

Comparison between intermediate and severe coronary stenoses and clinical outcomes of an OCT-guided PCI strategy

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Aims We compared optical coherence tomography (OCT) features of intermediate and severe coronary stenoses in patients with stable angina and acute coronary syndrome (ACS), and tested the clinical impact of an OCT-based strategy for treating intermediate stenoses.

Methods The study enrolled 135 consecutive patients with either ACS or stable angina and a single de-novo coronary stenosis. Patients were divided into two groups: intermediate stenosis defined as quantitative coronary angiography percentage narrowing less than 70%, or presence of angiographic vessel haziness and severe stenosis with percentage narrowing more than 70%. OCT was performed to assess features of plaque vulnerability and to measure the minimal lumen area. We also appraised the 12-month rate of major adverse event (MACE) of an OCT-guided strategy of percutaneous coronary intervention (PCI) based on the presence of thrombus and/or minimal lumen area less than 3.0 mm².

Results Fifty-six patients had intermediate stenoses, whilst 79 had severe stenoses. In the 'intermediate stenosis group', patients with stable angina had a lower asymmetric index ($P=0.02$) and a greater calcific arc ($P=0.0001$). In the 'severe stenosis group', intermediate lesions of patients with ACS exhibited a greater lipid arc as compared with

patients with stable angina ($P=0.03$). A higher prevalence of thin cap fibroatheroma was seen in patients with ACS of both groups. The incidence of MACE was not significantly different between patients with an intermediate stenosis who received PCI vs. optimal medical therapy on the basis of OCT findings ($P=0.26$).

Conclusions Intermediate coronary stenoses showed distinctive OCT-based features according to the initial clinical presentation. The adoption of an OCT-guided PCI strategy, based on the presence of coronary thrombus and significant vessel narrowing, led to encouraging results.

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Introduction

Intermediate stenosis is often defined as a non-obstructive vessel narrowing comprised between 30 and 70% at quantitative coronary angiography (QCA). They represent a grey zone for interventional cardiologists and often lead to controversies regarding the need to perform percutaneous coronary intervention (PCI).¹ Frequency domain optical coherence tomography (FD-OCT) is a high-resolution (20 μm) intravascular imaging modality that allows a detailed analysis of the intermediate plaques. FD-OCT accurately identifies lumen area contour and depicts anatomical features indicative of plaque vulnerability or instability, such as thin cap fibroatheroma (TCFA) or coronary thrombus.^{2,3}

In this study, we sought to assess the FD-OCT-based plaque features of intermediate coronary stenosis at angiography, in the clinical settings of stable angina

and acute coronary syndrome (ACS). In addition, we addressed the clinical utility of a strategy of PCI guidance of intermediate stenoses, based on the presence of coronary thrombus and/or a minimal lumen area (MLA) less than 3.0 mm².

Methods

Patient populations

A total of 135 consecutive patients were retrospectively included in the study, from December 2010 until March 2012. Among these, 56 patients had an angiographically defined intermediate stenosis, and 79 had a severe stenosis.

Inclusion criteria were as follows: for the intermediate stenosis group, presence of a single de-novo stenosis with a percentage stenosis less than 70% by QCA or the presence of angiographic vessel haziness defined as a

defect in the contrast filling of the coronary artery; for the severe lesion group, presence of a single de-novo stenosis more than 70% by QCA without haziness at angiography; presence of either stable angina or ACS on hospital admission; and successful baseline assessment with coronary OCT. Stable angina patients had to have signs of induced myocardial ischaemia at non-invasive stress tests,^{4,5} but there was no change in frequency, duration, or intensity of angina symptoms before hospital admission. ACS patients included unstable angina,⁵ non-ST-segment elevation myocardial infarction (NSTEMI),⁶ and ST-segment elevation myocardial infarction (STEMI).⁷

Exclusion criteria were as follows: left main stenosis; ostial stenosis; presence of overlapping vessels; a large side-branch (greater than 2 mm in diameter); in-stent restenosis or thrombosis; previous coronary artery bypass surgery; and stenosis location in a distal segment of the coronary tree that could not be imaged with OCT.

The study was conformed by the Declaration of Helsinki on human research, and informed consent was obtained from each patient.

Quantitative coronary angiographic analysis

Quantitative coronary angiography analysis was performed with a validated edge-detection system (CAAS Version 5.9, Pie Medical Imaging, Maastricht, the Netherlands). Reference vessel diameter, minimal lumen diameter, percentage of diameter stenosis, and stenosis length were measured in diastolic frames from orthogonal projections according to validated protocols⁸ for both intermediate and severe stenoses.

Frequency domain optical coherence tomography procedure and analysis of optical coherence tomography images

Frequency domain optical coherence tomography was performed with non-occlusive techniques, as previously described.⁹ After intra-coronary injection of nitroglycerin 200 µg, OCT images were acquired with a commercially available C7 system (LightLab Imaging Inc/St Jude Medical, Westford, Massachusetts, USA) after positioning of the C7 Dragonfly OCT catheter (LightLab Imaging Inc/St Jude Medical) distal to the target segment.

During OCT image acquisition, angiographic contrast media were injected through the guiding catheter with an automated power injector. The OCT pull-back speed was set at 20 mm/s, and the OCT images were calibrated adjusting the Z-offset. All OCT images were analysed offline in a centralized core lab (Rome Heart Research, Rome, Italy) using a dedicated OCT consol (LightLab Imaging Inc/St Jude Medical). The images were read by two readers (L.D.V. and F.P.) who were blinded to the protocol.

Frequency domain OCT analysis was then performed at the MLA site (MLA site analysis) and along the entire plaque (plaque analysis). At the MLA site, the following measurements were obtained: lumen area, minimal and maximal diameters, mean diameter, and asymmetric index, calculated as [(maximal diameter—minimal diameter)/maximal diameter]. An asymmetric index greater than 0.3 was indicative of asymmetric luminal narrowing. Plaque composition (lipid, fibrotic, and calcific), circumferential extension of lipid and calcium arcs, and a fibrous cap thickness were also measured as previously described.^{2,3}

Plaque analysis was performed along the entire plaque length in every cross-section. The analysis included presence of TCFA, plaque rupture, thrombus,^{10,11} micro-vessels,¹² and superficial calcified nodules.¹³ Measurements of plaque length cap thickness and lipid quadrants were also obtained.

Definitions of plaque components

A plaque was defined as lipid-rich if it contained two or more lipid quadrants. TCFA was defined as a lipid-rich plaque with a fibrous cap thickness of 65 µm or less.^{11,14,15} A micro-channel was defined as a no-signal tubulo-luminal structure without a connection to the vessel lumen, which was recognized on at least three consecutive cross-sectional OCT images.¹⁵ Thrombus was identified as an irregular-shaped mass with dorsal shadowing protruding into the vessel lumen or discontinuation from the surface of the vessel wall.¹⁰

Optical coherence tomography-guided treatment strategy for intermediate stenoses

Patients with an intermediate stenosis were treated with PCI if OCT showed a coronary intraluminal thrombus² and/or a MLA less than 3.0 mm², according to the procedural standards applied in our catheterization laboratory.¹⁶ The remaining patients received optimal medical therapy (OMT) only.

Definitions of follow-up clinical endpoints

Information about baseline characteristics and clinical events were obtained at 3, 6, 9, and 12 months with ambulatory visits, telephone contacts, or hospital medical records in case of coronary events.

The primary composite clinical endpoint included cardiovascular death, myocardial infarction (MI), and repeated revascularization. Secondary endpoints were each single endpoint of the primary composite (cardiovascular death, MI, or repeated revascularization). In detail, MI during follow-up was defined as an increase in cardiac biomarkers, with at least one value above the 99th percentile, along with at least one of the following: symptoms of ischaemia; new or presumed new significant ST-segment or T-wave changes, or new left bundle branch block; development of new pathologic Q waves

on an electrocardiogram; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or identification of an intra-coronary thrombus by angiography or autopsy.¹⁷ Repeated revascularization was defined as any repeated PCI to treat stent restenosis, or new PCI to treat intermediate stenosis for which intervention was deferred.

Statistical analysis

Normal distribution was assessed by the Kolmogorov–Smirnov test. Continuous variables were expressed as means \pm SD, and assessed with Student's *t* test; categorical variables were expressed as proportions and assessed with Fisher's exact test. value less than 0.05 was required for statistical significance. For statistical analysis, SPSS 17.0 (SPSS, Inc., Chicago, Illinois, USA) was used.

Results

Baseline patient characteristics

Baseline clinical features are shown in Table 1. Fifty-six patients out of 135 entered the intermediate stenosis group. Thirty patients (53%) had a stable angina, whilst 26 had an ACS (47%). Of these, 14 had NSTEMI/unstable angina, and 12 had STEMI. The severe stenosis group included 79 patients. Among them, 38 patients (48%) had stable angina, whereas the remaining 41 (52%) had ACS, with NSTEMI/unstable angina diagnosed in 21 patients, and STEMI in 20 patients.

Angiographic findings

Baseline angiographic findings are summarized in Table 2.

In the intermediate stenosis group, baseline %diameter stenosis was $53 \pm 15\%$ in the stable angina group and $56 \pm 15\%$ in the ACS group ($P=0.4$). The prevalence of vessel angiographic haziness was similar in the groups with stable angina and ACS. In the severe stenosis group, %diameter stenosis was $70 \pm 11\%$ in the stable angina group and $72 \pm 12\%$ in the ACS group ($P=0.3$).

Optical coherence tomography findings

Minimal lumen area site

In the intermediate stenosis group, patients with stable angina had larger MLA (3.5 ± 1.5 vs. 2.7 ± 1.3 mm²; $P=0.04$), but exhibited a lower asymmetric index (Fig. 1a) as compared with ACS (Fig. 1b) (0.24 ± 0.13 vs. 0.33 ± 0.15 ; $P=0.02$). Table 3 depicts plaque composition in the stable angina and the ACS group. In the presence of calcific MLA, the calcium arc was significantly higher in stable angina group (Fig. 1c) as compared with the ACS group (242 ± 57 vs. $114 \pm 35^\circ$; $P=0.0001$).

In the severe stenosis group, no difference was noted in the MLA between the ACS and the stable angina group (2.6 ± 0.8 vs. 2.3 ± 1.2 mm²; $P=0.22$). Consistently, the asymmetric index did not differ between the two groups ($P=0.94$). Lipid plaques were more commonly imaged in the ACS compared with the stable angina group ($P=0.03$).

Overall plaque

In the intermediate stenosis group, plaque length was not significantly different in patients with ACS as compared with patients with stable angina ($P=0.67$). TCFA (Fig. 2a) and thrombus (Fig. 2b) were significantly more common in ACS patients (26.9 vs. 6.7%; $P=0.04$ and 38.5 vs. 10%; $P=0.01$, respectively). However, no difference was found between the two groups in the incidence of plaque rupture (30.8 vs. 16.7%; $P=0.21$), as depicted in Table 4.

In the severe stenosis group, plaque length was significantly greater in patients with ACS as compared with patients with stable angina (14.2 ± 5.4 vs. 10.6 ± 4.4 mm; $P=0.002$). Presence of TCFA, thrombus, and ruptured plaque was significantly more common in the ACS group (68 vs. 44%; $P=0.03$, 48 vs. 0%; $P=0.0001$ and 75.6 vs. 31.6%; $P=0.001$, respectively), whereas calcified nodules were more frequently found in patients with stable angina (89.5 vs. 68.3%; $P=0.02$).

Table 1 Baseline clinical features

	Intermediate lesions (56)			Severe lesions (79)		
	SA (30)	ACS (26)	<i>P</i>	SA (38)	ACS (41)	<i>P</i>
Age [years (SD)]	68.8 (± 9.1)	64.3 (± 9.7)	0.17	71.4 (± 5.3)	70.2 (± 12)	0.73
Male sex [<i>n</i> (%)]	19 (63)	17 (65)	0.87	22 (60)	24 (58)	0.95
STEMI [<i>n</i> (%)]		12 (46)			20 (48)	
NSTEMI [<i>n</i> (%)]		14 (54)			21 (52)	
Hypertension [<i>n</i> (%)]	24 (80)	19 (73)	0.7	22 (58)	31 (76)	0.08
Diabetes mellitus [<i>n</i> (%)]	14 (46)	9 (35)	0.46	12 (31)	16 (39)	0.63
Current smoker [<i>n</i> (%)]	8 (27)	12 (46)	0.15	14 (37)	12 (29)	0.41
Dyslipidaemia [<i>n</i> (%)]	23 (77)	19 (73)	0.80	37 (97)	25 (61)	0.001
Family history [<i>n</i> (%)]	4 (13)	11 (42)	0.002	8 (21)	7 (17)	0.73
Previous PCI [<i>n</i> (%)]	14 (46)	10 (38)	0.44	16 (42)	13 (32)	0.33

ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment elevation myocardial infarction.

Table 2 Angiographic findings

	Intermediate lesions (56)			Severe lesions (79)		
	SA (30)	ACS (26)	<i>P</i>	SA (38)	ACS (41)	<i>P</i>
Lesion length [mm (SD)]	6.0 (3.0)	7.9 (3.0)	0.03	8.3 (6.5)	8.9 (7.4)	0.2
Obstruction diameter [mm (SD)]	1.9 (0.6)	1.8 (0.5)	0.60	0.8 (0.4)	0.6 (0.3)	0.41
Reference diameter [mm (SD)]	2.9 (0.7)	2.9 (0.7)	0.84	2.9 (0.4)	2.5 (0.6)	0.01
Percentage diameter stenosis [% (DS)]	53.1 (15.0)	56.1 (15.3)	0.47	70.2 (11.5)	72.7 (12.0)	0.32
Vessel haziness [<i>n</i> (%)]	8 (27%)	9 (35%)	0.52	0	0	

ACS, acute coronary syndrome; DS, diameter stenosis; SA, stable angina.

Optical coherence tomography findings in the presence of angiographic haziness

In the intermediate stenosis group, angiography revealed the presence of haziness in eight cases with stable angina (27%) vs. 9 (35%) with ACS.

Optical coherence tomography showed that, in the presence of stable angina, vessel angiographic haziness was due to calcified components in 87.5% and thrombus in 12.5%. On the contrary, in the presence of ACS, angiographic haziness was due to calcium in 33.3% and thrombus in 66.6%.

Optical coherence tomography-guided treatment strategy of patients with intermediate stenoses

Intermediate stenoses were treated with PCI in 33 out of the 56 patients (59%). PCIs were done more often in the ACS group, although the difference was not statistically significant (69.2 vs. 50%, respectively; $P=0.14$). PCI was performed in all 13 stenoses, showing a coronary thrombus, and in 10 out of 13 ruptured plaques (77%).

The median follow-up duration was 352 days (SD 29 days). One patient in the PCI-treated group died due to MI, whilst in the OMT group, one case with non-fatal MI and a second one with repeated revascularization were

reported. As a result, the primary endpoint of the composite of cardiovascular death, MI, and repeated revascularization was not significantly different between patients with an intermediate stenosis who received PCI vs. OMT on the base of OCT findings ($P=0.26$; Table 5).

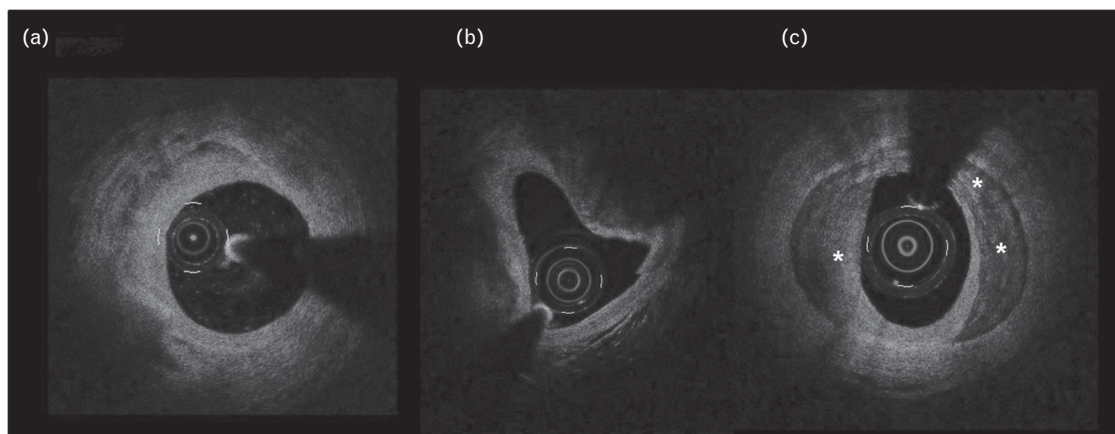
Discussion

In the present study, we investigated OCT features of plaque characteristics of angiographically defined, intermediate coronary stenoses on the basis of vessel narrowing or vessel angiographic haziness.

In the presence of an intermediate coronary stenosis, patients with stable angina or ACS showed different features at the MLA site. In the stable angina group, symmetric vessel narrowing with large calcification was typically observed, whereas an asymmetric vessel narrowing was more commonly imaged in ACS. Furthermore, a higher incidence of thrombus was found in the ACS group.

An intermediate stenosis is a common finding of coronary angiography that often leads to controversies regarding the treatment options to be applied. The use of intra-coronary diagnostic modalities including functional assessment of target stenosis (i.e. FFR)^{18–20}

Fig. 1



Optical coherence tomography-based characteristics of intermediate stenoses found at the MLA site. Panel a: A symmetric vessel narrowing characterized by a concentric thickness imaged in a patient with stable angina. Panel b: An asymmetric vessel narrowing with an irregular luminal contour imaged in a patient with ACS. Panel c: A calcified plaque with a large calcium plate (asterisks) extending deep in the media layer for 310 degrees imaged in a patient with stable angina. ACS, acute coronary syndrome; MLA, minimal lumen area.

Table 3 Optical coherence tomography results at the minimal lumen area site

	Intermediate lesions (56)			Severe lesions (79)		
	SA (30)	ACS (26)	<i>P</i>	SA (38)	ACS (41)	<i>P</i>
Measurement findings						
MLA [mm ² (SD)]	3.5 (1.5)	2.7 (1.3)	0.04	2.6 (0.8)	2.3 (1.2)	0.22
Mean diameter [mm (SD)]	2.0 (0.4)	1.7 (0.4)	0.01	1.8 (0.3)	1.6 (0.2)	0.03
Minimal diameter [mm (SD)]	1.7 (0.3)	1.4 (0.5)	0.01	1.4 (0.3)	1.3 (0.4)	0.20
Maximal diameter [mm (SD)]	2.3 (0.5)	2.1 (0.4)	0.04	2.1 (0.4)	1.9 (0.2)	0.02
Asymmetry index (SD)	0.24 (0.13)	0.33 (0.15)	0.02	0.30 (0.1)	0.30 (0.1)	0.94
Plaque findings						
Lipid plaque [<i>n</i> (%)]	17 (56.7)	17 (65.4)	0.62	33 (80.5)	34 (89.5)	0.03
Fibrous plaque [<i>n</i> (%)]	3 (10)	1 (3.8)		6 (14.6)	0	
Calcified plaque [<i>n</i> (%)]	10 (33)	8 (30.8)		2 (4.9)	4 (10.5)	
Lipid arc [degrees (SD)]	193.3 (73.2)	216.5 (61.4)	0.33	230.6 (91.8)	301.1 (79.2)	0.01
Calcific arc [degrees (SD)]	242.0 (57.8)	114.7 (35.1)	0.0001	96.1 (31.1)	107.4 (45.1)	0.78
Fibrous cap thickness [μm (SD)]	91 (53)	88 (65)	0.83	102 (34)	49 (23)	0.01

ACS, acute coronary syndrome; MLA, minimal lumen area; SA, stable angina.

is a valid option to decide whether to proceed with angioplasty or to defer interventions.

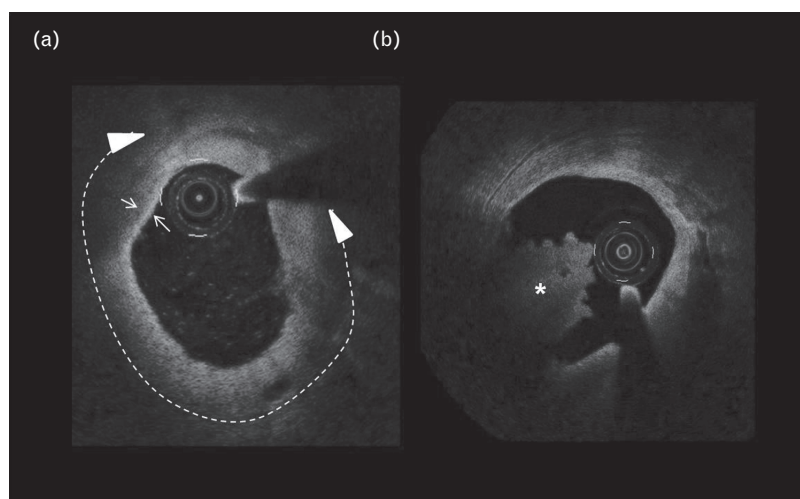
In the present study, we showed that intermediate stenoses with a vessel narrowing comprised between 30 and 70% by QCA have distinctive OCT-derived features that are related to the clinical presentation (stable angina or ACS). Currently, coronary angiography is the technique of choice to assess coronary atherosclerosis; however, it cannot depict the plaque beyond the lumen,²¹ and as a consequence is unable to provide information on plaque vulnerability.²

Previous angiographic studies stressed that plaque rupture can occur at the site of non-severely stenotic lesion.^{22–24} More recently, in-vivo studies using both intravascular imaging techniques or ex-vivo autoptical

studies showed that culprit plaques causing sudden death or MI tend to have a larger plaque burden with a thinner fibrous cap and a smaller lumen area, compared with stable or non-ruptured plaques.^{25–27}

In the present study, we identified a high prevalence of TCFA in intermediate stenoses visualized in patients with ACS. This conclusion is in line with other OCT studies pointing out that TCFA is often found in non-severely stenotic lesions.

Previous studies have also shown that in the setting of ACS ruptured plaque can be imaged in both culprit and non-culprit coronary vessels.^{28,29} Consistently with the previous data, in the present study, we found ruptured plaques at the site of intermediate narrowing in the presence of both stable angina or ACS.

Fig. 2

Optical coherence tomograph-based characteristics of intermediate stenoses found along the entire plaque. Panel a: TCFA is imaged in a patient with ACS. A large lipid pool (dashed line) extending for 270° exists, and is partially covered by a thin fibrous cap (approximately 60 μm) at 10 o'clock (arrows). Panel b: A coronary thrombus is imaged in another ACS patient. Thrombus is imaged as an irregular mass protruding into the lumen (asterisk). It shows a typical shadowing effect due to a high attenuation. ACS, acute coronary syndrome; TCFA, thin cap fibroatheroma.

Table 4 Optical coherence tomography results along the entire imaged plaque

	Intermediate lesions (56)			Severe lesions (79)		
	SA (30)	ACS (26)	P	SA (38)	ACS (41)	P
TCFA [n (%)]	2 (6.7)	7 (26.9)	0.04	17 (44.7)	28 (68.3)	0.03
Ruptured plaque [n (%)]	5 (16.7)	8 (30.8)	0.21	12 (31.6)	31 (75.6)	0.001
Calcified nodule [n (%)]	2 (6.7)	9 (34.6)	0.09	34 (89.5)	28 (68.3)	0.02
Micro-vessel [n (%)]	4 (13.3)	0	0.05	33 (86.8)	35 (85.4)	0.85
Thrombus [n (%)]	3 (10)	10 (38.5)	0.01	0	20 (48)	0.0001
Plaque length [mm (SD)]	9.6 (5.4)	10.1 (4.9)	0.67	10.6 (4.4)	14.2 (5.4)	0.002

ACS, acute coronary syndrome; SA, stable angina TCFA, thin cap fibroatheroma.

Vessel ulceration tended to occur without thrombus formation in patients with stable angina; in fact, only three ulcerated lesions were associated with thrombus. However, an accurate analysis of patients' clinical history revealed a recent (within 3–4 months) onset of anginal symptoms. Although these patients who exhibited ulcerated narrowing with thrombus did not meet the required clinical criteria to enter the unstable angina group⁵ at the time of the index procedure, they likely had a recent acute coronary event.

The present study showed that OCT can clarify morphological aspects of vessel angiographic haziness. In fact, in the intermediate stenosis group, the presence of vessel angiographic haziness was mostly associated with calcified plaques in stable angina and with thrombus in ACS. These findings not only confirm the distinctive aspects of stable angina and ACS in terms of plaque features, but also highlight how OCT can identify features that cannot be distinguished by angiography.

We finally showed that a strategy of percutaneous transluminal coronary angioplasty guidance, on the basis of the presence of coronary thrombus and/or a MLA less than 3.0 mm², lead to a good outcome, with a low incidence of adverse clinical events at 12 months, comparable to that of patients with intermediate stenoses who were left on medical therapy only. Our group has provided the first evidence of the clinical utility of an OCT-guided PCI approach in patients with severe coronary stenoses.³⁰

Although there is a need of larger prospective studies with long-term clinical follow-up, the present study shows the potential use of OCT as a pre-intervention guiding tool to select whether to treat culprit lesions in

addition to cardiac biomarkers, electrocardiographic changes, and angiography.

Conclusion

Intermediate coronary stenoses showed distinctive OCT-based features according to the initial clinical presentation. The adoption of an OCT-guided PCI strategy, on the basis of the presence of coronary thrombus and significant vessel narrowing, led to encouraging results. Despite the need for further large-scale studies, our results suggest the possible role of OCT to overcome the limits of coronary angiography for assessing intermediate stenosis and guiding primary treatment.

Limitations

The study lacks a sample size calculation, and we cannot exclude that a larger number of patients is needed to identify differences in terms of clinical outcome in patients with an intermediate stenosis treated with or without PCI on the basis of OCT findings. However, no study has previously studied the impact of MLA or thrombus detected by OCT in guiding PCI in a cohort of patients with a single de-novo intermediate stenosis.

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Table 5 Events at 1-year follow-up in patients treated with percutaneous coronary intervention vs. optimal medical therapy

	Intermediate lesion (56)		
	OMT (23)	PCI (33)	P value
Events at 1-year follow-up			
Cardiovascular death [n (%)]	0	1 (3)	0.45
Myocardial infarction [n (%)]	1 (4)	0	0.18
RR [n (%)]	1 (4)	0	0.18
Cardiac death, MI, RR [n (%)]	2 (9)	1 (3)	0.26

MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; RR, repeated revascularization.

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