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Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: An optical coherence tomography study☆,☆☆

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ABSTRACT

Background: Pathology studies have shown delayed arterial healing in culprit lesions of patients with acute coronary syndrome (ACS) compared with stable coronary artery disease (CAD) after placement of drug-eluting stents (DES). It is unknown whether similar differences exist in-vivo during long-term follow-up. Using optical coherence tomography (OCT), we assessed differences in arterial healing between patients with ACS and stable CAD five years after DES implantation.

Methods and results: A total of 88 patients comprised of 53 ACS lesions with 7864 struts and 35 stable lesions with 5298 struts were suitable for final OCT analysis five years after DES implantation. The analytical approach was based on a hierarchical Bayesian random-effects model. OCT endpoints were strut coverage, malapposition, protrusion, evaginations and cluster formation. Uncovered (1.7% vs. 0.7%, adjusted $p = 0.041$) or protruding struts (0.50% vs. 0.13%, adjusted $p = 0.038$) were more frequent among ACS compared with stable CAD lesions. A similar trend was observed for malapposed struts (1.33% vs. 0.45%, adj. $p = 0.072$). Clusters of uncovered or malapposed/protruding struts were present in 34.0% of ACS and 14.1% of stable patients (adj. $p = 0.041$). Coronary evaginations were more frequent in patients with ST-elevation myocardial infarction compared with stable CAD patients (0.16 vs. 0.13 per cross section, $p = 0.027$).

Conclusion: Uncovered, malapposed, and protruding stent struts as well as clusters of delayed healing may be more frequent in culprit lesions of ACS compared with stable CAD patients late after DES implantation. Our observational findings suggest a differential healing response attributable to lesion characteristics of patients with ACS compared with stable CAD in-vivo.

1. Introduction

The long-term risk for recurrent events is higher among patients with acute coronary syndromes (ACS) compared to those with stable coronary artery disease (CAD) after placement of drug-eluting stent (DES). Aside from non-device related factors, differences in arterial healing have been suggested as a potential explanation with a higher frequency of uncovered struts, fibrin deposition and inflammation observed in autopsy specimen [1]. Few studies using intravascular optical coherence tomography imaging also observed a higher rate of uncovered and malapposed stent struts among ACS patients but were limited to one year follow-up after DES implantation [2–4]. Owing to a possible association of uncovered and malapposed struts with the risk of late stent thrombosis [5] and the prevailing uncertainty with respect

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to the optimal duration of dual antiplatelet therapy, differences in arterial healing between patients with ACS and stable CAD after placement of DES remain clinically relevant. We therefore compared markers of arterial healing including strut coverage, protrusion, malapposition, and coronary evaginations among patients with ACS and stable CAD using OCT five years after implantation of early generation DES.

2. Methods

2.1. Patient population and lesion selection

The design and results of SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) and SIRTAX LATE (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization—Late) have been previously reported [6]. For the purpose of the present study, all consecutive patients undergoing angiographic follow-up at five years between December 2009 and July 2010 (n = 145) were eligible for OCT imaging. The flow of patients and reasons for exclusion are reported in the diagram (Fig. 1). In patients with more than one study lesion (n = 19), all lesions were randomly allocated a numerical code of 1, 2 or 3 by an independent statistician. OCT was routinely performed in the lesion with the lowest number. In none of these patients, the second or third lesion underwent OCT to respect the random selection. In four patients with multiple lesions, OCT was technically not feasible. Thus, in 15 patients suitable for final analysis, lesion selection was performed in a random manner. Among these patients, a total of 8 were ACS patients and only in two ACS patients, the imaging was done in the non-culprit lesion at baseline (culprit lesion defined according to ECG and ventriculography findings).

The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital, Switzerland. All patients provided written informed consent.

2.2. OCT imaging and analysis

OCT was performed with a time domain M2 system (Lightlab Imaging, Westford, Massachusetts) using a pullback speed of 2 mm/s and the non-occlusive flushing technique. After the diagnostic angiography and administration of 5000 IU unfractionated heparin, the ImageWire (Lightlab Imaging) was carefully advanced distal to the study lesion. Following administration of 200 μg of i.c. nitroglycerin, the target vessel was flushed through the guiding catheter with non-ionic, isosmolar contrast agent (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) using a power injector with flush rates between 3 and 4 ml/s. OCT pullbacks were assessed offline using a proprietary software (Lightlab Imaging, St. Jude Medical). Lesions were analyzed at cross sectional level with an interval of at 1 mm and assessed for strut coverage, malapposition, and protrusion by a single analyst blinded to patient and lesion presentation. All frames were reviewed by a second analyst, who in case of disagreement consulted with a third referee, with final decision based on consensus. Pullbacks were excluded in case >30% of the total stent length was not analyzable. Frames were considered not analyzable when >25% of the circumference was not visible due to insufficient flush or out of zoom. A strut was defined as a signal-intense bright spot with a typical dorsal shadowing. Thickness of strut coverage was measured as the distance between the endoluminal side of the strut in the midpoint of its long axis and the intersection of the lumen contour with the straight line between the endoluminal side of the strut and the gravitational center of the vessel. Struts were considered uncovered in case of a partial or complete absence of tissue coverage. Protrusion was defined as strut extension into the lumen for more than 160 μm but with no obvious separation from the vessel wall [7]. Apposition was assessed by measuring the distance between the center of the endoluminal strut surface and the intersection between lumen contour and the line connecting the center of the endoluminal strut side and the gravitational center of the vessel. Strut malapposition was defined as a distance ≥160 μm based on the consensus derived from the strut thickness of SES (153 μm) and PES (148 μm) plus the minimal axial resolution of OCT (10 μm). This consensus allowed a blinded assessment. Representative examples of uncovered, protruding or malapposed stent struts are presented in Fig. 2. Geographic maps were created displaying struts using color codes for strut characteristics, including strut coverage, apposition, and protrusion (Fig. 3). The resultant map represented the stented vessel cut longitudinally along the reference angle 0° (corresponding to the 12 o'clock position in the respective OCT cross section) and spread out on an area [7]. The stent maps of all lesions are depicted in Fig. 4.

Coronary evaginations (Fig. 2, example E) were suspected whenever the luminal vessel contour extended in a pouchlike fashion beyond the line connecting all stent struts (stent contour). Under these circumstances, the maximal radial distance between the circular line connecting all struts and the luminal vessel wall was evaluated using the

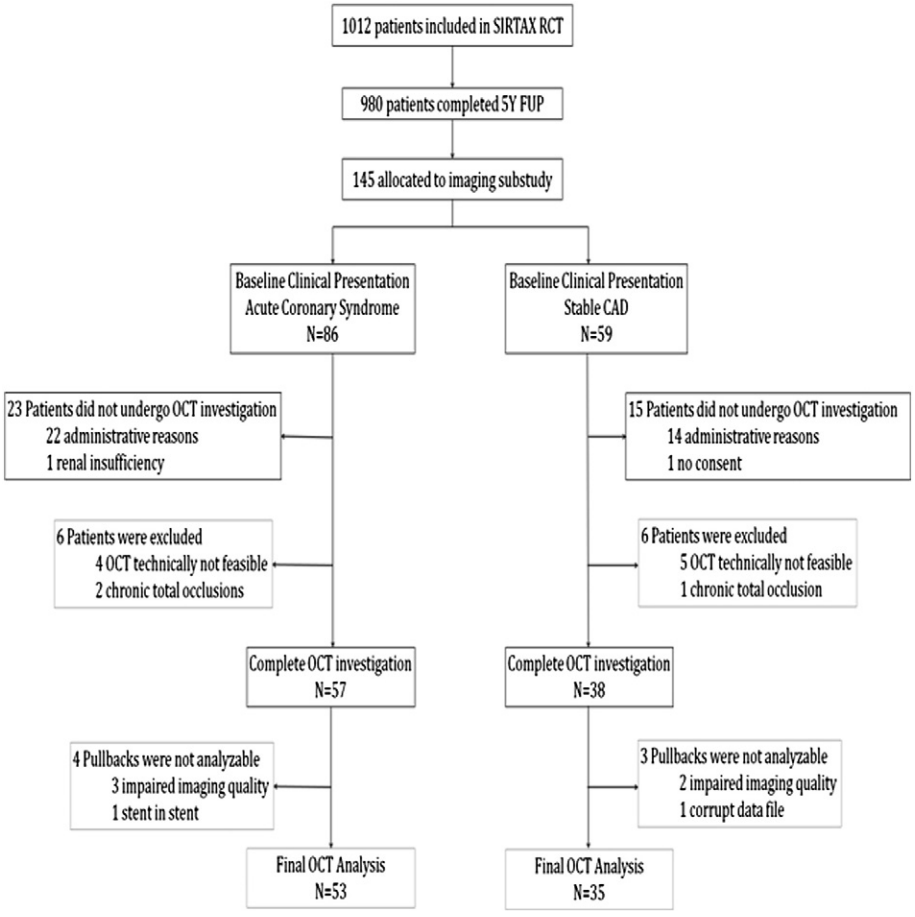

Fig. 1. Flow chart showing study design and patient flow.