



Editorial

Early Vascular Healing in Stable Patients Undergoing Percutaneous Coronary Interventions With Everolimus-Eluting Stents: Faster Than We Thought?

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See article by Shinke et al., pages 1513–1522 of this issue.

Dual-antiplatelet therapy (DAPT) is the standard treatment for the prevention of stent thrombosis (ST) after percutaneous coronary interventions (PCI) with stent implantation.¹ However, DAPT may be associated with bleeding complications, characterized by rates of morbidity and mortality similar to those of myocardial infarction.² Until the recent past, the use of drug-eluting stents (DESs) has not been advised in patients at high bleeding risk who were not eligible for prolonged DAPT.³ In contrast, the most recent European guidelines⁴ supported the use of new DESs as the standard therapy for the treatment of coronary stenosis, even in patients in whom DAPT cannot be sustained beyond 1 month. Even though the clinical feasibility and safety of 1-month DAPT has been proven,^{5,6} the microscopic mechanisms behind these clinical findings have never been evaluated directly.

Because of its high resolution (10 μm axial and 20 μm lateral), optical coherence tomography (OCT) is the most accurate *in vivo* technique for the detection of subtle morphologic details, including strut malapposition, plaque prolapse, and residual thrombus or dissections.⁴ Owing to its qualitative features, OCT is the ideal tool for the evaluation of vascular healing response and mechanism leading to stent thrombosis after stent implantation.^{7,8}

In the current issue of the *Canadian Journal of Cardiology*, Shinke et al. present the results of the **Multicenter Comparison of Early and Late Vascular Responses to Everolimus-Eluting Cobalt-Chromium Stent and Platelet Aggregation Studies in Patients With Stable Angina Managed as Elective Case (MECHANISM-Elective)** trial,⁹ a multicenter study focused on the results of OCT evaluation at the early and midterm follow-up of everolimus-eluting cobalt-chromium

stents (Co-Cr EESs; Xience Prime/Xpedition/Alpine; Abbott Vascular, Santa Clara, CA). One hundred patients undergoing OCT-guided PCI for stable coronary artery disease (CAD) were divided into 2 arms: Patients in the first arm underwent early OCT follow-up at 1 month, and those in the second arm underwent early OCT follow-up at 3 months. Both groups were evaluated at a 12-month midterm OCT follow-up. A total of 51 lesions (48 patients) in the 1-month cohort and 51 lesions (46 patients) in the 3-month cohort were assigned to the early OCT follow-up, and the midterm OCT follow-up was completed for 46 lesions and 41 lesions, respectively.

The authors demonstrated a significant progressive reduction in both undercovered ($P < 0.001$) and malapposed ($P < 0.001$) stent struts in both arms through the 3 time points. The details of the main findings of the study are summarized in [Figure 1](#).

The data show a progressive decrease in the presence of intrastent thrombus (IS-Th) in both groups: in the 1-month cohort, IS-Th rates went from 65.4% after PCI to 34.6% ($P = 0.01$) at the early follow-up, and to 4.3% ($P < 0.001$) at 12 months. A similar pattern was seen in the 3-month cohort, with the incidence decreasing from 74.5% to 11.8% ($P < 0.001$) and then to 0% ($P < 0.001$), respectively. The authors found no association between the incidence of IS-Th and residual platelet reactivity. Finally, irregular protrusions were observed in 21.8% of the patients on the OCT performed after PCI, but they had resolved at the early OCT follow-up in all cases.

The MECHANISM-Elective trial is the first prospective study performing an OCT evaluation of vascular changes at early (1-month) follow-up after PCI with the use of Co-Cr EESs in stable CAD patients. An early vascular response after the implantation of CoCr-EES was previously observed in the **Multicenter Comparison of Early and Late Vascular Responses to Everolimus-Eluting Cobalt-Chromium Stent and Platelet Aggregation Studies for Treatment of Acute Myocardial Infarction (MECHANISM-AMI)** 2-week follow-up study.¹⁰ In that registry, ST-segment-elevation myocardial infarction patients underwent OCT-guided primary PCI and a subsequent OCT follow-up at 2 weeks, which showed already significant improvements compared with the baseline evaluation. However, such a short follow-up still showed high

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See page 1432 for disclosure information.

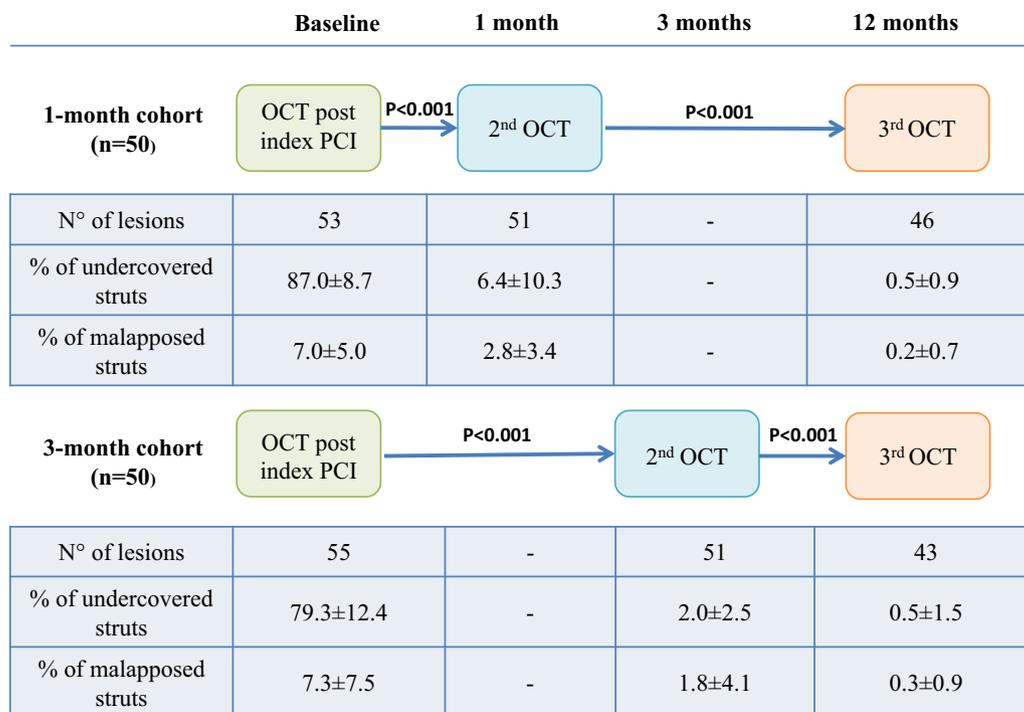


Figure 1. Optical coherence tomographic (OCT) findings at baseline, 1-, 3-, and 12-month follow-ups. PCI, percutaneous coronary intervention.

rates of uncovered stent struts (21%). Conversely, the OCT data at the early follow-up reported in the present study showed lower rates of uncovered struts in both the 3-month and, surprisingly, the 1-month cohorts (6.4% and 2.0%, respectively) compared with results from previous studies performing OCT follow-up at 3 months. In a recently published trial, Lee et al.¹¹ evaluated the rate of struts coverage at 3-months OCT follow-up in a population randomized to EESs and biolimus-eluting stents, showing incidences of uncovered struts of 8.9% and 8.2%, respectively. Likewise, in a study by Kretov et al.,¹² investigating patients undergoing PCI with ultrathin sirolimus-eluting stents, OCT analysis at the 3-month follow-up showed that 10% of struts were uncovered.

The early healing processes observed in the present paper could be explained by 2 main factors: the thin stent strut design of the CoCr-EES and the OCT-guided PCI. OCT-guided PCI has been associated with better results compared with angiography alone in terms of minimum lumen area and struts coverage.⁴ Lee et al.¹¹ had demonstrated that OCT-guided DES implantation (with either everolimus- or biolimus-eluting devices) caused a significant reduction, as much as 25%, in the rate of uncovered struts at 3 months after implantation (absolute mean difference of 2.8%) compared with the use of angiography alone.

The OCT features supporting early vascular healing observed in a population undergoing PCI with Co-Cr EESs has interesting implications in current clinical practice, particularly concerning the management of DAPT. The imaging data presented by Shinke et al. seem to support the recent clinical results of the **Short** and **Optimal** Duration of **D**ual **A**ntiplatelet **T**herapy After Everolimus-Eluting Cobalt-Chromium Stent (STOPDAPT-2) study.⁶ In that large (3045

patients) multicenter randomized trial, a 1-month DAPT (aspirin and clopidogrel) strategy followed by clopidogrel monotherapy resulted in a significantly lower rate of cardiovascular and bleeding events compared with a DAPT treatment lasting for 12 months (2.36% vs 3.70%; $P = 0.04$). Of note, in the STOPDAPT-2 trial, the majority of patients underwent PCI guided by intracoronary imaging. It is crucial to stress that among the patients screened for the study, 3459 subjects were not enrolled because of the clinical judgment of the attending physicians, suggesting the possibility of selection bias with the enrollment of patients with low ischemic risk.

The use of OCT might directly play a role in guiding safe discontinuation of DAPT, particularly in patients at high bleeding risk. The potential adoption of early OCT follow-up in stratifying patients to discontinue DAPT was investigated by Lee et al.¹¹ In that study, patients presenting < 6% uncovered stent struts at early (3-month) OCT follow-up were guided to discontinue DAPT whereas the others continued the standard therapy. The authors found no significant differences in the rates of adverse events between the 2 populations (0.2% vs 0.3%; $P = 0.80$). Of note, applying the same cutoff of percentage of uncovered struts to the population investigated by Shinke et al., almost all of the population (at least 95% of patients) would have been directed to short-term DAPT.

Nevertheless, the mere quantitative OCT evaluation (% of uncovered or malapposed struts) might not provide enough information to predict adverse events. Indeed, rather than the number of uncovered or malapposed struts, their patterns seem to be a crucial feature in the assessment of risk for ST, because continuous and long tracts of uncoverage and malapposition detected at the OCT analysis are related to a higher likelihood of ST.¹³ Moreover, ST can often be associated with

a clinical cause. In this regard, the only ST event reported in the present paper was observed 4 months after the index PCI, and was probably related to the discontinuation of antiplatelet therapy during hospitalization for acute cholecystitis. Unfortunately, no information on the OCT analysis at 3 months was provided by the authors, and therefore it is not possible to clarify the potential role of stent properties in this event.

In summary, this paper showed excellent results of Co-Cr EESs already at an early stage after PCI, with a significant reduction of IS-Th and undercovered and malapposed stent struts. Therefore, clinicians could be tempted by faster discontinuation of DAPT over a prolonged regimen to prevent ST. Although the results from STOPDAPT-2 trial seem to support this approach, it is important to stress that that study population was at low ischemic risk. Conversely, in large trials enrolling patients with acute coronary syndrome, a 12-month (or even longer) DAPT strategy has shown a significant reduction of new ischemic events,^{14,15} which was mainly driven by the reduction of non-lesion-related events. The OCT findings presented by Shinke et al. may support a shift from the idea of DAPT seen as a local therapy, for the prevention of device-related adverse effects, to a systemic one with the broader goal of reducing the burden of new cardiovascular ischemic events through an individualized management of DAPT duration based on the ischemic and bleeding risk profile of each patient.

Disclosures

The authors have no conflicts of interest to disclose.

References

- McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.
- Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J* 2017;3:804-10.
- Knuuti J, Wijns W, Saraste A, et al; Task Force for the Diagnosis and Management of Chronic Coronary Syndromes of the European Society of Cardiology (ESC). 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes [e-pub ahead of print]. *Eur Heart J*. Published online August 31, 2019, <https://doi.org/10.1093/eurheartj/ehz425>.
- Sousa-Uva M, Neumann FJ, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2019;5:4-90.
- Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;3:2038-47.
- Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;3:2414-27.
- Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation* 2016;1:650-60.
- Souteyrand G, Amabile N, Mangin LC, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J* 2016;3:1208-16a.
- Shinke T, Itoh T, Ishida M, Otake H, Terashita D, Fusazaki T, et al. Early and mid-term vascular responses to optical coherence tomography-guided everolimus-eluting stent implantation in stable coronary artery disease. *Can J Cardiol* 2019;35:1513-22.
- Morino Y, Terashita D, Otake H, et al. Early vascular responses to everolimus-eluting cobalt-chromium stent in the culprit lesions of ST-elevation myocardial infarction: results from a multicenter prospective optical coherence tomography study (MECHANISM-AMI 2-week follow-up study). *Cardiovasc Interv Ther* 2019;3:14-24.
- Lee S-Y, Kim J-S, Yoon H-J, et al. Early strut coverage in patients receiving drug-eluting stents and its implications for dual antiplatelet therapy: a randomized trial. *JACC Cardiovasc Imaging* 2018;1:1810-9.
- Kretov E, Naryshkin I, Baystrukov V, et al. Three-months optical coherence tomography analysis of a biodegradable polymer, sirolimus-eluting stent. *J Interv Cardiol* 2018;3:442-9.
- Adriaessens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation* 2017;1:1007-21.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;3:1791-800.
- Hahn JY, Song Y Bin, Oh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, noninferiority trial. *Lancet* 2018;391:1274-84.