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The Usefulness of Ryusei® Perfusion Balloon for Treating Acute Coronary Syndrome with Vulnerable Plaque

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Abstract

Background: Intracoronary thrombus followed by a rupture of unstable vulnerable plaque is a well-known cause of acute coronary syndrome (ACS). The no reflow/slow flow phenomenon is sometimes observed during a primary percutaneous coronary intervention (PCI) against ACS. It has already been shown that long inflation using a perfusion balloon (PB) is useful to remediate a coronary perforation. Thus, we investigated the usefulness of a PB for treating ACS. **Methods:** This study was a retrospective, single-center, observational study. One hundred-seven patients with ACS underwent PCI from January 2015 to December 2017 in our hospital. Fifty patients were treated by PB directly (PB group) and the remaining 57 patients were treated by another conventional balloon (C group). We used the Ryusei® balloon (Kaneka, Japan) as a PB. The clinical outcome was the incidence of the no reflow or slow flow phenomenon, the incidence of using IABP. **Results:** One patient in the PB group demonstrated slow flow phenomenon temporarily, and the coronary flow was quickly restored by thromboaspiration. In contrast, nine patients in the C group had occurrences of no reflow/slow flow phenomenon. Although all patients in the C group required stenting, some patients (24%) of the PB group did not require stenting. **Conclusion:** We found that the use of PB had a favorable effect on the treatment of ACS. Some patients completed PCI without a need for stenting.

Keywords

A Perfusion Balloon, Vulnerable Plaque, Acute Coronary Syndrome

1. Introduction

Acute coronary syndrome (ACS) usually occurs as a result of thrombus forma-

tion over a vulnerable, unstable, and fragile plaque, which undergoes rupture or erosion [1]. Vulnerable plaques are characterized by a large, lipid-enriched necrotic core overlaid with a thin fibrous cap [2]. High levels of low-density lipoprotein cholesterol (LDL-C) are a well-known risk factor for the development of atherosclerosis [1]. A search for determinants in the blood for these vulnerable plaques suggested that LDL-C is the best lipid predictor for the extent of atherosclerosis [3]. It has been shown that there is an association between elevated LDL-C and vulnerable plaque in the coronary arteries [4] [5]. Many studies demonstrated the capability of statins to stabilize vulnerable plaques via their pleiotropic effects, including lowering LDL-C level [6] [7] [8] [9].

No reflow/slow flow phenomenon is defined as a state of myocardial hypoperfusion in the presence of an epicardial coronary artery [10]. This phenomenon is sometimes observed during a primary percutaneous coronary intervention (PCI) against ACS [11]. It has been shown that the no reflow phenomenon occurs in 11% to 41% of ST-segment elevation myocardial infarction patients treated by primary PCI [12] [13]. The phenomenon is caused by the distal embolization of vulnerable plaque in the target vessel during PCI [14]. Although direct stenting is currently the representative method to circumvent the no reflow/slow flow phenomenon, the phenomenon is often observed even when using direct stenting [15]. In addition, it has been reported that distal protection devices are considered to be effective in preventing distal embolization, particularly in animal experimental studies [16]. A common practice is to use intra-aortic balloon pump (IABP) in patients with the no reflow phenomenon with the expectation of an increase in diastolic coronary flow and improved cardiac function [17]. The phenomenon is closely related to the clinical outcome of patients, and is one of the leading causes of death after PCI [18]. The purpose of this study is to investigate the usefulness of a Perfusion balloon (PB) in ACS patients with vulnerable plaque.

2. Methods

2.1. Subjects

This study was a retrospective, single-center, observational study. A flow diagram of patient selection is provided in **Figure 1**. We enrolled 124 consecutive patients who underwent primary PCI for ACS at our hospital for just 3 years between January 2015 and December 2017. Seventeen patients were excluded from the study: 4patients who were treated with direct stenting, and 13patients who had been medicated with a statin and the level of LDL-C was less than 100 mg/dL according the blood test. Among the remaining 107 patients, 50 patients were treated by PB directly (PB group) and the remaining 57 patients were treated by another conventional balloon (C group).

2.2. PCI Procedure

ACS was defined as myocardial infarction and unstable angina pectoris. All patients

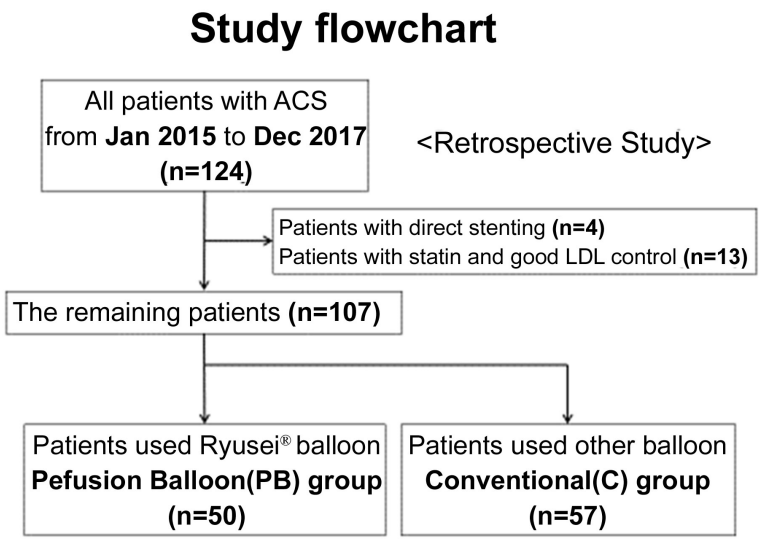

Figure 1. Study flowchart.

had angina and underwent PCI within 12 hours of symptom onset. Catheterization was performed through the femoral, brachial, or radial artery approach using a 6-Fr or 7-Fr sheath and catheters. All patients received a loaded dose of aspirin of 200 mg, clopidogrel 300 mg, or prasugrel 20 mg just before PCI. All patients also received heparin 5000 to 10,000 U in a weight-dependent manner before PCI.

First, we performed thrombus aspiration therapy if needed. Second, we used the Ryusei® balloon (Kaneka, Japan) for predilatation. We performed a long inflation (definitely 3 min) for the target vessel by the Ryusei® balloon in the PB group. At that time, we temporarily pulled a guidewire to increase the antegradecoronary flow during the long inflation (**Figure 2**). We used a non-compliant high pressure balloon or a semi-compliant balloon for 15 to 20 seconds in the C group. Each balloon size was decided by each operator based on the vessel reference by intravascular ultrasound (IVUS). We operators are all cardiologists and expert interventionists. We did not perform distal protection of the target vessel to capture the embolus during PCI in either group. Finally, at the discretion of the operator, we selected a bare metal stent (BMS), drug eluting stent (DES), or no stent after predilatation. The thrombolysis in myocardial infarction (TIMI) flow was measured during PCI all patients.

2.3. Perfusion Balloon

PB was designed to provide continuous transcatheter blood flow and thereby reduced myocardial ischemia during coronary angioplasty [19]. Therefore, PB had been used for a long inflation balloon angioplasty especially for in-stent restenosis and for small vessels, thrombus control, and the prevention of acute perfusion injury of acute myocardial infarction [19] [20] [21]. The production of PB had stopped in 2008, not only in Japan but throughout the world because it was replaced by stenting [19]. Ryusei® as a PB has been revived and modified by

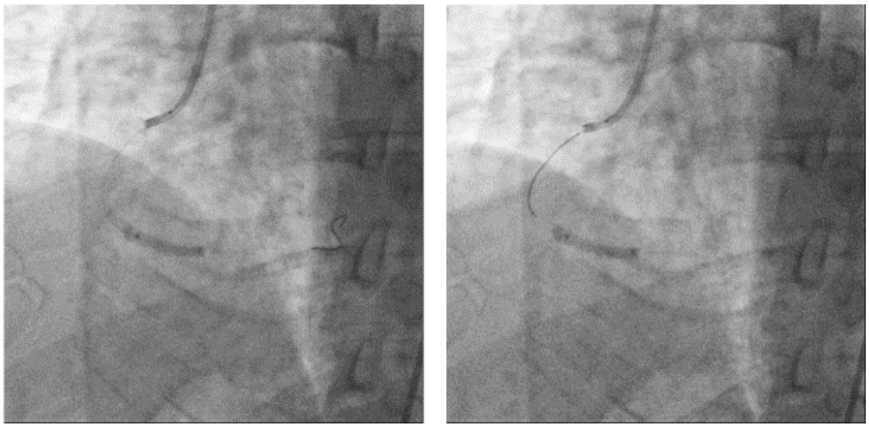

Figure 2. Perfusion balloon angioplasty. PCI for RCA lesion. (Right) Balloon angioplasty with PB in RCA lesion. (Left) Pulling a guidewire during predilatation to increase coronary flow.

the Kaneka Medix Corporation in Japan in response to the interests of interventionists [19]. Ryusei® has been improved by a low-profile tip in the passage of a catheter compared to past models. The instrument has 16 proximal perfusion holes (φ300 μm) and 8 distal perfusion holes (φ300 μm), which allows the blood flow from the distal to proximal balloon segment [19]. This PB has been primarily used for bailing out coronary perforation [19] [22]. It remains unclear whether the PB has a favorable effect on the treatment of ACS with a vulnerable plaque. It is said that both thrombus and vulnerable plaques are involved in the slow flow/no reflow phenomenon. There have much vulnerable plaques in the patients with unstable angina. That is the reason why we selected the ACS patients including unstable angina patients in the present study.

2.4. Outcomes

The primary outcome was the incidence of the no reflow or slow flow phenomenon, defined as absent flow (TIMI flow grade 0), incomplete filling (TIMI flow grade 1), or slow-reflow but complete filling (TIMI flow grade 2) of the culprit coronary artery during or at the end of the PCI as demonstrated by the coronary angiogram [23]. The worst/lowest flow grade was recorded. The definition of no-reflow also required the absence of coronary dissection or spasm that could cause a decrease in coronary blood flow [24]. The secondary outcome was the incidence of using IABP and all-cause mortality at 30 days. Operators used IABP in cases in which the no reflow/slow flow phenomenon could not be mediated by administering vasodilator drugs (e.g., Nicorandil and Nitroglycerin). The decision to insert IABP was left to the operator's discretion. Finally, the third outcome was the rate of using a stent.

2.5. Statistical Analysis

Data are presented as mean ± standard deviation (SD) or percentages. Comparisons between groups treated with versus without PB were performed using a t

test for continuous data, and the chi-square test or Fisher exact test for categorical data. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Clinical Characteristics and Angiography

The clinical characteristics of the 107 patients are listed in Table 1. Baseline clinical characteristics were not different between the PB group and the C group, except in their sex. There were few patients who had taken a single antiplatelet drug and a statin. No patients had taken dual antiplatelet therapy (DAPT) before onset. Target lesion characteristics are listed in Table 2. The target lesions in the PB group were more often located in the right coronary artery (RCA) and left circumflex artery (LCX), and less often in the left anterior descending artery (LAD) than those in the C group (RCA, 44% vs. 26%; LAD, 38% vs. 63%; LCX, 18% vs. 11%; p = 0.02). There were no differences in the quantitative coronary angiography (QCA) percent diameter stenosis between the two groups. The PCI was performed using one of two aspirators: Eliminate (Terumo®, n = 5) or Thrombuster (Kaneka®, n = 64). The BMS used included Liberte (Boston Scientific®, n = 2) and Integrity (Medtronic®, n = 10), and the DES used included Nobori (Terumo®, n = 5), Resolute (Medtronic®, n = 5), Promus (Boston Scientific®, n = 8), Xience (Abbot Vascular®, n = 2), Ultimaster (Terumo®, n = 25), and SYNERGY (Boston Scientific®, n = 38). Figure 3 shows that the predilatation balloon size of the C group was significantly smaller than that of the Ryusei® balloon of the PB group (2.60 mm vs. 3.02 mm, p = 0.02).

Table 1. Baseline patient characteristics.

	PB group	C group	p
Age (years)	64.62 ± 12.33	67.21 ± 12.71	0.29
Men rate (%)	94	80.7	<0.05
Height (cm)	166.54 ± 6.86	164.18 ± 8.72	0.13
Weight (kg)	68.67 ± 11.81	65.54 ± 13.02	0.20
Heart rate (bpm)	75.66 ± 18.48	80.84 ± 17.09	0.14
Sys. Pressure (mmHg)	135.22 ± 29.10	137.43 ± 29.17	0.70
Dias. Pressure (mmHg)	75.06 ± 19.10	74.02 ± 15.49	0.76
eGFR (ml/min/1.73 m^2)	64.06 ± 17.12	62.71 ± 23.66	0.08
Smoking (%)	62.0	47.4	0.13
LDL (mg/dl)	152.96 ± 47.16	138.59 ± 35.91	0.08
HbA1c (%)	6.56 ± 1.26	6.35 ± 1.49	0.45
Stain drug (%)	8.0	10.5	0.75
Antiplatelet drug (%)	12.0	10.5	1.00
Thrombectomy (%)	68.0	61.4	0.55

Sys. systolic, Dias. Diastolic, eGFR estimated glomerular filtration rate, LDL low-density lipoprotein, HbA1c glycosylated hemoglobin A1c.

Table 2. Angiographic findings.

	PB group	C group	p
Target vessels			0.02
RCA	22 (44%)	15 (26%)	
#1	14	9	
#2	8	2	
#3	3	3	
#4	4	0	
LAD	19 (38%)	36 (63%)	
#6	13	23	
#7	13	16	
#8	1	2	
#9	0	2	
LCx	9 (18%)	6 (11%)	
#11	2	1	
#12	2	0	
#13	5	4	
#14	0	1	
QCA			
DS (%)	98.6	97.1	0.10
TIMI flow			0.34
grade 0	25 (50%)	23 (40%)	
grade 1, 2, 3	25 (50%)	23 (60%)	

RCA right coronary artery, LAD left anterior coronary artery, LCx left circumflex artery, QCA quantitative coronary angiography, DS diameter stenosis, TIMI thrombolysis in myocardial infarction trial.

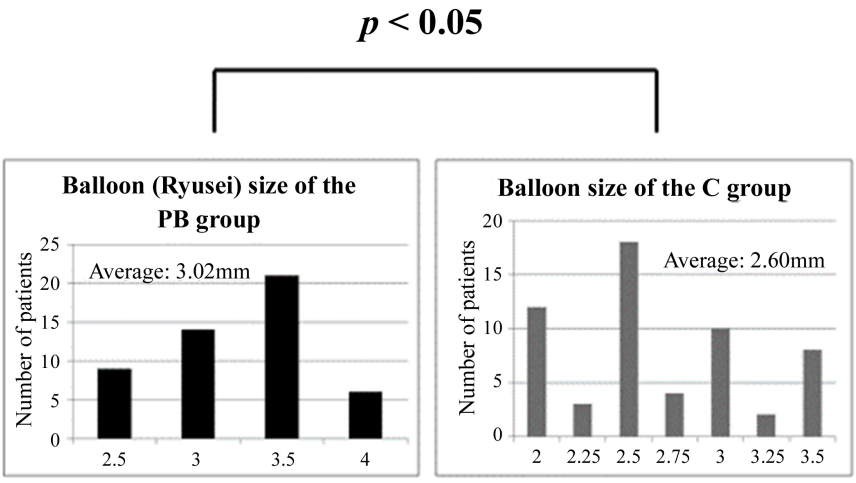

Figure 3. Comparing balloon size of the PB group with that of the C group. It shows that the predilatation balloon size of the C group was significantly smaller than that of the Ryusei® balloon of the PB group (2.60 mm vs. 3.02 mm, $p < 0.05$).

3.2. Clinical Outcomes

We first investigated the rate of the no reflow/slow flow phenomenon between the two groups. Figure 4 shows that the rate of no reflow/slow flow phenomenon of the PB group was significantly lower than that of the C group (2.00% vs. 15.79%, p = 0.02). Operators finally used IABP support for some patients who did not improve with the no reflow/slow flow phenomenon after administering vasodilator drugs or after the aspiration of embolus. All patients who had no reflow/slow flow phenomenon in the P group were completely or mostly cured by administering vasodilators only. Figure 5 shows that the frequency of using IABP during PCI of the PB group was not observed. In contrast, we occasionally used the IABP system in the C group even though the statistical analysis had no significance (0% vs. 8.77%, p = 0.06). There was no difference in all-cause mortality at 30 days between the two groups (0% vs. 3.51%, p = 0.497).

As stated previously, our primary aim was the examination of the rate of no reflow/slow flow phenomenon. We noticed that predilatation by Ryusei® resulted in the requirement of less dissection of the coronary artery in this trial. In the PB group, because some good results on angiography were seen after the initial ballooning in some patients, we finished the PCI for the treatment of ACS without stenting. We, thus, measured the rate of stentless PCI with the PB angioplasty only. Figure 6 shows that the rate of stentless PCI in the PB group was significantly higher than that of the C group (24% vs. 0%, p < 0.0001).

4. Discussion

The stabilization of vulner able plaques by statins is confirmed [6] [7] [8] [9]. Therefore, in such a situation, it is impossible to expecta quick effect of the statin. In the present study, there were a few patients who had taken statins. The

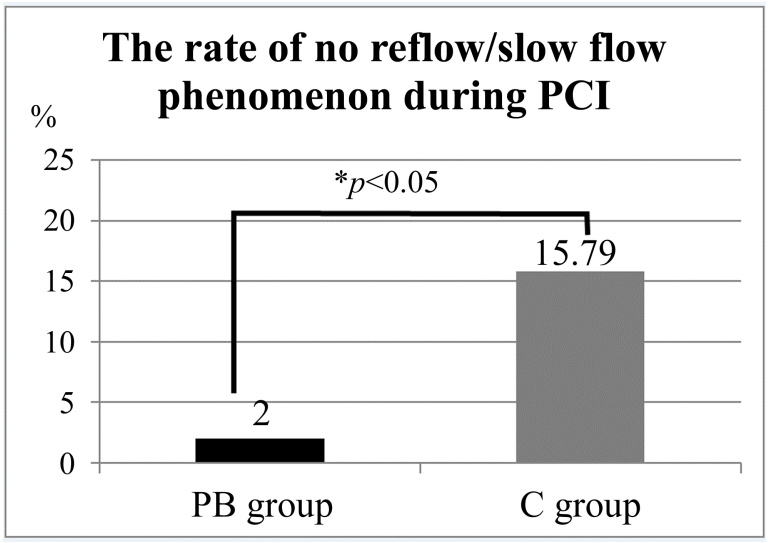

Figure 4. The rate of no reflow/slow flow phenomenon during PCI. It shows that the rate of no reflow/slow flow phenomenon during PCI of the PB group was significantly lower than that of the C group (2.00% vs. 15.79%, p = 0.02).

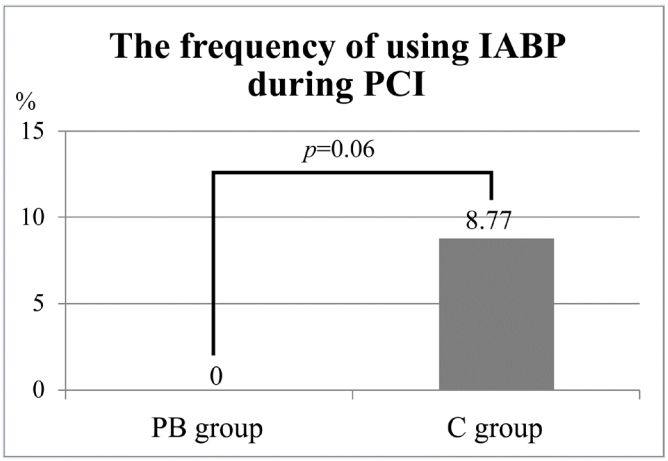

Figure 5. The frequency of using IABP during PCI. It shows that the frequency of using IABP during PCI of the PB group was not observed (0% vs. 8.77%, p = 0.06).

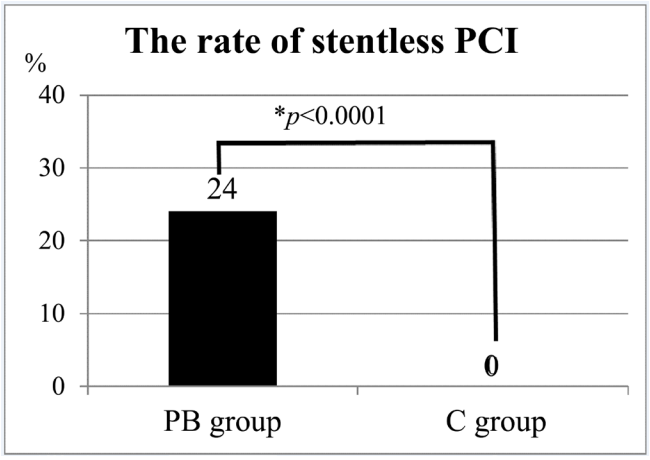

Figure 6. The rate of stentless PCI. It shows that the rate of stentless PCI in the PB group was significantly higher than that of the C group (24% vs. 0%, p = 0.00005).

patients who had a well-controlled LDL level were not contained in the two groups. It is considered that all enrolled patients had vulnerable plaques and had a high risk of evoking the no reflow/slow flow phenomenon.

It has been reported that using a smaller balloon for predilatation in severe stenotic lesions is better in dissection [25]. There was significant difference in the size both of balloon and in the stent in the C group. It is also considered that the operators theoretically and empirically tended to select a smaller size for predilatation to avoid distal embolism. As a result, balloon size for predilatation in the PB group was larger than that in the C group, but the rate of the no reflow/slow flow phenomenon of the PB group was lower than that of the C group. It may be possible for PB to gain the sufficient lumen size in the target lesion. As we learned from our experience with some slow flow phenomenon after using the Ryusei balloon, slow flow in the PB group was caused by using a bigger balloon compared to vessel size. Therefore, on key points of how to use PB, it is recommended that a relatively small balloon size should be selected and that

ballooning pressure should be started from a low level.

In the present study, we found that predilatation with a conventional balloon tends to result in a serious issue with the no-reflow phenomenon compared to using the Ryusei® balloon. And more, we completely finished the PCI by using the PB without IABP. It has recently been reported that long inflation using a perfusion balloon was effective to manage the large amount of thrombus in a stent [26]. Some trials have shown that an antiplatelet, GPIIb/IIIa inhibitor reduces the incidence of no-reflow in native vessel. However, it cannot be used clinically in Japan [27]. The PB might contribute to control not only vulnerable plaque but also thrombus. We suggested that long inflation with a Ryusei® balloon is a useful technique in ACS as well as treating thrombus in a stent.

Our first aim was to determine whether using a PB for ACS with vulnerable plaque can avoid the no reflow/slow flow phenomenon. However, some patients received PCI for ACS without stenting, and our data indicated that the rate of stentless PCI was approximately 25% of the PB group. Very often, coronary artery dissection occurs after predilatation of primary and elective PCI for ACS. Some patients underwent PCI without stenting because there were no observed severe dissections after Ryusei® ballooning in this study. It is considered that long inflation for predilatation may decrease the coronary dissection. As a result, using PB possibly contributes to stentless PCI. DAPT has been used in the patients with stenting, and increased bleeding is a well-known side effect [28]. Patients with stentless PCI didn't have to take DAPT for a long time even after ACS. Therefore, using PB could reduce the number of patients who require DAPT by stentless PCI. For example, using PB may be a useful technique for the ACS patients who need to take have surgery in the near future.

5. Study Limitations

There are several limitations to this study. First, it was not a prospective, randomized, or multi-center trial. Therefore, some already known or unknown confounding factors may have influenced the data. The result should be validated in a future prospective study. Second, selection bias may have occurred; for example, the treatment strategies and balloon type were selected by the operator. Third, some patients with ACS might not have a vulnerable plaque in their vessels. We did not routinely evaluate the amount of plaques in the study patients using IVUS.

6. Conclusion

We detected that the use of the Ryusei® balloon had a favorable effect on the treatment of ACS. Some patients treated by Ryusei® balloon underwent PCI without stenting.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ACS: acute coronary syndrome
LDL-C: low-density lipoprotein cholesterol
PCI: percutaneous coronary intervention
IABP: intra-aortic balloon pump
PB: perfusion balloon
IVUS: intravascular ultrasound
BMS: bare metal stent
DES: drug eluting stent
DAPT: dual antiplatelet therapy
RCA: right coronary artery
LCx: left circumflex artery
LAD: left anterior descending artery
QCA: quantitative coronary angiography