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Outcome of coronary lesions with deferred revascularization due to negative fractional flow reserve in subjects with acute coronary syndrome

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ABSTRACT

Objective: Revascularization of functionally non-significant stenoses in patients with stable coronary artery disease can safely be deferred as rate of adverse cardiovascular events is low. It is not clear whether fractional flow reserve (FFR) is just as accurate in acute coronary syndromes (ACS). The aim of this study is to assess the outcome of coronary lesions whose revascularization was deferred based on negative FFR values in subjects with ACS.

Methods: Patients with acute coronary syndrome and showing at least one coronary stenosis whose revascularization was deferred based on FFR value >0.80 were included in the study. The primary endpoint of the study was the rate of target lesion failure (TLF), a composite of cardiac events (cardiac death, myocardial infarction and any coronary revascularization) related to the initially deferred stenosis at three-year follow-up.

Results: A total of 319 patients (237 male), mean age 68 [59–74] years and 355 coronary lesions with deferred revascularization based on negative FFR values (0.88 ± 0.05) were selected. The rate of TLF was 6% at 1-year, 9% at 2-year and 12% at 3-year follow-up. TLF was driven by a new acute coronary syndrome in 75% of cases. The median time interval from FFR assessment to TLF was 457 [138–868] days.

Conclusions: In patients with acute coronary syndrome, the rate of TLF of the initially deferred coronary stenoses is 12% at 3-year follow-up and TLF occurred because of a new ACS in three quarters of cases.

1. Introduction

Fractional flow reserve (FFR) is a well-validated technique to guide coronary intervention by identification of lesion-level ischemia [1]. Revascularization of physiological significant stenoses is associated with improved cardiovascular outcomes and symptoms [2,3]. Conversely, non-significant stenoses are not associated with inducible ischemia and previous studies suggest their revascularization can safely be deferred as rates of cardiovascular death and myocardial infarction (MI) are low [2–8]. These data mainly refer to patients with stable coronary artery disease, whereas the diagnostic validity of FFR is less certain in subjects affected by acute coronary syndrome (ACS) due to some physiological concerns: first, FFR accuracy is critically dependent on the ability to achieve maximal hyperemia but microvascular vasodilatation may be impaired in ACS [9,10]. Second, ACS patients are likely to present variable degrees of left ventricle dysfunction and FFR measurement might be affected by left ventricle end diastolic pressure [11]. Third, FFR has the ability to identify vessels with physiologically restricted coronary flow, but cannot detect atherosclerotic plaques with

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unstable features which may present without flow limitation: no information is available about FFR assessment and FFR related outcome of these lesions [12].

The aim of this study is to assess the outcome of physiologically non-significant coronary stenoses in ACS patients, the revascularization of which was deferred due to negative FFR values.

2. Methods

This is a retrospective, multi-center, observational study. From January 2009 to December 2012, patients with ACS, including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) who underwent coronary angiography and FFR assessment of at least one borderline coronary stenosis were selected: only those patients with at least one lesion, the treatment of which was deferred based on a negative FFR result, were finally included in the study. STEMI patients were included in the study as long as FFR assessment was performed 3–4 days after primary PCI in a coronary artery different from the infarct-related one.

Coronary pressure measurement was performed with a 0.014-in. pressure wire (Radi Medical Systems, Uppsala, Sweden; or Jomed International, Helsinborg, Sweden). The wire was introduced through the guiding catheter, calibrated, advanced into the coronary artery and positioned 3 cm distal to the stenosis. Maximal hyperemia was induced by intravenous administration of adenosine (140 μg/kg/min for 5 min). FFR was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. In case of multiple FFR measurements for the same lesion, the minimal value obtained was used for analysis. The FFR cutoff value used to defer revascularization was 0.80 in all patients.

Patients were followed-up from the date of index FFR assessment for three years. All follow-up coronary angiograms were reviewed independently by a minimum of two investigators. If a patient had follow-up outside our institution, medical records including angiograms were obtained for review.

The primary endpoint of the study was the rate of target lesion failure (TLF), a composite of cardiac death, myocardial infarction and re-PCI related to the initially deferred stenosis.

The secondary endpoint was the rate of major adverse cardiovascular events (cardiac death, myocardial infarction, any coronary revascularization). Follow-up was carried out by either ambulatory visit or phone call three years after FFR measurement.

Distributions of continuous variables were tested with the Kolmogorov–Smirnov test and classified as either normally or non-normally distributed. Normally distributed variables are presented as mean ± SD, whereas non-normally distributed variables are presented as median [25th–75th percentile]. Binary and non-binary factors are presented as counts and percentages.

Before proceeding to the multivariate analysis, each independent predictor was tested for significance for each of the two endpoints. Comparisons between groups were performed with the Student's *t*-test or the Mann–Whitney test for the normally or non-normally distributed variables, respectively. The Chi-square test was used for categorical variables (binary and non-binary). This process was repeated for each of the two endpoints: incidence of TLF and a composite of myocardial infarction, death and any coronary revascularization. Significance threshold was set at $P < 0.05$ (two-sided). Parameters to be included in the two final models were selected using descending exclusion: an initial model was fit using all nineteen independent variables. Then the least significant variable was removed and the model updated. This process was repeated until there were only five variables remaining for the primary endpoint model and eight variables for the secondary model.

GraphPad Prism 4 (GraphPad, La Jolla, CA) and Rstudio (Rstudio, Boston, MA) software were used for the analyses.

3. Results

A total of 515 ACS patients with angiographic borderline coronary stenoses evaluated by FFR were initially screened: 330 of them showing at least one lesion with deferred revascularization due to negative FFR results were included in the study. For 11 of them, follow-up was not available so that the final study population consisted of 319 patients and 355 coronary lesions.

Clinical and angiographic features of the study population are listed in Table 1.

In 42% of cases, the deferred stenosis was hypothesized to be the culprit lesion: in the remaining cases, the culprit lesion was found in vessels different from those assessed by FFR and was treated by PCI. The primary endpoint (TLF) occurred in 12% of the index coronary lesions at 3-year follow-up (Fig. 1). In 75% of cases, TLF was associated to a new ACS (36% UA, 36% NSTEMI and 3% STEMI). The median time interval from FFR assessment to TLF was 457 [138–868] days (Table 2). Deferred stenoses that were hypothesized to be culprit lesions did not show any significant difference in the rate of TLF as compared to non-culprit lesions (Table 3).

The secondary endpoint, a composite of cardiovascular death, myocardial infarction and any coronary revascularization, occurred in 33% of patients at three-year follow-up (Table 4).

Comparison between index lesions with and without events suggested the following clinical variables as possible predictors of TLF: UA at clinical presentation, hypertension, peripheral vascular disease, higher syntax score and use of clopidogrel. However, both the univariate and multivariate analysis failed to detect any significance in the variables as predictors of events. Only for the secondary endpoint (composite of cardiovascular death, MI and any coronary revascularization) the variable "peripheral vascular disease" was a significant predictor of the event. When analyzed as part of a logistic regression model that includes 8 variables, the risk increase (odds ratio) of this variable was 3.03, with [1.39–6.54] as 95% confidence interval (Table 5).

4. Discussion

The main findings of this study are as follows: in patients with acute coronary syndrome, 12% of coronary stenoses initially deferred based on negative FFR results led to new cardiac events at three-year follow-up. TLF occurred within a median time interval of 15 months after FFR assessment and in three-quarters of the cases was driven by a new acute coronary syndrome.

These results are in contrast with previous data collected in stable patients and showing that physiologically non-significant stenoses are associated with a good prognosis with a rate of cardiac events <1%/year [2–8]. Three possible hypotheses may account for this discordance: first,

Table 1
Clinical and angiographic data of the study population ($N = 319$).

Variable	
Age (years)	68 [59–74]
Male	237 (74%)
BMI	45 [41–49]
CrCl (ml/min)	74 [57–92]
Diabetes	70 (22%)
Hypertension	234 (73%)
Hypercholesterolemia	194 (61%)
History of tobacco use	146 (46%)
Current smoker	66 (21%)
Previous stroke or transient ischemic attack	15 (5%)
Peripheral vascular disease	34 (11%)
Previous myocardial infarction	58 (18%)
Previous PCI	118 (37%)
Ejection fraction (%)	58 [50–62]
ECG evidence of ischemia at presentation	173 (54%)
Medication at the time of angiography	
Aspirin	299 (94%)
Clopidogrel	235 (74%)
Ticagrelor	26 (8%)
Prasugrel	12 (4%)
Statin	277 (87%)
Beta-blocker	214 (67%)
Calcium channel blocker	36 (11%)
Nitrate	116 (36%)
Clinical indication for coronary angiography	
Unstable angina	123 (39%)
NSTEMI	137 (43%)
STEMI	59 (18%)
PCI performed	190 (60%)
Index lesions (evaluated by FFR and deferred) no.	355
Index lesions location	
Left main	28 (8%)
Left anterior descending	206 (58%)
Circumflex	65 (18%)
Right	52 (15%)
Bypass	4 (1%)
Maximum stenosis (%)	55 [50–60]
FFR value	0.88 ± 0.05
Index lesion = culprit lesion	149 (42%)

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