Legends: The MACE curve showed that the incidence of MACE increased significantly in group II compared with group IV (*P*=0.006) MACE: cardiac death, target vessel-related myocardial infarction, revascularization.

Developmental history of FFR

After Pijls et al. (7) proposed the concept in 1993, FFR has been widely used in coronary artery lesion revascularization and in evaluation of the efficacy of PCI. FFR provides an accurate and reproducible measure of the hemodynamic significance of stenosis. Thus, FFR has become internationally recognized as a functional evaluation index in myocardial ischemia, and it has been upgraded to a class IA classification in multivessel PCI in the current European Society of Cardiology guidelines for coronary revascularization (9, 10). A large number of clinical and basic studies have demonstrated that an FFR value of <0.75 predicts myocardial ischemia with a specificity of 100%, whereas an FFR value of >0.80 functions as a negative predictor and exhibits greater than 90% sensitivity for the development of myocardial ischemia (1).

FFR threshold under dispute

Data related to the clinical significance of FFR have been reported in the FAME, FAMEII (11, 12), and DEFER studies (13) Two different FFR cutoff points (0.75 and 0.80) were applied, yielding positive results. FFR values between 0.75 and 0.80 are defined as the gray-zone, and whether to proceed to revascularization in these patients remains controversial. Legalery et al. (14) reported that deferred PCI in gray-zone patients resulted in a MACE incidence as high as 21% after 12 months of follow-up. Shiono et al. (15) reported that delayed PCI in patients with an FFR of 0.75–0.80 was more closely related to cardiovascular events than an FFR >0.80 after 5 years of clinical follow-up visits. By contrast, Lindstaedt et al. (16) showed that patients in the gray-zone who deferred revascularization had better outcomes than those who underwent revascularization. Many reports also indicate a better prognosis in gray-zone patients for delayed PCI; thus, some physicians are more inclined to use the latter (17-19). Therefore, how to address moderate coronary lesions with controversial FFR cutoff values remains a hot topic of discussion (20).

Study of hs-CRP

Recent studies have indicated that imbalances between proinflammatory and anti-inflammatory mechanisms result in the formation and development of coronary atherosclerotic heart disease and coronary atheroma (21). When a proinflammatory mechanism is dominant, the activation of an inflammatory reaction serves as an important risk factor for long-term MACEs, and restenosis. As an inflammatory marker, CRP is generally involved throughout the entire process of atherosclerosis and plaque rupture (22). CRP also enhances platelet activity and promotes the incidence of arterial thrombosis (23). Long-term endothelial dysfunction causes vessel-wall trauma, exacerbating pathological conditions in the coronary artery even in patients with stable angina. Increased CRP levels before intervention positively correlate with cardiovascular risk events and serve as independent risk factors for cardiovascular disease (24). Liuzzo et al. (25) reported that TVR patients with increased hs-CRP levels (≥3 mg/L) on admission had a higher incidence of MACE than did those with normal hs-CRP levels (<3 mg/L). At discharge, these patients also had higher readmission rates and higher risk of MI. Whether risk stratification could guide treatment selection in gray-zone patients remains unknown.

Individual therapeutics in FFR gray-zone

In the past, numerous studies focused on hs-CRP levels to evaluate different clinical types of CHD (26) or used coronary angiography and PCI as the judgment standard (27). Few studies focused on gray-zone patients. How patients with controversial values in the gray-zone should be treated remains undetermined. Indeed, patients with identical FFR values may show different clinical consequences (28). This point is worth pondering. The current study aimed to provide risk stratification of hs-CRP levels in patients with moderate coronary lesions and FFR gray-zone values, thereby guiding personalized treatment. Increased hs-CRP levels (≥3 mg/L) tended to trigger the rupture of vulnerable plaques, bleeding, and thrombosis (29). This triggering leads to a high incidence of cardiovascular events. Logically, an increased hs-CRP level may guide us toward initiating more aggressive anti-inflammatory treatment (i.e., high-dose statins); nevertheless, aggressive statin treatment alone is insufficient to improve the prognosis. The data in Table 2 demonstrate that patients with high hs-CRP levels had more complex lesions, and Figure 1 demonstrates poor prognosis in group II, requiring us to seek more solutions to decrease future cardiovascular events. PCI treatment immediately improved ischemia caused by stenosis and recovered normal myocardial blood supply. Improving myocardial hemodynamics may be a superior guide in decision making for complex lesions. However, no differences were noted in normal hs-CRP patients, who received different treatments (PCI or delayed PCI). In the case of no difference in prognosis, delayed PCI

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in patients with normal hs-CRP level can save medical expenses and avoid bleeding and potential stents related to complications. Kaplan–Meier curves in our study indicate that delayed PCI treatment in normal hs-CRP level patients is feasible.

The current study demonstrated that it is worth considering personalized treatment for FFR gray-zone patients based on the enhanced anti-inflammatory antiplatelet therapy of high-risk patients. Debate over numeric values regarding whether to delay PCI treatment in gray-zone patients not only lacks of predictive value but is also a one-sided view.

Study limitations

This study had several limitations. First, the study population included only patients with FFR values of 0.75–0.80 who were selected among patients with angiographically intermediate single-vessel stenosis (percent DS, 40%–70%). Whether the results are also suitable for multiple-vessel stenosis is unknown. Further evaluation will be needed to examine the influence of other confounding factors. In addition, not all of our data could be compared, because two patients were lost to follow-up. Second, clinical follow-up lasted only 12 months. Another limitation was the small sample size, which limited the statistical power and the strength of our conclusions. A larger sample size with a longer follow-up period is required to confirm the present results and to predict future coronary events.

Conclusion

Hs-CRP levels were a predictor for MACE, and risk stratification could guide treatment selection in gray-zone patients. An increased hs-CRP level indicated PCI, whereas normal levels suggested delayed PCI treatment. Patients with identical FFR values should receive different treatments.

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References

1. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, et al.; American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Circulation 2006; 114: 1321-41. [CrossRef]
2. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. J Am Coll Cardiol 2010; 55: 173-85. [CrossRef]
3. Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, Wolbink GJ, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999; 100: 96-102.
4. Guan H, Wang P, Hui R, Edin ML, Zeldin DC, Wang DW. Adeno-associated virus-mediated human C-reactive protein gene delivery causes endothelial dysfunction and hypertension in rats. Clin Chem 2009; 55: 274-84. [CrossRef]
5. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, et al. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. Int J Epidemiol 2009; 38: 217-31. [CrossRef]
6. Berry C, L'Allier PL, Grégoire J, Lespérance J, Levesque S, Ibrahim R, et al. Comparison of intravascular ultrasound and quantitative coronary angiography for the assessment of coronary artery disease progression. Circulation 2007; 115: 1851-7. [CrossRef]
7. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993; 87: 1354-67. [CrossRef]
8. Mendes R, Sousa N, Reis VM, Themudo-Barata JL. Prevention of exercise-related injuries and adverse events in patients with type 2 diabetes. Postgrad Med J 2013; 89: 715-21. [CrossRef]
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal definition of myocardial infarction. Circulation 2012; 126: 2020-35. [CrossRef]
10. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, et al. Guidelines on myocardial revascularization. Eur Heart J 2010; 31: 2501-55. [CrossRef]
11. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al.; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360: 213-24. [CrossRef]
12. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino PA, Piroth Z et al.; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014; 371: 1208-17.
13. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007; 49: 2105-11. [CrossRef]
14. Legalery P, Schiele F, Seronde MF, Meneveau N, Wei H, Didier K, et al. One-year outcome of patients submitted to routine fractional flow reserve assessment to determine the need for angioplasty. Eur Heart J 2005; 26: 2623-9. [CrossRef]
15. Shiono Y, Kubo T, Tanaka A, Ino Y, Yamaguchi T, Tanimoto T, et al. Long-term outcome after deferral of revascularization in patients with intermediate coronary stenosis and gray-zone fractional flow reserve. Circ J 2015; 79: 91-5. [CrossRef]

16. Lindstaedt M, Halilcavusogullari Y, Yazar A, Holland-Letz T, Bojara W, Mügge A, et al. Clinical outcome following conservative vs revascularization therapy in patients with stable coronary artery disease and borderline fractional flow reserve measurements. Clin Cardiol 2010; 33: 77-83. [CrossRef]
17. Kolli KK, van de Hoef TP, Effat MA, Banerjee RK, Peelukhana SV, Succop P, et al. Diagnostic cutoff for pressure drop coefficient in relation to fractional flow reserve and coronary flow reserve: A patient-level analysis. Catheter Cardiovasc Interv 2016; 87: 273-82.
18. Spagnoli V, Amabile N, Dillinger JG, Veugeois A, Logeart D, Henry P, et al. Myocardial Fractional Flow Reserve Measurement Using Contrast Media as a First-Line Assessment of Coronary Lesions in Current Practice. Can J Cardiol 2016; 32: 739-46. [CrossRef]
19. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al.; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014; 371: 1208-17.
20. Koo BK. The present and future of fractional flow reserve. Circ J 2014; 78: 1048-54. [CrossRef]
21. Gori AM, Cesari F, Marcucci R, Giusti B, Paniccia R, Antonucci E, et al. The balance between pro- and anti-inflammatory cytokines is associated with platelet aggregability in acute coronary syndrome patients. Atherosclerosis 2009; 202: 255-62. [CrossRef]
22. Sun H, Koike T, Ichikawa T, Hatakeyama K, Shiomi M, Zhang B, et al. C-reactive protein in atherosclerotic lesions: its origin and pathophysiological significance. Am J Pathol 2005; 167: 1139-48. [CrossRef]
23. Schwarzer R, Schnell-Inderst P, Grabein K, Gohler A, Stollenwerk B, Grandi N, et al. [Prognostic value and clinical effectiveness of high sensitivity C-reactive protein as a marker in primary prevention of major cardiac events]. Z Evid Fortbild Qual Gesundhwes 2009; 103: 319-29. [CrossRef]
24. Avanzas P, Arroyo-Espliguero R, Cosin-Sales J, Aldama G, Pizzi C, Quiles J, et al. Markers of inflammation and multiple complex stenoses (pancoronary plaque vulnerability) in patients with non-ST segment elevation acute coronary syndromes. Heart 2004; 90: 847-52.
25. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 1994; 331: 417-24. [CrossRef]
26. Rahimi K, Secknus MA, Adam M, Hayerizadeh BF, Fiedler M, Thiery J, et al. Correlation of exercise capacity with high-sensitive C-reactive protein in patients with stable coronary artery disease. Am Heart J 2005; 150: 1282-9. [CrossRef]
27. Bhatt DL. Inflammation and restenosis: is there a link? Am Heart J 2004; 147: 945-7. [CrossRef]
28. Li L, Li B, Xie H, Zhai CJ, Liu QW, Zhang HZ, et al. Long-term outcome of intravascular ultrasound application in patients with moderate coronary lesions and grey-zone fractional flow reserve. Coron Artery Dis 2016; 27: 221-6. [CrossRef]
29. Tousoulis D, Antoniades C,Nikolopoulou A, Koniari K, Vasiliadou C, Marinou K, et al. Interaction between cytokines and sCD40L in patients with stable and unstable coronary syndromes. Eur J Clin Invest 2007; 37: 623-8. [CrossRef]