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Full title:

Post-stenting assessment of Reendothelialization with optical Frequency domain imaging after Chronic Total Occlusion procedure: the PERFE-CTO study design and rationale

Short title:

Stent and artery evolution three months after chronic total occlusion recanalization

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ABSTRACT

Background: The treatment of chronic total occlusion of coronary arteries by percutaneous coronary intervention (CTO PCI) is one of the most representative technical advances in ischemic cardiomyopathy of last decade. However, how the complex histopathological remodeling and the new techniques affect healing processes after stent implantation remains unknown

Objective: The objective of the PERFE-CTO study is to analyze stent coverage, malapposition and other mechanical abnormalities 3 months after CTO recanalization using intravascular imaging.

Methods: In a French prospective interventional multicenter study, stent strut coverage, acquired malapposition and neointimal hyperplasia (NIH) proliferation will be systematically assessed with 3 months angiogram control and intracoronary optical frequency domain imaging (OFDI) after successful CTO PCI of more than 20 mm in length. The impact of routine systematical intracoronary imaging after these complex procedures will also be evaluated by measuring the rate of significant mechanical abnormalities (strut malapposition, edge dissection, thrombus) that was undetected by fluoroscopy alone and by complementary PCI when needed. Secondly, these data will be compared according to clinical characteristics, antiplatelet therapy use or desobstruction technique (antegrade vs. retrograde, true lumen vs. subintima). Each patient will undergo a one-year clinical follow-up. A total of 150 analyzed CTO lesions is expected.

Conclusion: The PERFE-CTO study will provide essential understanding of the early history after CTO recanalization and the identification of inadequate evolution (stent thrombosis, restenosis or late delayed stent endothelialization and cardiovascular outcomes) using intravascular imaging to improve long-term CTO results.

Clinical trial registration: NCT03209843

CONDENSED ABSTRACT:

The treatment of chronic total occlusion of coronary arteries by percutaneous coronary intervention (CTO PCI) is one of the most representative technical advances in ischemic cardiomyopathy of last decade. In a French prospective interventional multicenter study, stent strut coverage, acquired malapposition and neointimal hyperplasia (NIH) proliferation will be systematically assessed with 3 months angiogram control and intracoronary optical frequency domain imaging (OFDI) after successful CTO PCI of more than 20 mm in length. The impact of routine systematical intracoronary imaging after these complex procedures will also be evaluated by measuring the rate of significant mechanical abnormalities (strut malapposition, edge dissection, thrombus) that was undetected by fluoroscopy alone and by complementary PCI when needed. The PERFE-CTO

study will provide essential understanding of the early history after CTO recanalization and the identification of inadequate evolution (stent thrombosis, restenosis or late delayed stent endothelization and cardiovascular outcomes) using intravascular imaging to improve long-term CTO results.

Keywords

Chronic coronary total occlusion; Drug-eluting stent; Optical coherence tomography; Stent Enhancement

Abbreviations:

CTO: chronic total occlusion

PCI: percutaneous coronary intervention

NIH: neointimal hyperplasia

OFDI: optical frequency domain imaging

OCT: optical coherence tomography

MI: myocardial infarction

CABG: coronary artery bypass graft

CART: controlled antegrade and retrograde subintimal tracking

DES: drug-eluting stent

MLA: minimal lumen area

MLD: minimal lumen diameter

MSA: minimal stent area

IVUS: intravascular ultrasound

INTRODUCTION

The treatment of chronic total occlusion of coronary arteries by percutaneous coronary intervention (CTO PCI) is one of the most representative technical advances in ischemic cardiomyopathy of the last decade at experienced cardiology centers. This condition, which once required lengthy recovery from coronary artery bypass graft (CABG) surgery or conservative medical treatment, can now be managed safely with a high rate of success. The reported prevalence of CTO varies in the literature, depending on the clinical profiles of the

populations being examined. Retrospective studies indicate that 30% of patients with coronary artery disease could present a CTO on coronary angiography, and this incidence is higher in cases of prior CABG ^{1,2}.

Complex vascular remodeling

Knowing the histopathological processes of CTOs and their temporal variability remains essential to understanding the challenge of revascularization. CTOs can be divided in 3 interdependent segments. Between the proximal and distal caps, there is an intermediary occluded segment. The proximal cap seems more likely to be fibro-calcific than the distal cap, justifying the rationale for using retrograde strategies in percutaneous interventions^{3,4}. The lumen, intimal plaque (IP), media and adventitia are not spared from the complex remodeling that begins after occlusion, and important participation of inflammatory process is suggested by the massive infiltration of lymphocytes and monocyte-macrophages observed in each layer³. Postmortem observations have implications when CTO PCI is considered because dense fibro-calcific compositions and microcapillaries characterize older occlusions, which may indicate an adverse prognosis for revascularization and probable inability to cross the lesion with guide wire with a predisposition toward subintimal tracking. Other studies have suggested that structural remodeling is associated with functional impairments of the occluded vessel. Endothelial dysfunction and vasomotor tone disturbances could persist after recanalization, especially into distal segments^{5,6}. The recovery of vascular function is an area of focus for future trials⁷. Finally, the early development of collateral circulation in response to vascular occlusion and ischemia has been widely studied^{8,9} and its presence is strongly associated with lower rates of death or severe heart failure ^{10,11}. These insights leave open the question of how this chronic histological remodeling could affect the healing process of reendothelialization after PCI.

New stenting techniques can affect artery healing

Several techniques specific to CTO surgery are currently in use. For example, reverse-controlled antegrade and retrograde subintimal tracking¹² (CART) is one of the most commonly used methods¹³. This dissection/reentry technique can improve the recanalization success rate by using a septal collateral, an epicardial collateral or a bypass graft. A wire is first advanced in a retrograde manner through the collateral channel, reaching the subintimal space at the distal cap of a chronic total occlusion. Another wire is advanced in an antegrade manner and placed in the subintimal space. Then, a large balloon is inflated in this subintimal space to cross each wire, allowing the creation of an extraluminal channel. A new, artificial lumen is created by antegrade balloon

dilatation followed by antegrade angioplasty, and the chronic lesion is bypassed. The angiographic benefit is immediate, but few reports have described the evolution of this technique, which integrates a stent inside the medial artery, and it could have several unknown adverse long-term effects. We know that IVUS could show immediate intra-medial or extra-medial hematoma⁵ after CTO (even in true to true procedures) but healing consequences and possible late delayed struts endothelialization have been poorly studied.

Objectives of the study

The aim of PERFE-CTO is to assess stent and artery evolution 3 months after a successful CTO PCI procedure with OFDI: major acquired stent malapposition and delayed stent endothelialization are expected. Secondary objectives of the study are 1) to define usefulness of OFDI analysis after these complex procedures; 2) to assess the impact of the new PCI techniques on the healing process and compare antegrade vs retrograde, subintimal vs intraplaque wire tracking; 3) to evaluate the improvement of symptoms and the incidence of cardiovascular events after CTO PCI during a 12-month clinical follow-up.

METHODS

PERFE-CTO was designed as an interventional, prospective, multicenter study involving several university hospitals, general hospitals and private clinics under the leadership of principal investigator based in the Department of Cardiology, University Hospital of Poitiers, France. Both investigators are CTO surgeons who perform more than 50 CTOs per year. Half of them are full members of the EuroCTO Club. This open-label trial will be conducted according to the ethical principles of the Declaration of Helsinki and current guidelines for good clinical practice, and it has been approved by the ethical committee and the Institutional Review Board OUEST III under the reference 2016-A00867-44. The study is registered at ClinicalTrials.gov under the identifier NCT03209843. The authors are solely responsible for the design, conduct and all analyses of this study. The study design is summarized in *Figure 1*.

Patients

The main inclusion criterion is successful recanalization of more than a 20-mm length of CTO coronary artery, regardless of the crossing strategy used. Data collection, statistical analysis and postprocessing of OFDI runs for primary endpoint measurement will be performed at the central CoreLab investigation center of Clermont-Ferrand, France. With a final goal of 150 analyzed CTO lesions, adult patients who have benefited from a successful CTO PCI will be included between 2018 and 2020, after they have undergone the procedure. The

possibility of inclusion will be explained to every patient before the attempt at recanalization. Exclusion criteria include the absence of written informed consent; contraindication or inability to safely perform OFDI due to factors such as major coronary tortuosity; pregnancy or child-bearing potential in female patients; severe hemodynamic instability; severe chronic kidney disease, defined as a creatinine clearance < 30 ml/min; and severe coagulation disorders. At the time of inclusion, patient clinical characteristics such as age, sex, cardiovascular risk factors, heart failure with reduced ejection fraction, nonsevere chronic kidney disease, prior history of myocardial infarction (MI) or CABG and current treatment will be reported in an electronic case report form. Symptoms and assessment of cardiac viability and CABG dysfunction will complete the CTO history.

CTO PCI followed by immediate OFDI

In each participating center, the practitioner will report the CTO vessel and the SYNTAX and J-CTO scores. Technical data such as arterial access and the diameter of the guiding catheter, the total number of stents implanted and the total length of stents will be noted. Only new-generation drug-eluting Ultimaster® coronary stent systems (Terumo corporation®, Tokyo, Japan) will be used to obtain comparable data regarding reendothelialization processes. The Ultimaster® is a thin-strut (80 μ m), cobalt chromium, poly (DL-lactide cocaprolactone) biodegradable polymer (15 μ m), sirolimus-eluting stent. Successful crossing approaches for recanalization will be classified as antegrade, antegrade dissection reentry, retrograde and reverse CART. Any procedural complication, perfusion of GPIIb/IIIa inhibitor, fluoroscopy time, quantity of contrast used and dose-length product will define the safety endpoints. The appropriate stent size remains difficult in these occluded vessels; in this study, the size choice must not be helped by OFDI. According to practitioner habits, IVUS could be used at this stage but will not replace OFDI final analysis. A consideration of the optimal final angiographic result of the CTO PCI is essential before performing end-exam OFDI to assess the usefulness of intravascular imaging for revealing angiographically underdetected abnormalities. After ensuring that this optimal angiographic result has been achieved at what would normally be considered the end of the procedure, the surgeon will perform systematic OFDI over the entire length of each DES implanted. Immediate brief analyses will be performed, and the use of complementary therapies based on OFDI findings will be left to the discretion of the practitioner. Corrections of malapposition of stent struts and the optimization of stent expansion after OFDI should exclude persistent malappositions at 3 months and should only consider acquired malapposition. Each OFDI pullback will be sent to the CoreLab investigation center for postprocessing analysis. The minimal

lumen area (MLA, mm²), minimal lumen diameter MLD (mm), percentage of malapposed struts, and the presence of edge dissection or thrombus will be determined according to the expert consensus document of the EAPCI¹⁴.

New-generation OCT and OFDI are the gold standard intravascular imaging techniques that provide the best axial resolution (13 microns) and are usually used in studies specifically for stent assessment.

Three-month follow-up with OFDI

Coronary angiography will be systematically performed 3 months after CTO PCI with an additional OFDI exam during the same procedure. Each angiogram and OFDI pullback will be sent to the CoreLab investigation center for a postprocessing analysis. MLA, MLD, minimal stent area (MSA, mm²), percentage of neointimal hyperplasia (NIH) proliferation, percentage of malapposed struts, percentage of uncovered struts and the presence of edge dissection, thrombus or persistent hematoma will be measured. Additional PCI of the CTO segment, such as postdilatation or additional stenting, will be reported. To analyse potential enlargement of distal CTO vessel the MLA and the mean diameter will be measured at least 5 mm further the distal stent and compared to the same measure performed during the index procedure.

One-year clinical follow-up

Each participating center will perform a clinical evaluation of all included patients one year after CTO PCI. This evaluation can be performed directly with the subject during medical follow-up or indirectly via the patient's general practitioner and referring cardiologist if necessary. A standardized questionnaire will be provided at the end of the e-CRF. Occurrences of MI, new coronary angiograms, sudden death, hospitalization for cardiac disease and severe hemorrhage will be reported. Any new coronary angiogram will be noted, as well as any PCI or CABG that occurred during the one-year follow-up. In terms of symptoms, the Canadian Cardiovascular Society (CCS) grading system and New York Heart Association (NYHA) functional classification will be used to assess exertion-induced angina and dyspnea, respectively, one year after CTO PCI.

OFDI analysis and definition of endpoints

Second-generation optical coherence tomography (OCT) OFDI allows minimally invasive cross-sectional imaging of biological samples and has been selected for its high radial resolution compared with intravascular ultrasound (IVUS) (13 µm vs. 90 µm) and its advantages in terms of signal-to-noise ratio and lateral resolution

compared with first-generation OCT. Based on low-coherence interferometry, the reproducibility, accuracy and safety of this technology make OFDI a valuable ally for the study of coronary arteries and for guiding interventional procedures. From experimental research to routine use, OCT has become the gold standard for identifying vulnerable plaques and for optimizing/following up angioplasty^{15,16}. The imaging depth of 0.5-2 mm remains the main limitation of OCT. In the proposed study, OFDI will be performed using the Fastview® coronary imaging catheter (Terumo®, Tokyo, Japan) or the Dragonfly® coronary imaging catheter (Abbott vascular) **according to current guidelines for good clinical practice**¹⁴. Postprocessing analysis of immediate and 3-month follow-up OFDI pullbacks will be performed by 2 operators at an independent CoreLab in Poitiers, France (DACTIM-MIS : Data Analysis and Computation Through Imaging and Modeling- Mathematiques Images Santé CNRS 7348). Two-dimensional measurements will be taken of every millimeter over the entire stented coronary artery. MLA and MLD will be measured using semiautomatic contouring of the arterial lumen, and MSA will be computed using a manual delineation of the stent and corrected if necessary. NIH quantification of both the lumen area and stent area will also be performed for each slice, and the percentage of NIH proliferation, defined as $\text{NIH obstruction (\%)} = (\text{stent area} - \text{lumen area}) / \text{stent area} \times 100$, will be determined. Regarding stent malapposition, struts will be considered malapposed when the distance between the strut and the vessel wall is > 0.4 mm with longitudinal extension ≥ 1 mm¹⁴. An uncovered strut will be defined as having a neointimal thickness of 0 μm . The percentages of malapposition and uncovering will be measured every millimeter.

Statistical analysis and justification

We have scheduled an inclusion period from March 7, 2018 to January 14, 2020 during which we hope to include between 100 and 150 patients. A descriptive analysis will be conducted, reporting absolute numbers and percentages for categorical variables and means \pm standard deviations or median [25th-75th] when appropriate for continuous variables. Kaplan-Meier curves will be plotted to assess time from CTO PCI to cardiovascular events during a 12-month clinical follow-up. The factors associated with major acquired stent malapposition and delayed stent endothelialization 3 months after CTO recanalization will be identified in univariate analyses using student's t test (or non parametric Wilcoxon test if appropriate) for quantitative variables and chi-square test for qualitative variables. Then a multivariable logistic regression analysis will be performed using a manual backward procedure. All the variables associated with the dependent variable in univariate analysis with a P value < 0.10 will be considered in the maximal model. Best-fit final models will contain only the variables

showing an adjusted P value < 0.05. The analyses will be conducted on the entire sample of patients and secondly stratified according to the occurrence of a dissection. We will use SAS software (version 9.4; SAS Institute, Cary, NC, USA) for all analyses.

Perspectives of PERFE-CTO

The authors expect that the study findings will have multiple implications regarding our understanding of CTO PCI and the management of these patients. It is possible that CTO will present a different profile of reendothelialization after PCI compared to non-CTO PCI. The possible delay in stent struts endothelialization could motivate practitioners to re-evaluate the risk of stent thrombosis after CTO PCI in favor of extending the DAPT duration, although the long-term benefits of prolonged DAPT lasting more than 12 months have not been proven in retrospective cohort studies¹⁷. In our monocentric experience, new stenting techniques using lumen / media reentry, especially reverse-CART, appear to be more traumatic and could be responses to late aneurism and large stent malapposition due to delayed hematoma resorption. If this is the case, the usefulness of intracoronary imaging to assess angiographically underdetected mechanical abnormalities could be strengthened; it may even warrant systematic use, especially in complex procedures, as has been demonstrated for PCI in non-ST-elevation MI compared with fluoroscopy alone¹⁸. An understanding of these unknown mechanisms will help us to perform CTO PCI more safely and with better long-term results; additionally, it may lead to an assessment of the results of each technique (anterograde vs retrograde, subintimal vs intraplaque wire tracking) and the likely proposal of a systematic 3rd month OCT / OFDI control of complex CTO-PCI.

Limits of the study

Despite its amazing axial resolution, OFDI has poorest signal penetration than IVUS and the segmentation between subintimal and intraplaque remains too imprecise. We could have designed a combined study with IVUS and OCT but it will be then impossible to have a reliable comparison between the index procedure and 3 *months control*. We choose OFDI instead of IVUS to be more precise on struts malapposition and we accept the lack of causality that could have provided IVUS.

CONCLUSION

The development of revascularization techniques such as the retrograde approach, reverse CART and dissection reentry, has considerably expanded the horizons of CTO PCI in terms of the success rates and safety of

recanalization. However, the future findings of the PERFE-CTO study could indicate that complex vascular remodeling of chronically occluded vessels associated with potential shredding techniques are more inclined toward late-acquired stent malapposition and less neointimal proliferation and are likely to require a systematic third-month angiogram and OFDI control.

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This study is free of financial conflict of interest. All research grants were provided by a nonindustrial organization. The authors would like to thank the University Hospital of Poitiers Aliénor endowment fund and contributors for their generous contribution. None of the authors had conflict of interest. More information on the project's financing is available at www.fonds-alienor.fr/wpd-projects

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Figure 1: PERFE-CTO study protocol.

Legend: In the cathlabs, each successfully recanalized CTO will be analyzed by intracoronary OFDI immediately and 3-months after PCI with CoreLab postprocessing analysis.

Figure 2.

Right coronary OFDI CoreLab analysis. Legend: A and B = semiautomatic contouring of the lumen area and stent to compute MLA, MLD, MSA and NIH proliferation; C = example of a covered strut; D = example of an uncovered strut; E = example of a malapposed strut. Performed using the Lunawave® coronary imaging console and software (Terumo®, Tokyo, Japan).

Successful CTO PCI

Inclusion
Angiographic analysis

Immediate OFDI

OFDI analysis

Minimal lumen area
Minimal lumen diameter
Strut malapposition
Edge dissection
Thrombus

Three-month follow-up

Angiographic analysis

Three-month OFDI

OFDI analysis

Minimal lumen area
Minimal lumen diameter
Minimal stent area
NIH proliferation
Strut malapposition
Strut coverage
Dissection/thrombus

One-year clinical follow-up

