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THESE
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Par Monsieur Gael PITCHECANIN

Evaluation par tomographie en cohérence optique fréquentielle de la réendothelialisation des stents trois mois après la désobstruction d'une occlusion coronaire totale chronique

The Perfe-CTO Study
Post Stenting Ass**E**ssment of **R**e-endothelialization with O**F**DI after **CTO** procedure

COMPOSITION DU JURY

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
BMI	Body mass index
BMS	Bare-metal stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
cMRI	cardiovascular magnetic resonance imaging
CART	Controlled antegrade and retrograde tracking
CCS	Canadian cardiovascular society
CI	Confidence interval
CMR	Cardiovascular magnetic resonance
CRF	Case report form
CTO	Chronic total occlusion (of coronary artery)
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
DLP	Dose-length product
NOAC	New oral anticoagulant
ESC	European society of cardiology
HDL	High-density lipoprotein
HR	Hazard ratio
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter defibrillator
IP	Intimal plaque
IQR	Interquartile range
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCA	Left coronary artery
LCX	Left circumflex artery
LDL	Low-density lipoprotein
LM	Left main coronary artery
LV	Left ventricular
LVEF	Left ventricular ejection fraction

MACE	Major adverse cardiac events
MI	Myocardial infarction
MLA	Minimal lumen area
MLD	Minimal lumen diameter
NIH	Neointimal hyperplasia
NSTEMI	Non ST-elevation myocardial infarction
NYHA	New York heart association
OCT	Optical coherence tomography
OFDI	Optical frequency domain imaging
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
RCA	Right coronary artery
SAQ	Seattle Angina Questionnaire
SCAD	Stable coronary artery disease
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
UA	Unstable angina
VKA	Vitamin K antagonist
VTA	Ventricular tachyarrhythmia

ABSTRACT

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. Intracoronary optical frequency domain imaging is the gold-standard technique to evaluate vessel healing patterns following stent implantation. However, the number of FD-OCT studies investigating healing patterns after successful CTO recanalization is extremely limited and there are no randomized controlled trials of clinical outcomes with FD-OCT-guided vs angiography-guided CTO PCI.

The aim of the study is to assess in-stent reendothelialization after successful CTO PCI.

Methods: PERFE-CTO is a French prospective interventional, multicenter study. Its goal is to assess stent strut coverage, acquired malapposition and neointimal hyperplasia (NIH) proliferation by intracoronary imaging immediately after successful CTO PCI and at 3- month follow-up. The impact of systematic intracoronary imaging throughout these complex procedures has been measured by analysing the mechanical abnormalities undetected by fluoroscopy alone or which would have needed complementary PCI. Each case had a one-year clinical follow-up.

Results: From March 2018 to January 2020, 118 CTO lesions were analysed with a total of 30021 struts and 16617 millimeters of stents., The incidence of malapposition struts was 8,3% after stenting and 15% at the 3-month follow-up; and an acquired malapposition rate of 21%. The incidence of uncoverage at 3-month follow-up was 25.6% with a median percentage of neointimal proliferation per lesion of 6.3%. Intravascular imaging showed mechanical abnormality requiring further treatment in 31% while final angiographic analysis was considered optimal in 83% cases. We found an expansion of distal vessel after stent implantation at 3 months. There is no association between acquired malapposition and uncoverage struts and the recanalization technique used. No complication was found with systematic use of FD-OCT. CTO recanalization improved angina status at one-year clinical follow-up.

Conclusion: The PERFE-CTO study shows that CTO lesions and complex histological remodeling could be associated. This affects short-term healing after CTO PCI with higher incidence of strut malapposition and delayed endothelialisation, resulting in missing of neointimal coverage. Surprisingly, these abnormalities are not directly related with aggressive techniques used to recanalize the coronary artery. Knowing the high incidence of mechanical abnormalities unseen at angiography, systematic use of intravascular imaging should be considered to improve CTO recanalization.

1| BACKGROUND

Treating chronic total occlusion of coronary arteries by percutaneous coronary intervention (CTO PCI) is one of the most representative technical advances in ischemic cardiomyopathy during the last decade.

Intracoronary optical frequency domain imaging/Optical coherence tomography (OFDI/OCT) named as FD-OCT for the rest of the study represents the gold-standard technique to evaluate vessel healing patterns following stent implantation. However, the number of studies investigating FD-OCT healing patterns following successful CTO recanalization is extremely limited and there are no randomized controlled trials of clinical outcomes with FD-OCT-guided vs angiography-guided CTO PCI.

One could wonder how the new revascularization techniques can affect the healing process of the treated artery and its histopathological remodeling.

The aim of the study is to assess in-stent reendothelialization after successful CTO PCI.

1.1| Definitions and epidemiology

Assessed by arteriography, chronic occlusion of coronary artery is defined by the complete or near complete occlusion of a coronary artery with no or minimal downstream flow (Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1) for more than 3 months (1,2). Although, in the absence of serial angiograms, duration of occlusion is difficult to specify and must be often estimated from clinical informations and cardiovascular events.

Prevalence of chronic total occlusion (CTO) varies in the literature, depending on clinical profiles of populations being examined. Retrospective studies described that 30% of patients with coronary artery disease (CAD) could present a CTO on the coronary angiography, and this rate increase in case of prior coronary artery bypass graft (CABG). (3,4)

In the past, PCI CTO was traditionally limited by relatively low success rates around 50%, which meant that CABG was the gold standard in terms of complete revascularization. However, as success revascularization rate may exceed 80 to 85%; complex lesions are more frequently tackled by interventional cardiologists. (5–7). Advanced materials, new methods, and the development of several techniques as anterograde/retrograde approach or antegrade/retrograde dissection and reentry, has enabled high procedural success rates with reasonably low periprocedural major complications.

Lesion complexity was assessed by means of the J-CTO score from which 5 independent

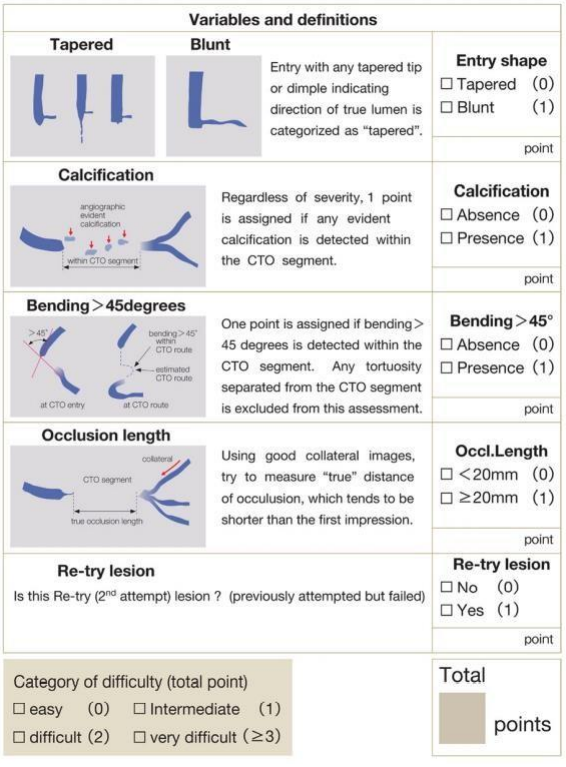

Figure 1 : J-CTO score

predictors were statistically selected into the Japanese CTO registry (figure 1), (8).

Previously failed attempt, a blunt proximal cap, the presence of any calcification within the CTO segment, a bending > 45 degrees and an occlusion length > 20 mm were more likely associated with technical failure and categorized CTO lesions in 4 difficulty groups with varying likelihood of successful crossing within 30 minutes.

1.2| Pathobiology of CTO

The histopathological progression of CTO in human coronary arteries, whilst incompletely understood, dependents on the duration of the CTO. Most data pertaining to the pathophysiology of human CTO formation is based on post-mortem data, rather than consecutive in-vivo assessment.

Knowing the histopathological processes of CTO and their temporal variability remains an essential condition to understand challenge of revascularization.

CTOs occur after a plaque rupture of atherosclerosis with bidirectional formation of thrombus. Relatively soft at start, the thrombus becomes organized over time; and are replaced by type III collagen and dense fibrous tissue.

CTOs could be divided in 3 interdependent segments. Between proximal and distal caps there is an intervening occluded segment. The proximal cap is described to be more likely fibro-calcific than the distal cap, explaining the rationale behind the percutaneous retrograde strategies (9,10).

Lumen, intimal plaque (IP), media and adventitia are not spared from the complex remodeling after occlusion, with an important participation of inflammatory process suggested by massive infiltrate of lymphocytes and monocyte-macrophages observed in each layer (9). Regarding age-related changes in IP composition, softer cholesterol-laden and foam cell-rich IP decrease significantly over time whereas fibrocalcific IP increase in older lesions (9) (Figure 2). Advanced fibrotic CTO lesions could undergo negative remodeling. These changes negatively impact the likelihood of successful PCI.

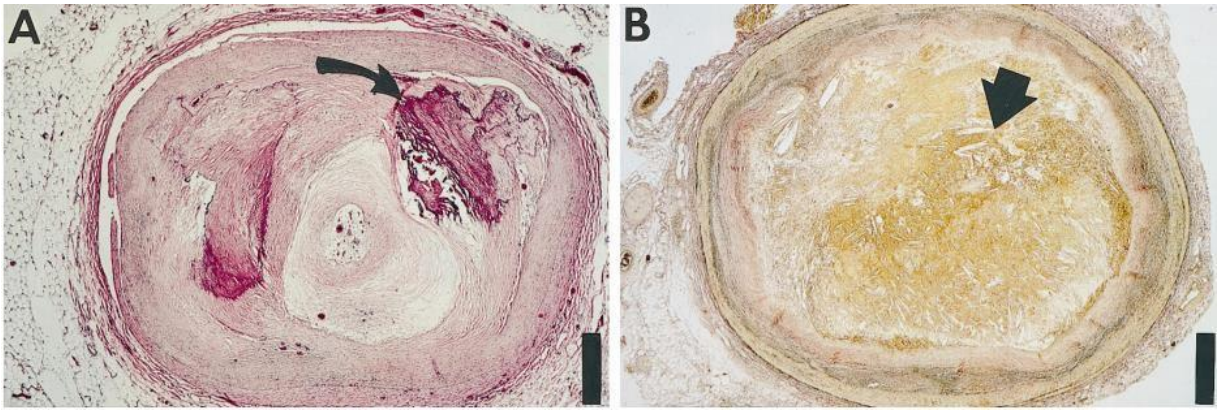

Figure 2: Low power view of representative hard fibrocalcific chronic total occlusion with extensive calcifications (A); low power view of representative soft lipid-laden chronic total occlusion intimal plaque with extensive cholesterol deposition (B). Reproduced from Srivatsa et al.(9)

Another key finding is the tapered character of the proximal cap compared to CTOs where cap appears blunt on angiography, because it suggests a shorter occlusion, a looser fibrous tissue with prominent neovascularisation and recanalization (10).

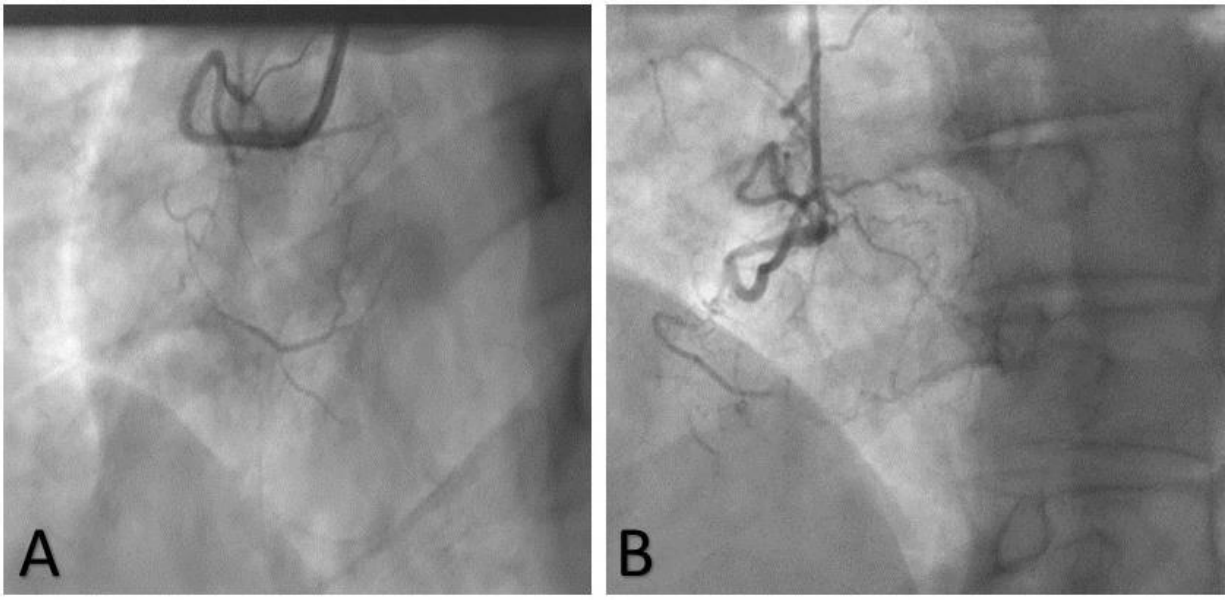

Image 1: Example of blunt (A) and tapered (B)

These post-mortem observations have implications when CTO PCI is considered because dense fibro-calcific composition and micro capillaries characterize older occlusions with some adverse profiles of revascularization and probable inability to cross the lesion with guide wire with predisposition to subintimal tracking.

Thanks to the progress of intracoronary imaging, in vivo investigations dealing with histopathological remodeling in CTOs have been developed and new insights into tissue characteristics have been published.

Using virtual histology intravascular ultrasound (IVUS) in 50 patients affected by CTO, Guo et al. distinguished two different patterns of CTOs. The large majority of them had fibroatheroma occupying the length of the occluded segment with a significantly more necrotic core and dense calcium suggesting that initial acute event leading to the development of a CTO might be a ruptured atherosclerotic plaque with bidirectional thrombus formation as acute coronary syndrome (ACS), the second pattern is explained by atherosclerosis progression characterized by lesions with more fibrotic and fibrofatty plaques (11).

Other studies suggested that structural remodeling was associated with functional impairments of the occluded vessel. Endothelial dysfunction and vasomotor tone disturbances could persist after recanalization, especially into distal segments (12,13) .

After CTO recanalization, a collateral regression has been observed (14) but it appears that these pathways are still recruitable in case of re-occlusion.

However, the impact of this chronic histological remodeling on the healing process of stent reendothelialization after PCI is still unknow?

1.3| Benefits of CTO revascularization

Improvement of long-term clinical outcomes after CTO recanalization has been widely debated, mostly because the randomized trials on this subject are lacking.

However, many studies have explored this complex question.

1.3.1 Mortality and overall survival

Mehran et al, evaluated long-term clinical outcomes in 1,791 patients who underwent PCI of 1,852 CTO at 3 tertiary care centers in the United States, South Korea, and Italy during 5 years follow-up. Procedural success was obtained in 1,226 (68%) patients and was an independent predictor of a lower cardiac mortality (hazard ratio [HR]: 0.40, 95% confidence interval [CI]: 0.21 to 0.75, $p< 0.01$) and reduced need for CABG (HR: 0.21, 95% CI: 0.13 to 0.40, $p< 0.01$) (15).

Similar results were observed by Teramoto et al. and showed that, the 738 patients who benefited CTO PCI during the average 4 years of follow-up had a cumulative all-cause death significantly reduced in the success group (compared with the failure group) (16), with an 89% rate of successful recanalization.

In a large-scale observational multi-center registry, Christian Roth et al. analysed the impact of current therapeutic concepts in 6630 CTO patients comparing successful CTO revascularization (3906 patients) either by PCI or CABG (412 patients), failed CTO-PCI (1479 patients) and optimal medical therapy (OMT) alone (833 patients). They observed a significant long-term benefit in regard of mortality with revascularization compared to OMT independently from revascularization (17). Patients experiencing failed CTO PCI displayed long-term outcome comparable to patients undergoing OMT and might be a potential target for further revascularization attempts by CABG. These results were completed with 2 meta-analyses. Successful CTO PCI has been associated with a reduced need for CABG, and may provide a long-term survival benefit compared to non-successful revascularization (18,19).

The DECISION-CTO trial (Drug-Eluting Stent Implantation vs Optimal Medical Treatment in Patients with CTO) and EUROCTO (Evaluate the Utilization of Revascularization or Optimal medical therapy for the treatment of Chronic Total coronary Occlusions) are randomized controlled trials with systematic comparaison of CTO-PCI and OMT. In the DECISION-CTO trial, 834 patients were randomly assigned to CTO-PCI (n=417) or OMT (n=398) group as an initial treatment strategy for CTO lesions. During a median follow-up of 4 years, the incidence of the composite endpoint of death, myocardial infarction, stroke, and target vessel revascularization was similar between the PCI and OMT groups. However, the study was ended before the needed number of subjects could be enrolled, and as such, it suffers a lack of statistical power. Also, the high number of crossovers in the OMT group may have led to underestimate the effect of CTO-PCI strategy. In EUROCTO, at 12 months, the cardiovascular event rate was a secondary endpoint, and it was comparable between the CTO-PCI and OMT groups. Both the DECISION-CTO trial and EUROCTO were ended prematurely with a low enrolment (407 instead of the planned 1200 patients in EUROCTO and 834 instead of the planned 1 284 patients in DECISION CTO), and were underpowered because of an insufficient sample size, the midterm follow-up duration and the significant crossover (20% in DECICSION CTO).

In a large-scale cohort of consecutive patients with CTO lesions, Park et al have explored the difference between CTO-PCI and OMT. An overall reduction in the 10-year rate of cardiac death was observed in the study, mainly driven by a reduction between 3 and 10 years, but not within the first at 3 years. The 3-year rate of cardiac death was similar between the OMT and PCI groups, which is consistent with the results of the DECISION-CTO trial and EUROCTO. After 3 years, the event curve of cardiac death showed a significant divergence in favour of CTO-PCI, which can be partly explained through a greater increase of acute myocardial infarction in the OMT group (OMT versus CTO-PCI between 3 and 10 years; 6.0% versus 2.7%, respectively) (20).

So, the CTO is more beneficial on the long-term survival. But the debate remains open, and these observational studies could not be a substitute for a randomized controlled trial.

1.3.2 Heart failure/ Left Ventricular Function

Given that CTO revascularization help identifying myocardial ischemia/viability (21) and CTO is associated with heart failure with reduced ejection fraction (HFrEF) (22), we can expect that recanalization would improve cardiac functions.

A meta-analysis of 34 studies published between January 1980 and November 2017 with 2804 patients demonstrated that successful CTO PCI is associated with statistically significant increase in mean LVEF by 3.8% during a mean follow-up of 7.9 months (23).

In the EXPLORE (Evaluating Xience and left ventricular function in Percutaneous coronary inter-vention on occLusiOns After ST-Elevation myocardial infarction) trial, evaluating 136 patients with ST-segment elevation myocardial infarction, additional PCI of CTOs did not result in improvement on left ventricular ejection fraction (LVEF) and lower left ventricular (LV) end-diastolic volume as assessed by cardiovascular magnetic resonance imaging (cMRI) at 4 months follow-up compared with 144 patients without CTO PCI.

However, most of these studies were retrospective or included control groups with suboptimal medical therapy.

The REVASC (Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion) trial is the first randomized, prospective trial to evaluate whether PCI of CTO improves LV function in patients with stable coronary artery disease. The results reported no additional effect on segmental wall thickening in the CTO territory of 101 patients in comparison with the no CTO PCI group of 104 patients after 6 months.

In patients with chronic ischemic LV dysfunction, improvement of dysfunctional but viable myocardium may not occur until 3 to 6 months after revascularization.(24) However, Bondarenko et al studied the time course of functional recovery after revascularization of hibernating myocardium on 35 patients using contrast enhanced CMR. Functional myocardial recovery started at 3 to 6 months with continuing improvement up to 24 months, suggesting that recovery of systolic function can be further delayed up to 24 months, especially in myocardial segments with higher extent of hyperenhancement.(25) Detection of changes in LV function may, therefore, require long-term follow-up after revascularization particularly in CTO patients.

1.3.3 Symptoms

Concerning effectiveness of CTO revascularization for relieving symptoms, Rossello et al. demonstrated that successful recanalization of CTO in 47 patients was followed by significant improvement of life quality assessed by global physical and mental health status and increase performance in the 6-minute walk test (26).

Symptomatic relief has been one of the main goals of CTO revascularization and one of the most common reasons for referral.

Despite this, there are surprisingly few randomized trials comparing the difference between symptoms/quality of life with CTO revascularization versus medical therapy. EURO-CTO (Evaluate the Utilization of Revascularization or Optimal medical therapy for the treatment of Chronic Total coronary Occlusions) was the first randomized trial to study the effect of CTO revascularization on quality of life as a primary outcome and at 12 months follow-up. 137 patients were randomized to OMT and 259 randomized in CTO PCI. Results showed a significant improvement in life quality as assessed by the Seattle Angina Questionnaire (SAQ score) (27).

These results were completed by other studies like OPEN-CTO and DECISION CTO.

OPEN-CTO (Outcomes Patient Health Status and Efficiency in CTO), is a multicenter, prospective, observational registry of CTO patients undergoing PCI with 1000 consecutive patients included. It showed significant symptomatic relief with improved SAQ quality of life scores and decreased dyspnea and depression scores (PHQ-8) (5).

DECISION CTO (Drug-Eluting Stent Implantation vs Optimal Medical Treatment in Patients with CTO) looked at the cardiovascular outcomes of ‘routine’ CTO-PCI against medical therapy among patients with at least 1 CTO. Although symptomatic relief was not the primary endpoint, there were no significant differences in quality-of-life metrics at 1 year, including SAQ score and EQ-5D visual analogue scale (28).

From the VACTO primary and secondary studies (29,30) presence of CTO should be also considered as an independent predictor for occurrence and recurrence of ventricular tachyarrhythmia (VTA), and we can expect further studies to find that CTO recanalization will be associated with decrease incidence of arrhythmias and sudden death.

Recently, the IMPACTOR-CTO (Impact on inducible Myocardial ischemia of PercutAneous Coronary inTervention versus Optimal medical theRapy in patients with Right coronary artery Chronic Total Occlusion) trial randomly assigned patients with isolated CTO of the right coronary artery (RCA) to either PCI (n=32) or OMT (n=33). Obedinskiy et al found that the decrease in myocardial ischaemia burden at 12 months (primary endpoint) was significantly higher in the PCI group, compaired with the OMT group (13.9±6.1% vs. 0.3±4.2%; $p<0.01$). Functional status, quality of life and 6-min walk test were also improved in the PCI group.

1.3.4 Cardiovascular events

Successful CTO PCI was associated with significant lower risk of major adverse cardiovascular events (MACE), lower risk of stroke and less need for CABG compared with failed procedures in two powerful meta-analysis (19,31). Furthermore results remain controversial about effect of CTO revascularization on the risk of myocardial infarction (32).

Benefits remain uncertain, even if several meta-analyses suggested a strong association between successful CTO PCI and survival or improvement of symptoms and better cardiac function.

1.4| Crossing strategies

From the PROGRESS CTO score, a proximal cap ambiguity, the absence of operable collaterals and the presence of moderate or severe tortuosity were all predictive variables of failed PCI (33).

To fix these difficulties with a safe and effective crossing algorithm, two approaches appeared over years.

First, The "hybrid" Northern American approach (figure 3) (6,34) which goal is to recanalize CTO in the shortest possible period with a minimal radiation and contrast exposure. A dual coronary injection guides the operator's choice between an anterograde or retrograde approach, depending on an appropriate collaterality, the quality of the target at the distal cap and the ambiguity of the proximal cap.

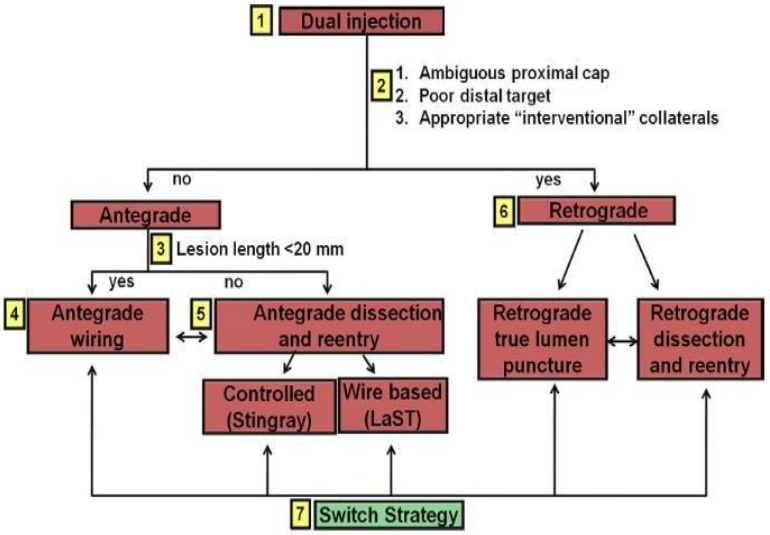

Figure 3 : The hybrid approach

Moreover, a lesion length exceeding 20 mm will be a strong argument for techniques using subintimal space as antegrade dissection reentry or reverse controlled antegrade and retrograde tracking (reverse CART) (34).

Secondly, the Japanese approach uses an innovative algorithm in order to treat coronary chronic total occlusion (Figure 4) (35).

The aim was to privilege "true lumen to true lumen" with guidewire manipulation time as priority. The length of the lesion wasn't a criterion for dissection reentry. Moreover, decision of stopping the procedure was taken when total guidewire manipulation time was superior to 3 hours.

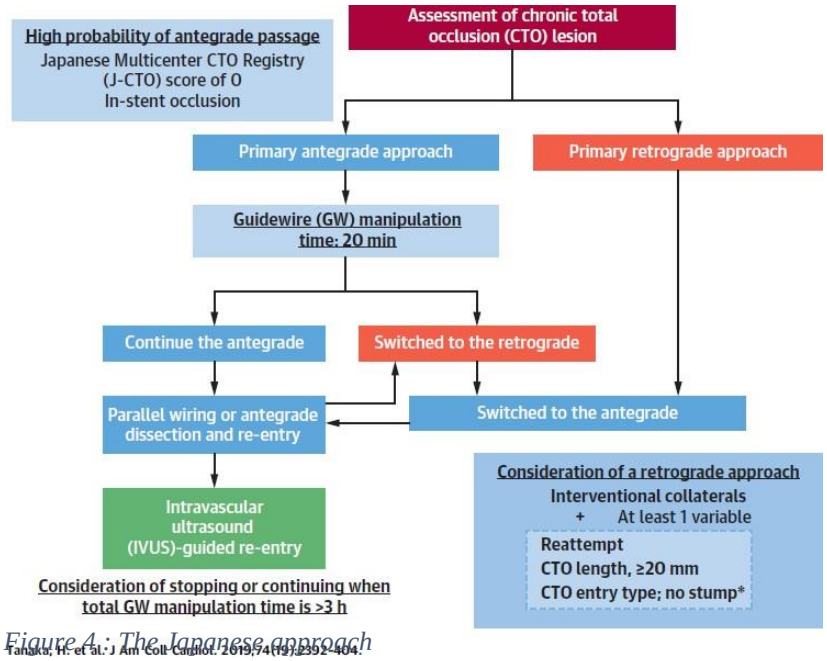

Figure 4 : The Japanese approach
Tanaka, H. et al. J Am Coll Cardiol. 2019;74(19):2392-404.

1.5| Concerning FD-OCT

The angiography only has a limited performance for showing important features of the 3D coronary vessel anatomy, the position of stent struts, and the exact wire positions and is therefore suboptimal for guiding PCI. Second generation optical coherence tomography (OCT) FD-OCT allows minimally-invasive cross-sectional imaging of biological samples and has been selected for its high radial resolution in comparison with IVUS HD (13 µm vs. 22 µm). It also has advantages in term of signal-to-noise ratio and lateral resolution in comparison with first generation OCT. Based on low-coherence interferometry, the reproducibility, accuracy, and safety of this technology make FD-OCT a precious ally to study coronary arteries and to guide interventional procedures.

Yet, FD-OCT presents some limitations. First, it has a lower tissue penetration depth (0.5–2 mm) than IVUS (5–6 mm). It also needs a good blood clearance (by contrast injection 12 to 20ml per run) during pull-back because of the attenuation of the light signal by red blood cells. In practice, it is the same condition that angiography (heparin, aspirin, nitrates) with 6 Fr catheter at minimum.

Currently, FD-OCT is performed using the Fastview® coronary imaging catheter (Terumo®, Tokyo, Japan) or the Dragonfly® coronary imaging catheter (Abbott vascular, Europe) with similar resolutions.

Caracteristics of Fastview Terumo :

- 150 mm pullback at one time
- Pullback speed 5 to 40mm/s
- Frequency 158 pictures /s

Caracteristics of Dragonfly Optis imaging catheter (Abbott):

- 54 to 74 mm pullback at one time
- Pullback speed 20 mm/s
- Frequency 100 pictures /s

From experimental research to routine use, FD-OCT has become the gold standard technique to identify vulnerable plaques, coronary dissections, tissue protrusions, uncovered struts, persistent/late-acquired stent malapposition and mosthly underexpansion; and thus it optimizes PCI results (36,37).

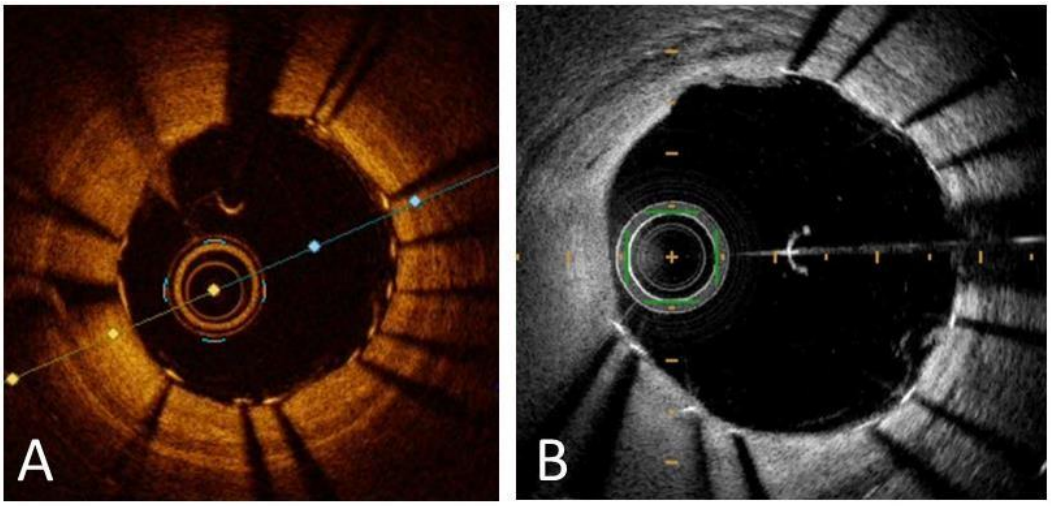

Image 2 : Representatives OCT (A) and OFDI (B) images

1.6| Objectives of the study

The objective of PERFE-CTO (Post-stEnting assessment of Reendothelialization with optical Frequency domain imaging aftEr Chronic Total Occlusion procedure) is to assess in-stent reendothelialization 3 months after successful CTO PCI procedure with FD-OCT.

The secondary objectives of the study are:

1) to define usefulness of immediate and short-term FD-OCT analysis after these complex procedures.

2) to assess the impact of the crossing strategy on the reendothelialization process.

3) to evaluate the improvement of symptoms and the incidence of cardiovascular events (MACE) after CTO PCI during a 12-month clinical follow-up.

4) to assess the impact of a systematic FD-OCT control at 3 months.

Besides improving the understandings of the healing process after CTO PCI, the authors would like to show the different profile of reendothelialization of recanalized CTO lesions compared with of non-CTO lesions. This could lead to reconsidering duration of dual antiplatelet therapy (DAPT) and clinical follow-up of these patients after successful CTO PCI.

1.7| Pilot study

The PERFE-CTO pilot study was realized by Gamet and Levesque and included 13 patients enrolled in Poitiers. (2016)

After the analysis of 13 CTO lesions with a total of 18,765 struts and 1864 crossections, the incidence of malapposition after stenting and at 3-month follow-up was estimated at 5,5% and 5,7% respectively. The incidence of uncoverage at 3-month follow-up was 14,8% with a median percentage of neointimal proliferation per lesion of 3,78%.

Strut coverage process was significantly delayed into the distal stent segment.

Overall, OFDI showed mechanical abnormality requiring further treatment in 31% of cases despite the final angiographic analysis considering the results optimal.

In conclusion, the preliminary results of this pilot study and the literature review, suggest that complex histological remodeling could affect short-term assessment of vascular response after CTO PCI with higher incidence of strut malapposition and longitudinal heterogeneity about neointimal coverage.

2.| METHODS

Perfe-CTO has been designed as an interventional, prospective and multicentric 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. Conducted according to the ethical principles of the Declaration of Helsinki and the current guidelines for good clinical practice, this open- label trial has been approved by the ethical committee and the Institutional Review Board OUEST III under the reference 2016-

A00867-44. This study is registered on ClinicalTrials.gov under the identifier NCT03209843. Authors are solely responsible for the design, the conduction and all the analyses of this study

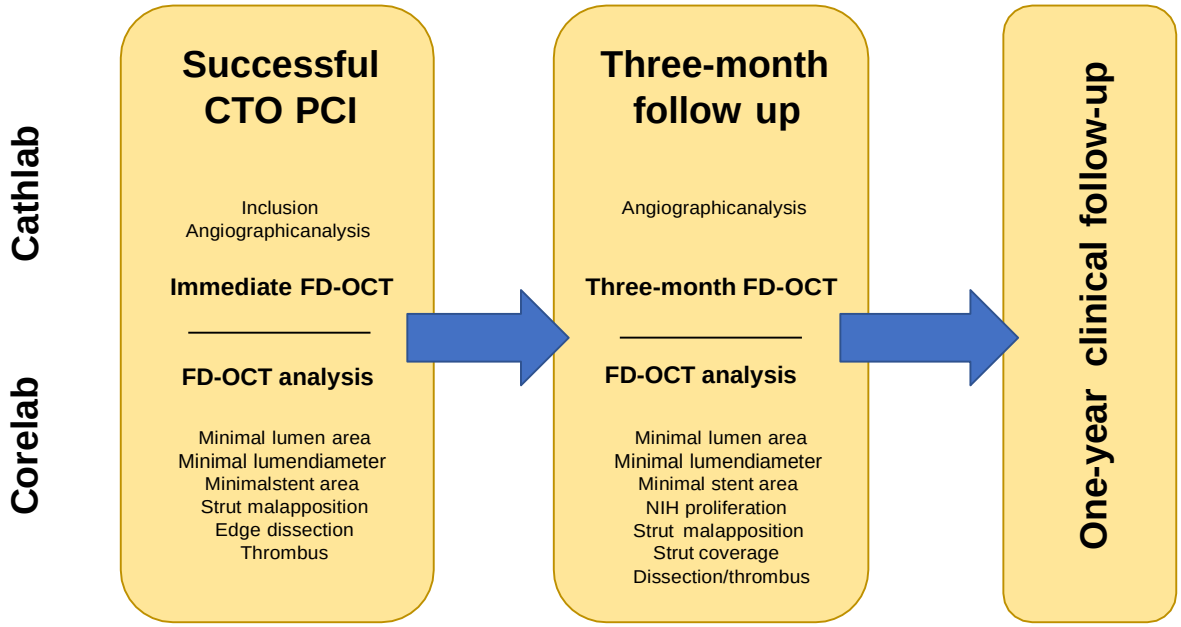

Figure 5 : Study design

2.1| Patients

The selection of patients for CTO PCI and the possibility to switch between recanalization strategies have been left to the practitioner in accordance with the current guidelines for good clinical practice. Data collection, statistical analysis and post-processing on FD-OCT runs for primary endpoint measurements have been performed at the central independent Corelab investigating center.

Exclusion criteria were failed CTO, the absence of written informed consent, a contraindication or impossibility to realize a safe FD-OCT because of a major coronary tortuosity, pregnancy or women with child-bearing potential, a severe hemodynamic instability, a severe chronic kidney disease defined by a creatinine clearance < 30 ml/min and severe coagulation disorders.

At the time of inclusion, clinical characteristics of the patient as age, gender, cardiovascular risk factors, heart failure with reduced ejection fraction (HFrEF), non-severe chronic kidney disease, prior history of myocardial infarction (MI) or CABG and current treatment have been reported on an electronic case report form. Symptoms, assessment of cardiac viability and CABG dysfunction completed the CTO history.

2.2| Centers

7 French centers have contributed to this study : the university hospital of Clermont-Ferrand, Pasteur clinic of Essey-les-Nancy, the general hospital of Grenoble, the university hospital of Toulouse, the university hospital of Nîmes, the clinic confluent of Nantes and the university hospital of Poitiers.

Centers were selected because of their experience and their great number of imaging and PCI CTO cases per year. Operators were required to realize more than 50 CTO PCI per year and more than 50 OCT per year in order to be included.

2.3| CTO PCI

In each participating center, the practitioner has reported the CTO vessel, the SYNTAX and J-CTO scores. Technical data as arterial access and diameter of guiding catheter, the total number of stents implanted with total stents length have been noticed.

Only new generation drug-eluting Ultimaster® coronary stent system (Terumo corporation®, Tokyo, Japan) has been used in order to obtain comparable data regarding reendothelialization processes. The Ultimaster® is a thin-strut (80 µm), cobalt chromium, poly (DL-lactide co-caprolactone) biodegradable- polymer (15 µm), sirolimus-eluting stent.

Successful crossing approaches for recanalization has been firstly classified as antegrade, antegrade dissection reentry, retrograde and reverse CART. Any procedural complication, perfusion of GPIIbIIIa inhibitor, fluoroscopy time, quantity of contrast used, estimated length of subintimal space, and dose-length product (DLP) defined the safety endpoints.

An optimal angiographic result of the CTO PCI was a mandatory condition before immediate FD-OCT in order to assess the usefulness of FD-OCT in revealing angiographically under-detected abnormalities. Every complementary technique used to obtain this result as balloon dilatation had to be strictly reported by the practitioner on the eCRF and then, a final FD-OCT run was realized after every complementary action.

2.4| Immediate FD-OCT

After ensuring an optimal angiographic result as if procedure would be considered normally concluded, the operator will realize a systematic FD-OCT over the entire length of each new generation drug eluting stent (DES) implanted. Immediate brief analysis and complementary therapies induced by FD-OCT have been left to the discretion of the practitioner. The immediate correction of FD-OCT detected malappositions prevents persistent malappositions from occurring; that way the only malappositions detected at 3 months-follow-up would be the acquired ones.

Each FD-OCT pullback has been sent to the independent Corelab investigating center in Poitiers, France (LRCOM i3M -DACTIM-MIS team: Data Analysis and Computation Through Imaging and Modeling- Mathematiques Images Sante / LMA/CNRS 7348) for a post-processing analysis. The minimal lumen area (MLA, mm^2), the minimal lumen diameter MLD (mm), the percentage of malapposed struts, the presence of edge dissection or thrombus have been measured. After spotting the best cross-section, measurements were made every each 5mm approximately. Then the procedure was repeated and between 0-5mm after the stents in the distality of artery and finally 10mm after the stents when it was possible. Estimated time for a 10 mm processing analysis was estimated at 30 minutes.

2.5| Three-month follow-up

A coronary angiogram has been systematically performed 3-months after CTO PCI with FD-OCT. As in the first procedure, the immediate brief analysis, the complementary therapies, and the eventual changes in DAPT therapy induced by FD-OCT were left to the operator's discretion and strictly reported on the eCRF.

Each FD-OCT pullback has been sent to the Corelab investigating center for a post-processing analysis. MLA, MLD, minimal stent area (MSA, mm^2), percentage of neointimal hyperplasia (NIH) proliferation, percentage of malapposed struts, percentage of uncovered struts and the presence of edge dissection, thrombus or persistent hematoma have been measured. After spotting the best cross-section, measurements were made every each 5mm approximately. Then the procedure was repeated and between 0-5mm after the stents in the distality of artery and finally 10mm after the stents when it was possible. Estimated time for a 10 mm processing analysis was estimated at 45 minutes.

2.6| One-year clinical follow-up

Each participating center performed one year after CTO PCI a clinical evaluation of all patients included. This was achevied directly during the subject's medical follow-up or indirectly via his general practitioner and referring cardiologist if necessary. A standardized questionnaire has been provided at the end of the e-CRF. The occurrence of MACE, sudden death, hospitalization for cardiac disease and severe haemorrhage was reported. Any new coronary angiogram was notified, as well as any PCI or CABG which would occur during this one-year follow-up. About symptoms, the Canadian Cardiovascular Society (CCS) grading system and New York Heart Association (NYHA) functional classification have been used to assess exertion-induced angina and dyspnoea respectively one year after CTO PCI.

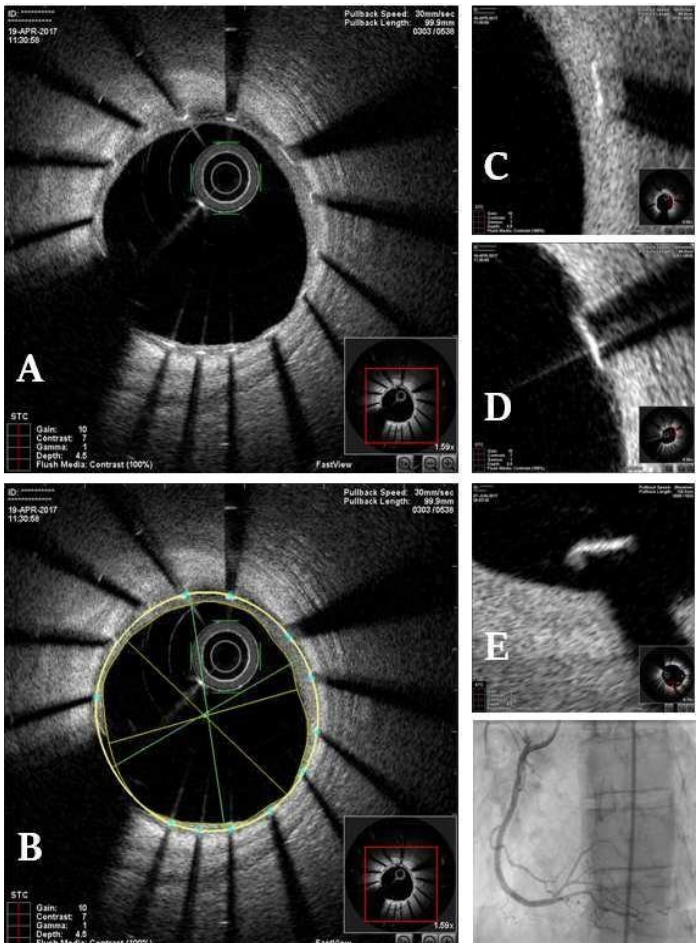

Figure 6. Right coronary OFDI CoreLab analysis. Legend: semiautomatic contouring of the lumen area and stent to compute MLA, MLD, MSA and NIH proliferation (A and B); example of a covered strut (C); example of an uncovered strut(D); example of a malapposed strut (E) Performed using the Lunawave® coronary imaging console andsoftware (Terumo®, Tokyo, Japan).

2.7| FD-OCT analysis, definition of endpoints

In the study FD-OCT has been 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. Post-processing analysis of immediate and 3-month follow-up FD-OCT pullbacks have been performed by 2 operators. MLA and MLD were measured from the semi-automatic contouring of the arterial lumen whereass MSA was computed using a manual delineation of the stent and corrected if necessary. NIH quantification has also been assessed in each slice of both lumen area and stent area, thus giving a percentage of NIH proliferation, defined as NIH obstruction (%) = (stent area–lumen area)/stent area x 100. Regarding stent malapposition, struts have been considered malapposed when distance between the centre reflection of the strut and the vessel wall exceeds 300 µm.(38) Figure 6. The malappostion must concern a dial minimal radius of 90 degrees and a minimal length of 1 millimeters for this criterion to be fulfilled. An uncovered strut has been defined as having a neointimal thickness of 0 µm. Underexpansion has been defined as MSA covering less than 80% of the average reference lumen area. Percentages of malapposition and uncoverage have been measured every 5 millimeters approximately in the best cross-section.

2.8| Statistical analysis

Continuous variables are reported as means with standard deviations (SD) or medians with interquartile ranges (IQR). Categorical variables are reported as numbers and percentages of patients. Differences between groups were assessed using the Wilcoxon rank sum test for continuous variables and the chi-square test, McNemar test (or Fisher exact test when the expected cell value was <5) were used for categorical variables.

We evaluated the factors associated with stent reendothelialization and acquired stent malapposition 3 months after CTO recanalization, in univariate analyses using student's t-test (p values <0.05) or Wilcoxon matched-pair signed-rank test. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3.| RESULTS

3.1| Patients, lesions, and procedural characteristics

A total of 124 patients with CTO recanalization procedures have been enrolled between March 7, 2018 and January 14, 2020. We excluded 6 patients from this study owing to difficulties in FD-OCT data collection and loss to the clinical follow-up. In the end, 118 patients were included in this study (Figure 7).

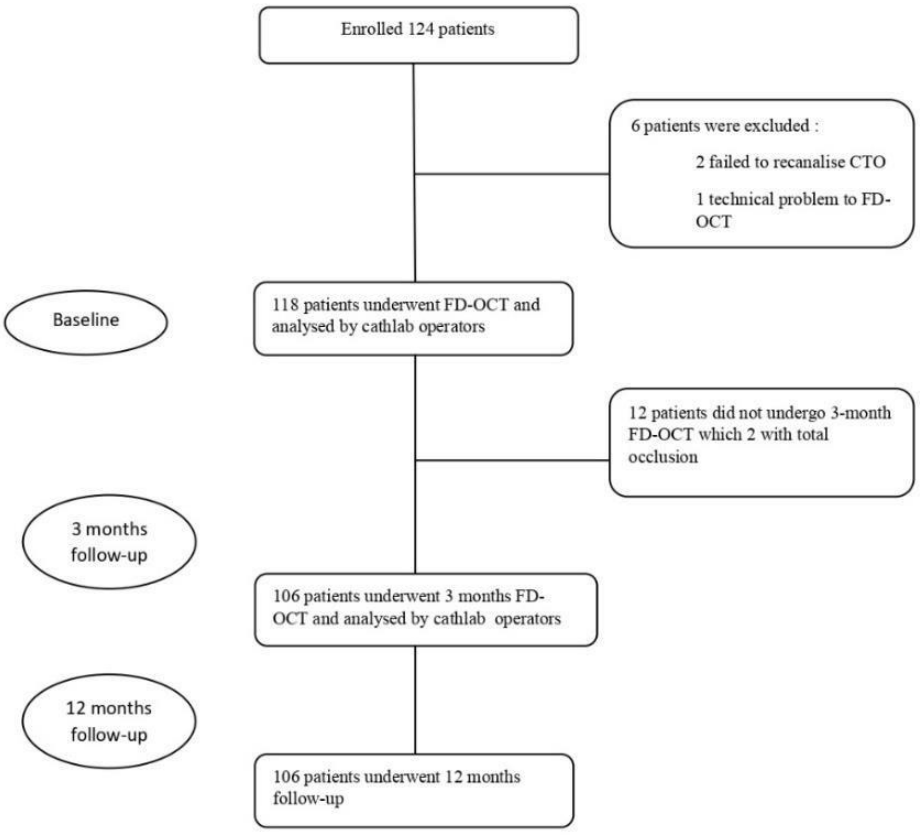

Figure 7: Flow chart

Patients characteristics at baseline are summarized in Table 1. Most patients were men (87%), and mean age was 66 ± 11 years. The most common cardiovascular risk factor was hypertension (59%) followed by active tobacco use (42%), diabetes mellitus (30%), hypercholesterolemia (28%), obesity (23%), and family history (19%). Mean LVEF was 52,4% ± 12.7%. Myocardial viability was sought in 97 (81%) patients by echocardiography (n=25), stress echocardiography (n=23), myocardial MRI (n=17), myocardial scintigraphy (n=32). 2 (2%) patients and 1 (1%) patient presented an angina CCS IV and dyspnoea NYHA IV respectively.

	All (N=118)
Clinical features	
Age y, Mean (SD)	63.20(11.71)
Male, n (%)	103 (87)
Diabetes, n (%)	35 (30%)
Hypertension, n (%)	70 (59%)
Hypercholesterolemia, n (%)	33 (28%)
Current smoking, n (%)	49 (42%)
Obésity, n (%)	27 (23%)
First degree heredity coronary artery disease, n (%)	22 (19%)
Prior MI, n (%)	40 (34%)
Strokes, n (%)	5 (4%)
Prior CABG, n (%)	6 (5%)
MDRD clearance, Mean (SD)	82.05(30.10)
Symptoms	
Syncope, n (%)	0 (0%)
Ventricular tachyarrhythmia, n (%)	4 (3%)
Heart failure , n (%)	12 (10%)
No symptoms, n (%)	42 (36%)
Angina status, n (%)	
CCS I	83 (70%)
CCS II	21 (18%)
CCS III	12 (10%)
CCS IV	2 (2%)
Dyspnea status, n (%)	
NYHA I	83 (70%)
NYHA II	28 (24%)
NYHA III	6 (5%)
NYHA IV	1 (1%)
Viability	
Exam with viability in territory of CTO vessel	
Echocardiography , n (%)	25 (21%)
Stress echocardiography , n (%)	23 (19%)
Myocardial RMI, n (%)	17(14%)
Myocardial scintigraphy , n (%)	32 (27%)
None, n (%)	27 (23%)
FEVG, Mean (SD)	52.43(12.73)
Therapy	
Antiplatelet therapy , n (%)	114(97%)
Acetylsalicylic acid, n (%)	111(94%)
Clopidogrel, n (%)	57 (48%)
Ticagrelor, n (%)	25 (21%)
Prasugrel, n (%)	2 (2%)
Oral anticoagulation, n (%)	11 (9%)
Vitamin K antagonist , n (%)	2 (2%)
New oral anticoagulant, n (%)	9 (7%)

Table 1: Patients characteristics at baseline

In term of CTO target vessel distribution (Table 2), the right coronary artery (78%) was the most concerned, followed by left anterior descending artery (16%) and left circumflex artery (10 %). J-CTO score had an average of 2 (2 to 3) and successful recanalization was mostly obtained by antegrade crossing (52%). The implanted stents covered an average, length of 79.2 ± 26.9 mm. Procedural complication occurred in 7 cases (6%). Final angiographic analysis was considered optimal in 110 patient (93%) while 6 patients (5%) needed a FD-OCT control for malapposition and underexpansion.

Table 2: Regarding baseline procedural characteristics

	All (N=118)
CTO vessel	
Left anterior descending, n (%)	19 (16%)
Right coronary artery, n (%)	92 (78%)
Left circumflex, n (%)	12 (10%)
Estimated lenght occlusion (mm), Mean (SD)	37.1 (21)
J-CTO score, Median (IQR)	2 (2-3)
0	0 (0%)
1	19 (16%)
2	47 (40%)
3	31 (26%)
4	15 (13%)
5	2 (2%)
SYNTAX score, Mean, (SD)	17 (8)
Recanalisation technique	
Antegrade wiring, n (%)	61 (52%)
Retrograde, n (%)	25 (21%)
CART, n (%)	3 (3%)
Reverse CART, n (%)	19 (16%)
Dissection and reentry, n (%)	21 (18%)
Estimated subintimal lenght, Mean (SD)	22 (25)
Stents per CTO, n (SD)	3 (1)
Stent lenght (mm), Mean (SD)	79 (27)
PCI on another artery during the procedure, n (%)	26 (22%)
Fluoroscopic time before FD-OCT min, Mean (SD)	35 (27)
Angiographic analysis post-PCI considered optimal, n (%)	110 (93%)
Malapposition suspected in angiography, n (%)	4 (3%)
Procedural complication, n (%)	7 (6%)

3.2| Immediate FD-OCT

FD-OCT was carried out and analysed immediately at cathlab by operators. If complementary treatment was performed, a final FD-OCT was realized as the control FD-OCT.

A total of 118 FD-OCT analyses were realized, among which 92 were done by OFDI and 16 by OCT.

Immediate FD-OCT (Table 3) revealed abnormalities in 41 (35%) procedures even if final angiographic analysis was considered optimal. In these 41 patients, there were 19 (16%) cases with malappositions, 18 (15%) cases with underexpansion, 2 (2%) cases with thrombi, and 5 (4%) cases with dissection. Overall, 40 (34%) patients justified a complementary treatment: 35 (40%) patients needed a balloon dilatation (30%) and 4 (3%) needed new stents.

On optimal outcomes, fluoroscopy time post FD-OCT and contrast volume per FD-OCT was 36min and 20ml (IQR: 16 to 40) respectively. On non-optimal outcomes, fluoroscopy time post FD-OCT and contrast volume per FD-OCT was 36.5min and 24ml (IQR: 17 to 33) respectively. In terms of contrast volumes per FD-OCT and fluoroscopy time post FD-OCT there was no significant difference between optimal and non-optimal outcomes (p=0.8 and p=0.55). No procedural complication per FD-OCT occurred.

Table 3: Immediate FD-OCT at Cathlab

	All (N=118)
Analysis ad-hoc FD-OCT, n (%) (optimal outcomes)	77 (65%)
Fluoroscopy time post FD-OCT min, Mean (SD)	36 (31)
Contrast volume per FD-OCT ml, Median (IQR)	20 [16 ;40]
Analysis ad-hoc FD-OCT, n (%) (Non optimal outcomes)	41 (35%)
Dissection, n (%)	5 (4%)
Thrombus, n (%)	2 (2%)
Underexpansion, n (%)	18 (15%)
Malapposition, n (%)	19 (16%)
Others, n (%)	2 (2%)
Fluoroscopy time post FD-OCT min, Mean (SD)	36.5 (25)
Contrast volume per FD-OCT ml, Median (IQR)	24 [17 ;33]
Procedural change introduced by FD-OCT, n (%)	40 (34%)
Balloon post dilatation, n (%)	35 (30%)
Implantation new stent, n (%)	4 (3%)
GP2B3a, n (%)	2 (2%)
Procedural complication per FD-OCT, n (%)	0 (0%)

No significant difference in-term contrast volume per FD-OCT and fluoroscopy time post FD-OCT between optimal and non-optimal on analysis ad-hoc respectively (p=0.8 and p=0.55).

3.3| Clinical, angiographic and FD-OCT data at 3 months

Angiographic and FD-OCT data at 3 month-follow-up (Table 4), were analysed immediately at cathlab by operators as immediate ad hoc analysis.

The median interval between CTO PCI and three-month follow-up with systematic FD-OCT was estimated at 3 (2.9 to 3.2) months.

Major bleeding occurred in 2 patients, 6 patients required hospital admission in a cardiologic unit and one case had stent thrombosis (ST).

Angiographic analysis at 3 months showed non optimal outcomes in 20 (17%) cases with 8 (7%) restenosis, 2 (2%) occlusions, 6 (5%) dissections, and 7 (7%) lesions. Furthermore, 11 (9%) cases needed FD-OCT control outside the protocol.

While final angiographic analysis was considered optimal in 87 (74%) patients, FD-OCT at 3 months revealed abnormalities in 48 (41%) procedures with significant malapposition requiring complementary balloon dilatation. These complementary treatments have increase time of DAPT in 32 (27%) cases.

Contrast volume injected per FD-OCT was estimated at 35ml (IQR: 17 to 63). No procedural complication per FD-OCT occurred.

Table 4: Clinical, angiographic, FD-OCT data at 3 months in Cathlab analysis

	All (N=106)
Clinical	
Median follow-up months, (IQR)	3 (2.9;3.2)
All cause death	0 (0%)
Stent thrombosis relating to CTO, n (%)	1 (1%)
Severe bleeding, n (%)	2 (2%)
Hospital admission in cardiology, n (%)	6 (5%)
Discontinuation antiplatelet therapy, n (%)	1 (1%)
Angiographic analysis	
Optimal outcomes, n (%)	98 (83%)
Non optimal outcomes, n (%)	20 (17%)
Restenosis, n (%)	8 (7%)
Occlusion, n (%)	2 (2%)
Persistent distal stenosis, n (%)	5 (4%)
Persistent proximal stenosis, n (%)	2 (2%)
Dissection/ Hematoma, n (%)	6 (5%)
Malapposition suspected in angiography, n (%)	23 (19%)
Analysis ad-hoc FD-OCT	
Optimal outcomes, n (%)	70 (59%)
Non optimal outcomes, n (%)	48 (41%)
Needed balloon post dilatation, n (%)	36 (31%)
Needed implantation new stent, n (%)	6 (5%)
Others	11 (9%)
Procedural complication per FD-OCT	0 (0%)
Contrast volume per FD-OCT ml, Median (IQR)	35(17 ;63)
Change antiplatelet therapy or duration, n (%)	32 (27%)

Significant difference between optimal angiography analysis and optimal ad-hoc FD-OCT (p<0.0001).

3.4| FD-OCT analysis

The analysis of FD-OCT morphometric data at baseline and at 3 months (Table 5), was analysed by corelab DACTIM.

15695 struts at baseline and 14326 struts at 3 months were analysed, among which 1418 (9%) and 2068 (14.4%) were respectively malapposed, corresponding to a median percentage of 8.3 % and 15% malapposed struts per patients respectively ($p<0.0001$) (Table 5 and figure 8). The acquired stent malapposition rate at 3 months was 20.7%. There was an association between stented length and acquired stent malapposition. Indeed, the stented length was significantly shorter in case of acquired malapposition, (Table 6: 63 ± 25 versus 83 ± 26mm ($p=0.0013$)). No significant association was found between acquired malapposition at 3 months and the nature of recanalized artery or the technique used.

A malapposition was suspected by angiography for 81 patients at baseline and 92 patients at 3 months, corresponding to a median percentage of 5 % and 25% respectively. The malapposition factors detected by FD-OCT and angiography, permit us to compare malapposition for 79 patients at baseline and 88 patients at 3 months by contingency methods. Among the 54 cases of malapposition found by FD-CTO at baseline, only 4 cases had malapposition seen in angiography (7%). In the 25 patients without malapposition in FD-OCT, there are no patient with malapposition suspected in angiography ($p<0.0001$). Likewise at 3 months, among the 80 cases of malapposition in FD-OCT group, only 20 cases had their malapposition revealed by angiography (26%). Among 8 patients without malapposition in FD-OCT, only 2 patients have their malapposition suspected in angiography ($p<0.0001$). (Figure 10).

Percentage of NIH proliferation was estimated at 6.34% per patients. 44% of patients had a NIH proliferation percentage between 0 and 30% (including 8 patients without NIH proliferation); 31% between 30 and 60%; and 26% between 60 and 100%.

On the 14326 analysed struts, 3664 were uncovered at 3 months, corresponding to a median percentage of 25,6% per patients (Table 5 and figure 8).

In Table 5, the estimated MLA (mm^2) and MSA (mm^2) were 7.20 ± 1,81 and 7.11 ± 1.74 respectively at baseline; versus 7.77 ± 2.0 and 7.44 ± 1.68 respectively at 3 months. At baseline, MLD measured at 0-5mm from the distality of the stent and at 10 mm from the distality of the stent was 1.89 ± 0.44 and 1.77 ± 0.49 respectively. At 3 months the measured MLD was 2.21 ± 0.46 and 2.16 ± 0.45 respectively. At 0 to 5 mm from the distality of the stent, there was a lumen diameter expansion of 23% ($p<0.0001$) at 3 months. Likewise, at 3 month-follow-up, the lumen diameter expansion at 10 mm from the distality of the stent was about 21% ($p<0.003$) at 3 months (Figure 9). So, there was a significant enlargement of lumen diameter in distality at 3 months.

Only 2 patients had a reocclusion detected by angiography at the 3 month-follow-up. At 3 months, 48 patients (41%) had received a complementary treatment (balloon post dilatation for 36 patients (31%) and new stents for 6 patients (5%)). Length stent was significantly bigger in case of complementary treatment (Table 8: 84 ± 27 versus 73 ± 27mm ($p=0.04$)). No association was found between the length stent, the nature of recanalized artery and the technique used.

The Table 7, shows that the technique used doesn't have a significant impact on the incidence of malapposition and delayed of reendothelialization respectively ($p=0.11$; $p=0.66$).

Table 5: FD-OCT analysis by Corelab

	Immediate N=118	3 months N=106	p Value
Total number of analyzed struts, n	15695	14326	-
Total length of analyzed stents mm,	8722	7895	-
Total length of analyzed stented/patient, mm, Mean (SD)	76 (29.65)	77.4 (27.53)	0.27
Minimal stent area, mm², Mean (SD)	7.11(1.74)	7.44 (1.68)	<0.0001
Minimal lumen area, mm², Mean (SD)	7.20(1.81)	7.77 (2.00)	<0.0001
Median % NIH proliferation/patient	NA	6.34 (4.38)	-
MLD at 0 to 5mm distal to the stent, Mean (SD)	1.89(0.44)	2.21(0.46)	<0.0001
MLD at 10mm distal to the stent, Mean (SD)	1.77(0.49)	2.16(0.45)	0.003
Malapposition			-
Malapposition in FD-OCT, n (%)	84 (71%)	92 (78%)	0.0013
Malapposed struts, n (%)	1418 (9%)	2068 (14.4%)	-
Acquired malapposition, n (%)	NA	23 (20.7%)	-
Mean % of malapposed struts/patient	8.3 (11.18)	15 (14.29)	<0.0001
Uncoverage			
Uncovered struts, n	NA	3664/14326	-
Median % of uncovered struts/patient	NA	25.60 (17.53)	-
Median % of uncovered frames/patient	NA	59.19 (72.29)	-
Frequency of frames/patients with [0-30] % uncovered struts, n (%)	NA	23 (23%)	-
Frequency of frames/patients with [31-60] % uncovered struts, n (%)	NA	23 (23%)	-
Frequency of frames/patients with > 60% uncovered struts	NA	55 (54%)	-

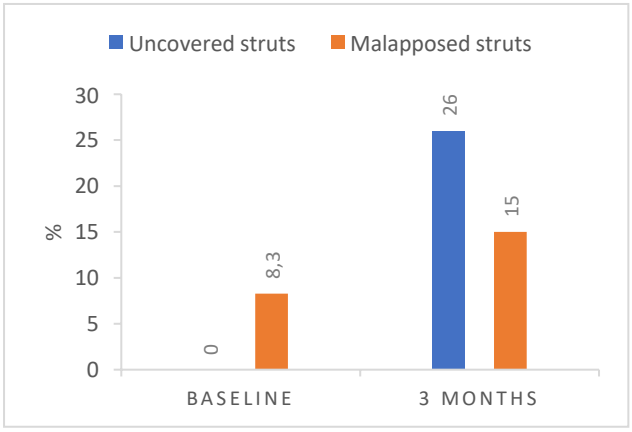

Figure 8: Percentage of uncovered struts and malapposed struts per patients

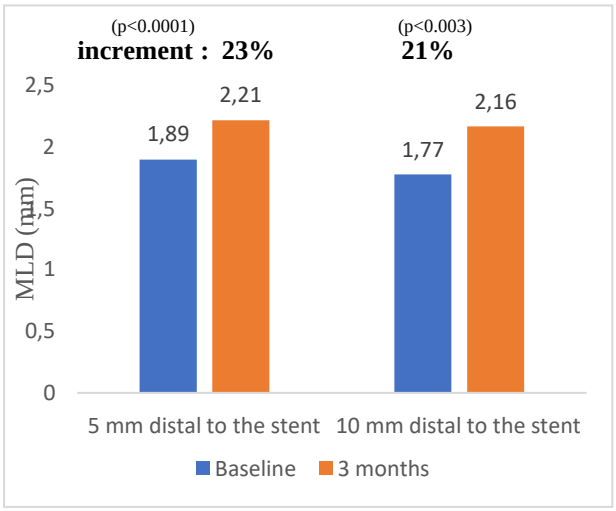

Figure 9: Enlargement of a vessel segment 5 mm proximal and distal to the stent

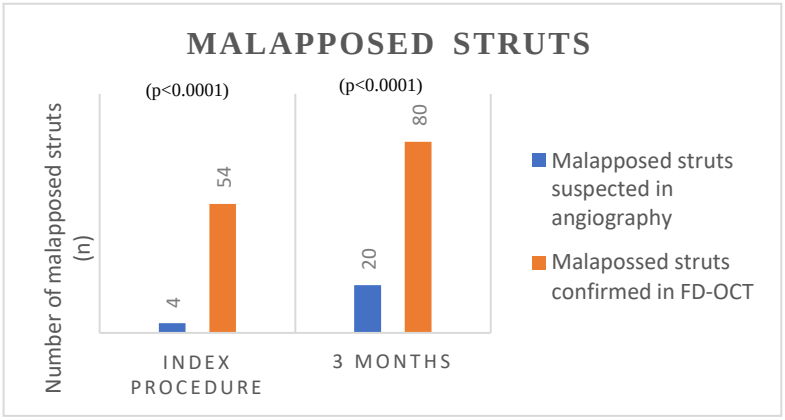

Figure 10: Malapposition struts suspected in angiography versus confirmed on FD-OCT

Table 6: relation between total stented length, recanalized artery, technique used and risk of acquired malapposition

Risk of acquired malapposition	All(n=111)	No (n=88)	Yes (n=23)	p
Total stented length mm, Mean (SD)	79 ± 27	83 ± 26	63 ± 25	**0.0013**
Recanalized artery				
Left anterior descending, n (%)	19 (16%)	11 (12%)	7 (30%)	0.0547
Right coronary artery, n (%)	92 (78%)	72 (82%)	14 (61%)	0.0631
Left circumflex, n (%)	12 (10%)	9 (10%)	3 (13%)	0.4295
Technique used				0.2259
Antegrade wiring, retrograde, n (%)	70 (63%)	53 (60%)	17 (74%)	
CART, reverse CART, dissection and reentry, n (%)	41 (37%)	35 (40%)	6 (26%)	

Table 7: relation between risk of acquired malapposition, delayed of reendothelialization and technique used

Technique used	All(n=101)	Antegrade wiring	Retrograde, CART, reverse CART, dissection and reentry	p
Risk of acquired malapposition, n (%)		15 (27%)	8 (15%)	0.11
Frequency of cross-section with reendothelilization, % (SD)		60 (26)	59 (30)	0.66

Table 8: relation between total stented length, recanalized artery, technique used and complementary treatment

Complementary treatment	All (n=103)	Yes (n=48)	No (n=55)	p
Total stented length mm, Mean (SD)	79 ± 27	84 ± 27	73 ± 27	**0.0422**
Recanalized artery				
Left anterior descending, n (%)	19 (16%)	9 (19%)	8 (15%)	0.5664
Right coronary artery, n (%)	92 (78%)	38 (79%)	41 (75%)	0.3359
Left circumflex, n (%)	12 (10%)	3 (6%)	9 (17%)	0.1003
Technique used				0.1239
Antegrade wiring, retrograde, n (%)	68 (66%)	28 (58%)	40 (73%)	
CART, reverse CART, dissection and reentry, n (%)	35 (34%)	20 (42%)	15 (27%)	

3.5| Clinical outcomes

Concerning the 12-month follow-up (Table 9), MACE data was missing in 10 patients. 2 deaths from any cause, 1 case of severe bleeding, and 1 case of stent-thrombosis were detected. No angina and no dyspnoea were found in 86% and 68% of cases respectively. At 12 months, there was a significant improvement on angina status ($p<0.001$) whereas no difference on dyspnea status was reported ($p=0.42$) (Figure 11).

Table 9: Clinical outcomes at 12 months

	All (N=118)
Median follow-up months, (IQR)	12.0 (11.8 ;12.2)
Contact method	
Others	2 (2%)
Family	8 (7%)
Patient	98 (83%)
Missing	10 (8%)
All cause death, n (%)	2 (2%)
Stent thrombosis relating to CTO, n (%)	1 (1%)
Severe bleeding, n (%)	1 (1%)
Hospital admission in cardiology, n (%)	8 (7%)
New angiography, n (%)	5 (4%)
PCI, n (%)	3 (3%)
CABG, n (%)	1 (1%)
Angina status, n (%)	
CCS I	101 (86%)
CCS II	4 (3%)
CCS III	1 (1%)
CCS IV	0 (0%)
Missing	12 (10%)
Dyspnea status, n (%)	
NYHA I	80 (68%)
NYHA II	19 (16%)
NYHA III	6 (5%)
NYHA IV	1 (1%)
Missing	12 (10%)

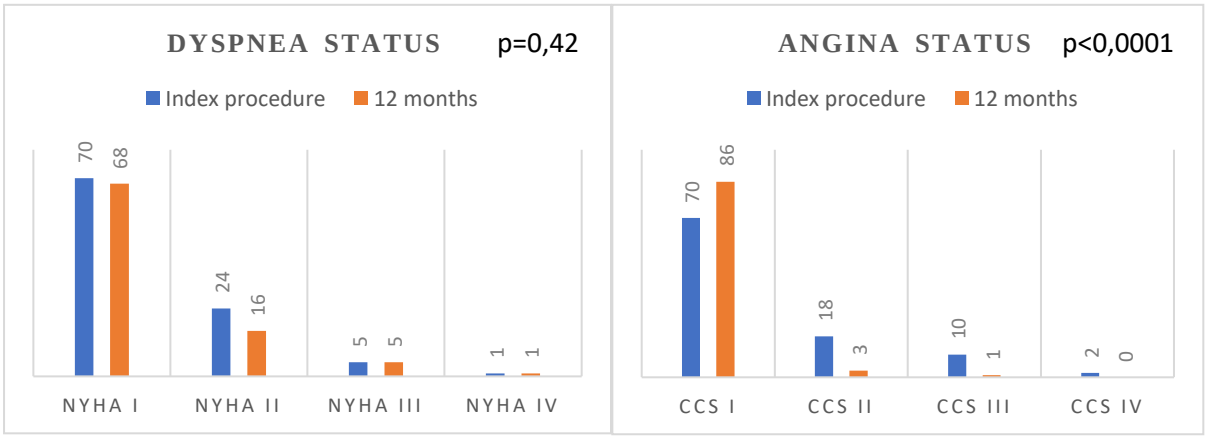

Figure 11: Cumulative dyspnea and angina at index procedure at 12 months follow-up

4.| DISCUSSION

To our knowledge, PERFE-CTO is the first study investigating routine FD-OCT at index PCI and at 3-month follow-up after successful CTO recanalization.

The major findings of this study are: 1) Abnormalities are undetected in one third of cases, ; 2) A high rate of malapposed and uncovered stent struts in CTO-PCI at 3-month follow-up; 3) A hight rate of acquired malapposition at 3 months in CTO-PCI; 4) The absence of correlation between acquired malapposition and the recanalization technique in CTO-PCI; 5) The absence of correlation between level of reendothelialization at 3 months and the recanalization technique in CTO-PCI too.

The confirm findings of this study are: 1) A high rate of uncovered stent struts at 3-month follow-up; 2) An improved distal vessel expansion of 23%, 3 months after successful recanalization; 3) An improved angina status after CTO recanalization 4) The safety and the accuracy of FD-OCT.

4.1| Procedure optimization

FD-OCT performed after the index PCI detected one third of insufficient result despite the final angiography considering the result to be optimal.

Underexpansion and malapposition were the most frequent abnormalities and their correction would probably decrease the restenosis or reocclusion rates. Indeed, we found a low reocclusion rate (2%) or restenosis rate (8%) in comparaison with previous studies. In the litterature concerning CTO patients, data on angiographic follow-up reocclusion rate are scarce and its incidence varies greatly from 7.5% to 9.4% between 3 and 6 months (48,56). Data on FD-OCT guidance in CTO lesions are also poor as few randomized studies had evaluated IVUS-guided DES implantation in CTO-PCI. Kwon et al (39) showed that subjects with post-stent IVUS evaluation had a significantly decreased risk of reocclusion and restenosis after CTO-PCI with DES compared with those without post-stent IVUS assessment. These findings were completed by the Air-CTO study which showed reduced in-stent restenosis and a trend towards a lower rate of definite stent thrombosis with IVUS-guided stent optimisation versus angiographic guidance only (40) . Other studies showed that IVUS-guided PCI was superior to angiography-guided PCI in reducing the risk of major adverse events (39). Taking into consideration these data, we could suppose that use FD-OCT guided PCI does better than angiography alone in CTO lesions, in particular to correct undexexpansion and malapposition. Indeed, in the ILUMIEN study (41) OCT-guided PCI was non-inferior to IVUS-guidance and improved stent expansion and procedural success compared to angiography-guided PCI in non-CTO lesions.

4.2| Risk of Malapposition

Known as a predictive factor of stent thrombosis and cardiovascular outcomes, malapposition is widely considered as an unavoidable endpoint in every study dealing with the safety of new generation DES or comparing techniques of PCI. In the PESTO French multicentric registry (37), first or second-generation stent thrombosis were associated with a mechanical abnormality in 96% of cases, with a majority of malapposition. If severe diameter stenosis, calcified and long lesions are independent predictors of stent malapposition (41), then CTO could seem to be the perfect substratum for these mechanical abnormalities. However robust data are lacking in

this domain compared to the non-CTO-patients. In the ACE-CTO study Sherbet et al (42) found in 62 patients a rates of malapposition strut (9.2%) after CTO PCI using everolimus-eluting-stent. Like the previous studies (42,43), our results confirms a hight incidence of malapposition (15%) following CTO recanalization. These results are significantly higher than previous studies in non-CTO patients, which detected in 0.5 to 2.9% of malapposition struts (44,45). As a reminder, we corrected the detected malappositions immediately at the end of the procedure in order to detect acquired malappositions only. These acquired malappositions are common and have variable severity. These incompletely understood and likely multifactorial abnormalities were described in the ISAR-OCT-CTO study (46). They occurred after 13.6% of subintimal recanalization strategy and after 6.6% of intraplaque recanalization strategy, without any OCT control at the index procedure. In addition Xhepa et al, showed that malapposition was significantly higher in subintimal recanalization strategy compared to anterograde strategy (46). To our knowledge with his systematically immediate FD-OCT at index PCI and at 3 months follow-up, PERFE-CTO is the first observational study to report an acquired malapposition rate of 21% in CTO lesions. Surprisingly, our findings confirm the absence of correlation between the recanalization technique and the presence of uncovered struts or acquired malapposition. Furthermore, we have found a correlation between acquired malapposition and length stent whereas malapposition at index procedure was independent from subintimal recanalization. There are several potential explanations for the high rates of stent strut malapposition and incomplete stent coverage after CTO stenting. Therefore, negative remodeling with lumen area increase after recanalization and mechanical stresses on the stent structure caused by the calcified vessel wall could be keys to understand the higher rates of strut malapposition observed in our study in comparison with the literature dealing with non-CTO PCI. As mentioned previously, successful revascularisation of such lesions often requires a subintimal wire position and a distal re-entry with disruption of the vessel integrity with resultant formation of intramural hematoma and stent implantation in the subintimal space. Indeed, some studies showed that implantation stent are therefore located within the subintimal layer of the vessel wall (15,45) and stenting of the false lumen caused stent malapposition (46). Thus, resorption of intramural hematomas and implantation stent are an alternative mechanism for the occurrence of strut malapposition.

4.3| Delayed re-endothelialization

In our study, a significant percentage of uncovered struts (25,6% per patients) was found 3 months after implantation, indicating that re-endothelialization was delayed. The duration of complete healing with DES in humans is unknown and changes with each stent modification. The healing process is multifactorial and partly depends on the type of drug eluting stent, the form and the thickness of struts, the stent length, the inflammation, the stent recoil, and the antiplatelet therapy. In recanalization cases, the most dreaded complication would be restenosis (also known as excessive healing), either than delayed healing. We are therefore reminded that we used the same stent for all procedures. CTO lesions trigger thrombus organisation, inflammation and the constitution of a proteoglycan matrix around smooth muscle cells as well as calcification. Artery recanalization techniques can affect vessel integrity resulting in extensive injury of the adventitial layer. This mechanism, combined with eccentric plaque compression during stent implantation of CTO lesions may contribute to uncoverage and malappositon. Moreover, penetration of a necrotic core, overlapping stent placement and excessive stent length represent barriers to stent coverage (47). Additionally, multiple stent

implantation and longer lesions may also be responsible for this adverse effect in CTO patients. By performing the anterograde wiring technique it is believed that re-entry into the true lumen occurs through microchannels without disruption of vessel integrity and may result in a better stent healing (48–50). However, in this study no significant difference was found concerning the observed approaches, suggesting due to the lack of data, that antegrade wiring, dissection and re-entry techniques are equal concerning coverage and apposition. In several studies, a percentage of uncovered struts exceeding 30% was identified as a predictive factor for stent thrombosis (ST)(47,48). Taniwaki et al, used OCT to examine 64 patients who developed very late stent thrombosis (ST) during a median of 5- year follow-up after their index procedures (49). The cause of these events was identified using OCT for 98% of cases, including strut malapposition (34.5%) and uncovered struts (12.1%) (49). In line with our result, Jia et al comparing CTO and non-CTO vascular responses with OCT 6-months after PCI using sirolimus-eluting stent showed 23.4% uncovered struts in CTO lesions (42). In our study, one third of immediate FD-OCT revealed at least one significant anomaly. Our uncovered percentage at 3months would have been even higher without complementary balloon dilatation, all the more so as one third of cases needed complementary balloon dilatation at 3 months. Indeed, in the ALSTER-OCT-CTO registry, Heeger et al showed 31.1% of uncovered struts in CTO patients at the 6 month-follow-up (43). These results require further research to be investigated.

4.4| Distal luminal diameter

As shown previously, the distal luminal diameter of the CTO vessel increases significantly after recanalization at 3 months. In their recanalized CTO cases, Galassi et al, measured the luminal diameter at 5 mm from the distality of the stent, and found 2.0 ± 0.52 mm at post-PCI and 2.25 ± 0.50 mm at follow-up ($p < 0.001$). Hong et al(50) evaluated the findings of a 12-month serial IVUS exam in 69 CTO lesions treated with new-generation DES. They found that expansion of the distal vessel increased in two-thirds of these patients. Even if our results are in line with the previous studies, our measures are more accurate than those using two dimensional (2D) quantitative coronary angiography (QCA) or IVUS. Limitation of QCA is that it provides a 2D outline of the vessel lumen with an inevitable reliance on geometrical assumptions to assess dimensions (51) ; whereas with the hight resolution of FD-OCT, we are able to precisely measure in luminal diameter between the index PCI and the follow-up after recanalization rather than relying on QCA. In 91 CTO patients, Gomez-Lara et al showed a notable lumen and vessel enlargement. This might be caused by chronic hypoperfusion, potentially leading to stent-vessel mismatch (52). The follow-up of these hypoperfusion aeras would sometimes reveal significant stenosis at the distality of the CTO lesion, even after successful recanalization. Angiography performed immediately after CTO recanalization might underestimate the size of distal vessel so, it would be interesting to use a FD-OCT-guide procedure to choose the optimal stent size. The association between distal vessel expansion and clinical outcomes is unclear and data is missing. Indeed, on a substudy of Primary Stenting of Occluded Native Coronary Arteries (PRISON) III and IV trials, patients with significant stenosis at the distality of recanalized the CTO lesion showed comparable angiographic and clinical outcomes than those without vessel narrowing in the same segment(53). So, further larger studies are necessary to elucidate the associations between clinical outcomes and distal vessel expansion.

4.5| Clinical implication

Currently, several studies have showed the accurancy and safety of FD-OCT in PCI guidance for non-CTO lesions. In the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study, Meneveau et al (54) showed that OCT-guided PCI was safe and did not increase procedural complications. Other studies successfully demonstrated the safety and the efficacy of intravascular imaging for coronary artery lesions (55) In line with these findings, our study confirms the safety and accuracy of FD-OCT for CTO lesions by demonstrating that no procedural complication occurred. Furthermore, FD-OCT guidance in CTO PCI doesn't significant increase contrast volume and fluoroscopy time. When FD-OCT was performed, total fluoroscopy time was 36min and the contrast volume went from 20ml to 24ml.

As previously referenced in EURO-CTO (27), CTO recanalization improved quality of life assessed by SAQ score. Similarly, we demonstrate that FD-OCT guided CTO recanalization reduce angina status.

All procedures were performed by skilled and experienced interventional cardiologists. Thus the results might be different if less experienced operators were involved. We should probably leave these procedures at experienced interventional cardiologists's hands in order to ensure the greatest possible result.

4.6| Perspective

CTO present a different profile of reendothelialization after PCI compared to non-CTO PCI. In several studies, DAPT duration is one of the most important therapeutic implications on risk of stent thrombosis. The possible delay in stent struts endothelization and the high frequency of malapposition 3 months after CTO PCI could lead practitioners to re-evaluate the stent thrombosis risk in order to extend the DAPT duration, although the long-term benefits of prolonged DAPT over 12 months have not been proven in retrospective cohort studies(56).

As demonstrated for PCI in non-ST-elevation myocardial infarction (NSTEMI) in comparison with fluoroscopy alone in DOCTORS study(54), we could propose a systematic use of intra-coronary imaging in complex procedures in order to rule out angiographically underdetected mechanical abnormalities in CTO lesion. Moreover, a systematic 3rd month FD-OCT control would be useful to perform CTO PCI more safely and with better long-term results.

4.7| Limitations

Our study has several limitations. First, because of its design as an interventional multicenter study, we were not able to calculate the number of subjects which would be needed to achieve enough power. Finally, the clinical follow-up period may have been insufficient and a longer clinical follow-up at 1 year and at 5 years would probably be more relevant.

5.| CONCLUSION

Development of revascularization techniques have considerably expanded the horizons of CTO PCI, specially concerning the success rates and the safety of the procedures. The findings of PERFE-CTO study confirm that complex vascular remodeling of chronically occluded vessel

could lead to higher rates of acquired stent malapposition and delay in neointimal proliferation. Even with harsh recanalization methods, there is no correlation between the technique used and acquired malapposition and uncovered struts. Thus, a systematic third month angiography and FD-OCT control could be useful. Furthermore, an algorithm relying on a malapposition classification should be useful to help the physician optimizing their future procedures; thus leading to greater outcome for the patients.

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RESUME

Introduction : Le traitement des occlusions coronaires totales chroniques (CTO) par angioplastie dans des centres expérimentés est un des grands progrès de la dernière décennie dans la prise en charge de la cardiopathie ischémique. La tomographie en cohérence optique fréquentielle (OFDI) intra-coronaire est la technique de référence pour évaluer la cicatrisation des artères coronaires après l'implantation d'un stent. Cependant le nombre d'études analysant cette cicatrisation après la revascularisation de ces CTO est limitée et il n'existe aucune étude randomisée contrôlée sur l'utilisation de l'OFDI pour guider les angioplasties dans les CTO.

Méthodes : PERFE-CTO est une étude française multicentrique prospective interventionnelle, dont l'endothelialisation des stents, la mal-apposition des mailles de stent et le pourcentage de prolifération néo-intimale ont été systématiquement évalués par coronarographie et OFDI immédiatement et à 3 mois après leur implantation lors de la désobstruction de l'artère. L'impact de l'utilisation systématique de l'OFDI lors de ces procédures complexes a été mesuré en analysant les anomalies mécaniques ayant été sous détectées en angiographie ou ayant nécessité un traitement complémentaire. Un suivi clinique d'un an a été réalisé pour chaque patient.

Résultats : 118 CTO ont été analysés soit un total de 30021 mailles et 16617 millimètres de stents. A 3 mois, 25,6% des mailles n'étaient pas recouvertes et étaient associées à un pourcentage moyen de prolifération néo-intimale de 6,3% par lésion. La mal-apposition immédiatement après angioplastie puis à 3 mois concernait respectivement 8,3% et 15% des mailles par patient. La malapposition acquise était de 21%. Le recours à l'OFDI a révélé une anomalie justifiant un traitement complémentaire dans 31% des cas alors que le résultat angiographique final était considéré optimal dans 83% des cas. La malapposition acquise ainsi que les mailles non recouvertes ne dépendaient pas de la technique utilisée. Le diamètre distal du vaisseau en aval du stent était augmenté de manière significative à 3 mois. Aucune complication n'a été retrouvée à la suite de l'utilisation systématique de l'OFDI. La revascularisation des CTO a entrainé une amélioration de l'angor à un an.

Conclusion : L'étude PERFE-CTO montre que les CTO sont associés à un remodelage histologique complexe qui semble affecter à court-terme la cicatrisation après angioplastie par une grande incidence de mal-apposition notamment acquise et un retard d'endothelialisation entrainant un défaut de recouvrement néo-intimal. De manière surprenante ces anomalies n'ont pas de lien direct avec les techniques utilisées parfois agressives lors de la désobstruction de l'artère. Ainsi afin d'améliorer les procédures de désobstruction des CTO, le recours systématique de l'imagerie endo-coronaire pourrait être envisagé au vu de l'incidence élevée des anomalies mécaniques non visualisées à l'angiographie.

Mots clés : CTO, OCT, OFDI, malapposition acquise, ré-endothelialisation, mailles non recouvertes

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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