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 Cardioi 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 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
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 were 186 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 vasodilation, intracoronary injection of 200 μg nitroglycerine 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...
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.

| Group | Group I | Group II | Group III | Group IV | P value |
|-------|---------|----------|-----------|----------|---------|
| Age (years) | 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 (48) | 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/m²) | 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)

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...
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/
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

| 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 (+) |

**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          | 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 II**

| Age/gender | Target Vessel | DS (%) | Baseline FFR | Revascularization FFR | Hs-CRP (mg/L) | MACE Month | Reason for revascularization |
|------------|---------------|--------|--------------|-----------------------|---------------|-------------|-------------------------------|
| 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**

| Age/gender | Target Vessel | DS (%) | Baseline FFR | Revascularization FFR | Hs-CRP (mg/L) | MACE Month | Reason for revascularization |
|------------|---------------|--------|--------------|-----------------------|---------------|-------------|-------------------------------|
| 1          | 55/M          | RCA    | 62           | 0.77                  | 0.73          | 2.3         | 11.0 ECG(+) |

**Group IV**

| Age/gender | Target Vessel | DS (%) | Baseline FFR | Revascularization FFR | Hs-CRP (mg/L) | MACE Month | Reason for revascularization |
|------------|---------------|--------|--------------|-----------------------|---------------|-------------|-------------------------------|
| 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.
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.
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 pro-inflammatory 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...
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.

Acknowledgments: Grants, contracts, and financial support: Vital Science and Technology Development Planning Department of Shandong Province, China (grant no. 2015GSF118045).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – LL, QL, BL; Design – LL, ZL, BL; Supervision – LL, QL, ZL; Fundings – LW, BL; Materials – QL, ZL, LW; Data collection & or processing – LW, JW; Analysis & or interpretation – JW, LS; Literature search – QL, LS, BL; Writing – LL, LS; Critical review – BL.

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