

Does optical coherence tomography optimize results of stenting? Rationale and study design

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Background To date, no randomized study has investigated the value of optical coherence tomography (OCT) in optimizing the results of coronary angioplasty for non-ST-segment elevation acute coronary syndromes.

Methods DOCTORS is a randomized, prospective, multicenter, open-label clinical trial to evaluate the utility of OCT to optimize results of angioplasty of a lesion responsible for non-ST-elevation acute coronary syndromes. Patients (n = 250) will be randomized to undergo OCT-guided angioplasty (use of OCT to optimize procedural result, including change to strategy with the possibility of additional interventions) or angioplasty under fluoroscopy alone.

The primary end point is the functional result of the angioplasty procedure as assessed by fractional flow reserve (FFR) measured at the end of the procedure. Secondary end points include safety of OCT in the context of angioplasty for ACS, percentage of patients in whom OCT reveals suboptimal result of stenting, percentage of patients in whom a change in procedural strategy is decided based on OCT data, correlation between quantitative measures by OCT and FFR, determination of a threshold for quantitative OCT measure that best predicts FFR ≥ 0.90 , and identification of OCT variables that predict postprocedure FFR. Adverse cardiac events (death, recurrent myocardial infarction, stent thrombosis, and repeat target lesion revascularization) at 6 months will be recorded.

Conclusion The DOCTORS randomized trial (ClinicalTrials.gov NCT01743274) is designed to investigate whether use of OCT yields useful additional information beyond that obtained by angiography alone and, if so, whether this information changes physician strategy and impacts on the functional result of angioplasty as assessed by FFR. (Am Heart J 2014;168:175-181.e2.)

Background

Optical coherence tomography (OCT) is a recent imaging modality that yields cross-sectional images with a spatial resolution 10 times greater than that of intravascular ultrasound (IVUS). Optical coherence tomography uses a near-infrared light source to obtain intracoronary images.

This technique is increasingly used to evaluate vulnerable atherosclerotic plaques and assess immediate and long-term results of stenting.¹ Indeed, the utility of OCT has been most extensively studied in the setting of stent

implantation, to assess postprocedural results with a view to further optimizing outcomes.²⁻⁶ Optical coherence tomography may have potential advantages as compared to angiography or IVUS for the analysis of lesion characteristics. However, the real clinical impact of various OCT-defined abnormalities in these and other lesion features remains unknown.⁷ A recent observational study suggested that the use of OCT could improve the outcome of patients undergoing percutaneous coronary intervention (PCI).⁸ Nonetheless, it remains to be investigated whether the use of additional interventions will translate into a benefit in clinical terms or, on the contrary, be deleterious.

To date, no randomized study has investigated the value of OCT in optimizing the results of angioplasty, specifically in the context of non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS). The use of OCT in the setting of acute coronary syndromes (ACS) may present several additional advantages, by rendering visible certain features that characterize unstable lesions, but which often cannot be seen by angiography alone.⁹

In this context, the DOCTORS study aims to evaluate whether OCT-guided angioplasty will provide useful clinical information beyond that obtained by angiography, whether this information will subsequently modify physician behavior and treatment choices, and impact on the

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functional result of angioplasty as assessed by fractional flow reserve (FFR) measured after stent implantation of a lesion responsible for NSTEMI-ACS.

Study design

The DOCTORS study is a randomized, prospective, multicenter, open-label clinical trial involving 7 university teaching hospitals and general (nonacademic) hospitals in France. This study was approved by the Institutional Review Board of the University Hospital of Besancon, France. The study is registered on ClinicalTrials.gov under the identifier NCT01743274. This study is funded by the French government's national hospital research program (Programme Hospitalier de Recherche Clinique). The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Study end points

Optical coherence tomography analysis will be performed per lesion.

Primary end point

The primary end point of the study is the functional result of the angioplasty procedure as assessed by FFR measured at the end of the procedure (the average of 3 consecutive measures will be recorded and compared between groups).

Safety end points

Safety of OCT in the context of angioplasty for ACS will be assessed by the following criteria:

- Procedural complications (no reflow, coronary perforation, occlusive dissection, spasm, stent occlusion, PCI-related myocardial infarction [MI] as assessed by peak troponin at 24 hours postprocedure, change in creatinine clearance at 24 hours vs baseline);
- Duration of the procedure (in minutes);
- Fluoroscopy time (in minutes); and
- Quantity of contrast medium used (in milliliters).

Secondary "technical" end points

1. To estimate the percentage of patients in whom OCT reveals a suboptimal result of angioplasty, as assessed by the presence of any 1 or more of the following criteria:

- Incomplete coverage of the lesion by the stent,
- Residual stenosis upstream or downstream from the stent,
- Edge dissection,
- Presence of thrombus,
- Tissue protrusion through the stent struts, and
- Stent malapposition.

2. To estimate the percentage of patients in whom a change in procedural strategy (viz, a change in any 1 or

more of the following parameters) is decided based on the information obtained from OCT images:

- Diameter and length of implanted stents,
- Supplementary balloon inflations,
- Implantation of supplementary stent(s),
- Use of glycoprotein (GP) IIb/IIIa inhibitors,
- Use of thrombo-aspiration, and
- Use of rotational atherectomy.

3. To determine a threshold value for quantitative OCT measure (ie, minimal lumen diameter and minimal lumen area) that best predicts an FFR value ≥ 0.90 .

4. To identify quantitative OCT variables (ie, minimal lumen diameter and minimal lumen area) that predict FFR as measured at the end of the initial angioplasty procedure.

5. Comparison between online and offline analyses of OCT data.

Six-month clinical follow-up

Adverse cardiac events at 6 months will be recorded, through telephone contact with the patient, general practitioner, or cardiologist. *Adverse events* are defined as the occurrence of any 1 or more of the following: death, recurrent MI, stent thrombosis, and/or repeat revascularization of the target lesion.

Patient population

The inclusion and exclusion criteria for the study are detailed in the [Table](#). Patients will be recruited from among all patients scheduled to undergo PCI at any of the participating centers for an infarct-related artery presenting a single lesion without diffuse disease on the culprit artery. Baseline demographic and clinical data will be recorded, including age; sex; smoking status; hypertension; hypercholesterolemia; diabetes; obesity (defined as a body mass index >30 kg/m²); family history of cardiovascular disease; prior history of infarction, stroke, peripheral arterial disease, heart failure, chronic renal failure, angioplasty, or coronary artery bypass graft surgery; indication for coronary angiography; and extent of disease. Medication administered during the procedure and in-hospital will also be recorded.

Randomization

All patients scheduled to undergo coronary angiography for ACS without persistent ST-segment elevation and presenting an indication for coronary revascularization by angioplasty will be considered eligible. Randomization will be performed after initial coronary angiography, once the operator has identified the lesion responsible for the ACS, and after verification of the inclusion and exclusion criteria and after informed consent has been obtained before catheterization. Randomization will be performed using consecutive sealed opaque envelopes containing the treatment arm allocated to the patient.

Table. Inclusion/exclusion criteria for the DOCTORS study**Inclusion criteria**

Patients aged 18-80 y inclusive, admitted for ACS with the following symptoms:

- Clinical signs of ischemia (chest pain) at rest lasting for at least 10 min in the previous 72 h;
- AND at least 1 of the following 2 criteria:

New ST-segment depression ≥ 1 mm or transitory ST-segment elevation (<30 min) (≥ 1 mm) on at least

2 contiguous leads of the electrocardiogram; OR

- Elevation (>upper limit of normal) of cardiac enzymes (creatinine kinase-MB, troponin I or T)

AND presenting an indication for coronary angioplasty with stent implantation of the target lesion (single lesion on the culprit artery without diffuse disease on the same vessel) considered to be responsible for the ACS.

AND written informed consent.

Exclusion criteria

Potential subjects who meet any of the following criteria will be excluded from the study:

- Left main stem disease;
- In-stent restenosis;
- Presence of coronary artery bypass grafts, cardiogenic shock, or severe hemodynamic instability;
- Severely calcified or tortuous arteries;
- Persistent ST-segment elevation;
- One or more other lesions considered angiographically significant, or nonsignificant diffuse disease, located on the target vessel;
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min);
- Bacteremia or septicemia;
- Severe coagulation disorders;
- Pregnancy;
- Patients who refuse to sign the informed consent form.

The envelope numbers will be recorded in the patient's file at randomization to minimize potential bias. Randomization will be stratified by center.

Angioplasty procedure

Percutaneous coronary angioplasty of the lesion responsible for the ACS symptoms will be performed via the femoral or right radial approach according to current guidelines,^{10,11} with implantation of one (or more) drug-eluting or bare-metal stents, at the operator's discretion. Patients will be pretreated with aspirin and clopidogrel (loading dose of 600 mg) or other P2Y₁₂ receptor inhibitor, according to current guidelines. The choice of anticoagulant during angioplasty (unfractionated heparin, low-molecular-weight heparin, bivalirudin) as well as the option to use GP IIb/IIIa inhibitors will be at the operator's discretion. An association of aspirin and clopidogrel (or other P2Y₁₂ inhibitor) will be maintained for 1 year after the procedure.

Before angioplasty, an intracoronary bolus of 200 mg isosorbide dinitrate will be administered to prevent coronary spasm. The lesion responsible for the symptoms will be visualized in 2 orthogonal incidences and placed

in the center of the fluoroscopy screen. The recording of angiosequences will begin with a view of the angioplasty catheter filled with contrast medium for the purposes of quantitative analysis.

The randomization procedure will randomly allocate patients to 1 of 2 groups:

In the first group ("OCT group"), OCT will be performed to optimize the results of angioplasty. The procedure will be performed according to usual practice, with or without predilation before implantation of 1 or more stents (drug eluting or bare metal). In this group, OCT will be performed after initial coronary angiography and at the end of the angioplasty procedure. Several OCT runs can be performed, as required, during the procedure. The operator will have the possibility to change procedural strategy according to the data immediately available on the OCT images, with the possibility of additional interventions. In particular, the operator will be required to evaluate the following parameters, based on the OCT images acquired:

Before angioplasty: quantitative measure of the reference diameter and reference area of the vessel and the length of the lesion; presence of thrombus (or not) and, if so, extent of thrombus; presence of calcification (or not) and, if so, extent of calcification.

After stent implantation: quantitative measure of minimal lumen diameter and minimal lumen area, reference lumen diameter and reference lumen area, minimal stent area, presence of thrombus, presence of edge dissection above or below the stent, protrusion of tissue through the stent struts, optimal lesion coverage, malapposition of the stent struts with the vessel wall, suboptimal stent deployment.

In the OCT group, the guidelines for procedural strategy incorporating online OCT information are as follows:

1. The length and diameter of the stent to be implanted are to be chosen based on the quantitative measures of reference vessel diameter and lesion length by OCT.
2. Additional balloon inflations should be performed in case of stent malapposition or underexpansion. Stent underexpansion is deemed to be present when the ratio of minimal stent area to reference lumen area is $\leq 80\%$.
3. Additional stent implantation(s) should be performed to rectify incomplete lesion coverage (including edge dissection).
4. Use of GP IIb/IIIa inhibitors and/or thromboaspiration should be systematically considered in case of presence of thrombus.
5. Rotational atherectomy should be considered in case of circumferential calcifications.

The operator should take these parameters into account in deciding on subsequent strategy for the rest of the procedure, with a view to optimizing the final angiographic result.

In the second group (“Control Group”), the angioplasty procedure will be guided by traditional fluoroscopy alone, performed before and after stent implantation.

In both groups, FFR will be measured at the end of the procedure, once the operator considers the result of the angioplasty to be optimal. The average of 3 consecutive FFR measures will be recorded. The procedure is then considered to be finished, and no further interventions will be undertaken, regardless of the FFR value obtained at this final measure.

Fractional flow reserve measurement

Fractional flow reserve will be measured using a pressure wire (St Jude Medical, Uppsala, Sweden) equipped with a light source located 30 mm from the extremity of the catheter. The wire is introduced above the lesion responsible for the ACS symptoms, and the FFR is calculated as the ratio between average distal pressure and the average aortic pressure recorded during maximal hyperemia induced by injection of an intracoronary bolus of 150 μ g of adenosine, followed by a flush of isotonic saline of 10 mL.

Optical coherence tomography image acquisition and analysis

Optical coherence tomography images will be acquired using the FD-OCT C7XR system (Lightlab Imaging Incorporated, Westford, MA) and 6F guide catheter compatible Dragonfly Duo catheter (St Jude Medical). The catheter is introduced into the coronary artery via a standard 0.014” angioplasty wire, after prior injection of an intracoronary bolus of nitroglycerin. To adequately remove all blood from the imaging site, nonocclusive flushing will be performed using continuously injected contrast medium via an automated power injector, and the OCT catheter will be pulled back at a speed of 20 mm/s, which should guarantee sufficient time to acquire images of a 50-mm-long segment. Imaging will be terminated prematurely in case of patient intolerance, coronary spasm, arrhythmia, or hemodynamic instability. Optical coherence tomography images will be analyzed online and offline using Lightlab software. All OCT images will be centrally analyzed in the coordinating center (University Hospital of Besancon) by 2 independent operators. These operators will be blinded to the angiographic findings, procedural strategy, and final FFR value. The contours of the arterial lumen will be traced using an automatic multipoint detection algorithm, with the possibility of manual correction, to obtain quantitative measures of the different vessel and lesion areas and diameters.

Optical coherence tomography criteria for the definition of the end points were defined according to recent recommendations and established definitions.^{1,12,13}

Data coordination

All data management and analysis will be performed centrally at the Cardiology Department at the coordinating center (University Hospital of Besancon, France), where a dedicated team of data managers will be responsible for data collection and monitoring. Computerized checks will be performed to verify the coherence of the data, and queries will be generated in case of inconsistencies. A formal data monitoring process will be overseen by the Clinical Research Management Department (Délégation à la Recherche Clinique et à l’Innovation) of the coordinating center (University Hospital, Besancon, France), who will be responsible for sending independent monitors to each site regularly to monitor files and check data entry.

This is a physician-initiated, institutionally sponsored study, and therefore, the authors are solely responsible for the design and conduct of this study as well as analysis of the results and drafting of publications.

Statistical analysis

Quantitative variables will be expressed as mean \pm SD for normally distributed variables, and median (interquartiles) for nonnormally distributed variables. Categorical variables will be expressed as number (percentage). Quantitative data will be compared using the Student *t* test or Mann-Whitney *U* test, and qualitative variables, using the χ^2 or Fisher exact test, as appropriate. Event-free survival will be modeled using the Kaplan-Meier method between groups and compared using the log-rank test. *P* < .05 will be considered statistically significant. All analyses will be performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

Based on an average FFR value after stent implantation of 0.92 with a SD of 0.07,¹⁴ under the hypothesis that the use of OCT would improve FFR by 0.03 U, at an α risk of 5% and a β risk of 10%, 115 patients are required in each arm. To account for patients lost to follow-up, technical failures, or images unsuitable for analysis, an additional 10% of subjects will be added, making a total of 250 patients to be included in the study.

Discussion

The randomized DOCTORS trial is designed to investigate whether the use of OCT on top of angiographic guidance will impact on the functional result of angioplasty, as assessed by FFR measured at end of the procedure in patients with NSTEMI-ACS. The limitations of angiographic guidance for coronary procedures are well established, whereas there is conflicting evidence regarding the role of IVUS in improving clinical outcomes when used to guide PCI.^{15–21} Because of its high spatial resolution, OCT may present additional advantages compared to both angiography and IVUS for the analysis of stents and nearby structures, despite the limited penetration of OCT into tissue.^{1–3,12,13}

To date, no randomized clinical trials have been performed to directly compare angiographic plus OCT guidance with angiographic guidance alone for PCI. Prati et al⁸ recently reported data from a large cohort study suggesting that the use of OCT could improve clinical outcomes of patients undergoing PCI. In the OCT group, there was evidence of potentially serious procedural features that were not visible on angiography, leading to additional interventions being performed in 35% of patients. A significant reduction in the primary endpoint of cardiac death or myocardial infarction was observed in patients undergoing OCT-guided PCI as compared to those treated with angiographic guidance alone. In addition, data regarding the safety and feasibility of OCT-guided PCI in this setting were reassuring.

Interestingly, the prevalence of ST-segment elevation MI and NSTEMI-ACS was 25.7% and 33.4%, respectively, in the OCT group of the CLI-OPCI study.⁸ The use of OCT in the setting of ACS may present several additional advantages, by rendering visible certain features that characterize unstable lesions, but which often cannot be seen by angiography alone.⁹ For example, the discovery on OCT images of a thrombus not visible by angiography alone may lead the physician to change the pharmacological environment of the procedure. Similarly, an OCT run performed poststent implantation could show a lesion not completely covered by the stent, thus leading to the implantation of 1 or more additional stents, or OCT could reveal substantial protrusion of tissue or thrombus through the stent struts. The real prognostic value of such findings, how they should be managed, and whether this will change the patient's prognosis remain to be established. In the DOCTORS study, we will perform an OCT run before angioplasty as well as after stent implantation, thus making it possible to anticipate potential complications but also to fine tune the procedure to optimize the final result. Therefore, it is clear that the additional information yielded by OCT imaging could have important implications for management and outcomes.

In designing this study, we sought to define relevant variables and cut-off values for quantitative OCT measurements justifying additional intervention, but data on the natural history of OCT-defined adverse features are sparse.⁷ We took a pragmatic approach, choosing OCT variables that are easy to identify and measure, to guarantee that OCT guidance could be easily implemented in routine clinical practice, if shown to be advantageous. In this context, most of the definitions of variables and features are based on available expert consensus documents.^{1,12,13} Nonetheless, the 80% threshold chosen to define optimal stent deployment in this study remains open to controversy. In the MUSIC study, optimal stent deployment was defined as in-stent minimal lumen area $\geq 90\%$ of the average reference lumen area, plus symmetrical expansion and complete

apposition of the stent over its entire length along the vessel wall.²² These criteria, or variations thereof, have been applied in a number of studies evaluating the utility of IVUS guidance for stent implantation, with conflicting results.^{15,16,22-24} Meta-analysis of randomized trials of IVUS guidance for stent implantation from the pre-drug-eluting stent era reported an overall benefit in terms of acute procedural results, with a corresponding reduction in angiographic restenosis, repeat revascularization, and major adverse events, albeit without a benefit of death and MI.²⁵ Interestingly, it was reported that all 3 MUSIC criteria for optimal stent deployment were met in 56.1% to 64% of patients, indicating that these criteria are perhaps somewhat stringent.^{15,23} Despite using the MUSIC criteria, these studies did not report better outcomes than other investigations with more inclusive criteria for stent deployment. In our experience from the multicenter randomized RESIST study,¹⁶ using a threshold of 0.8 for optimal stent expansion (ie, minimal stent area $>80\%$ of the average of proximal and distal reference lumen areas) makes it possible to achieve the criteria in a larger proportion of patients (80%) with similar results. For this reason, we chose to adopt this 80% threshold in the DOCTORS study.

Regarding the choice of FFR as the primary end point to assess the functional result of angioplasty with or without OCT, it has been established that FFR is useful in several clinical settings, including stable coronary disease and ACS.²⁶⁻²⁹ Fractional flow reserve has become an indispensable tool to guide revascularization³⁰ and has also been shown useful for the evaluation of the final result of angioplasty with stent implantation.^{14,31,32}

In the DOCTORS study, lesion severity before angioplasty will not be evaluated using FFR because this would likely influence physician strategy and induce a bias that would preclude identification of the contribution of OCT imaging alone to the change in procedural strategy. Our inclusion criteria are in line with current guidelines for the management of NSTEMI-ACS, namely, early revascularization of the culprit lesion.¹⁰ Conversely, FFR will be used at the end of the procedure to evaluate the functional result of angioplasty with stent implantation. Indeed, FFR measured after stent implantation has been shown to be significantly correlated with major adverse events, repeat target lesion revascularization, and a combined end point of death/MI at 6 months.¹⁴ This study by Pijls et al¹⁴ was performed in the bare-metal stent era, with the major driver for events being repeat revascularization. In today's context, we cannot exclude the possibility that the greater use of drug-eluting stents may reduce the rate of adverse events through a reduction in restenosis. Fractional flow reserve in this situation can nonetheless be considered as a surrogate end point for clinical criteria. It has been reported that, in patients with a poststent FFR of ≥ 0.90 , event rates were between 4.9% and 6.2%. Conversely, patients with

poststent FFR <0.90 had an event rate of 20.3% at 6 months.¹⁴ Based on these findings, we chose a cut-off of ≥ 0.90 for our secondary objective of identifying OCT factors predicting adequate outcome.

This threshold seems to be clinically important because patients with a value below this level have a 3-fold increase in the risk of events (20.3% in patients with poststent FFR 0.80-0.90). Based on these data, the number needed to treat (NNT) to avoid 1 event with the use of OCT is 7 patients (6% event rate in the OCT arm vs 20% event in the non-OCT arm, relative risk 0.32 [95% CI 0.15-0.68], relative risk reduction 68% [95% CI 85%; 31.8%]). To outweigh the additional complexity and cost of OCT procedure, the potential gain (mirrored by the NNT) must be considerable for the routine use of this procedure to be justified. Accordingly, an NNT of 7, in our view, satisfies these criteria.

Study limitations

The foremost limitation of this study is its open-label nature. We cannot exclude the possibility that the operator's choice of strategy will be modified by the simple fact of knowing the arm of treatment to which the patient has been allocated. However, to minimize the potential for any bias, the study protocol has been designed to orient physician strategy as much as possible based on objective criteria recommended in consensus documents.^{1,12,13} Secondly, although we hypothesize that OCT-guided angioplasty will improve outcome, we cannot exclude the possibility that any additional interventions may also aggravate the situation and be detrimental to final procedural outcome. Indeed, increased use of stent implantations and a greater volume of contrast medium for repeated fluoroscopy images could potentially translate into greater troponin release post-procedure and/or more deterioration of renal function (as assessed by creatinine). Finally, this study is not primarily designed to address the impact of OCT guidance on clinical outcomes or to identify the individual contribution of each OCT finding to any overall impact that may be observed on prognosis. Indeed, we cannot exclude that the measure of FFR alone may not fully reflect the extent of any impact of OCT on outcome.

Conclusion

Despite the widespread use of OCT, randomized clinical trials assessing its impact on procedural or cardiovascular outcomes have never been performed. The DOCTORS study is a randomized, prospective, multicenter, open-label clinical trial aiming to evaluate whether OCT guidance during angioplasty with stent implantation will provide useful information beyond that obtained by angiography alone and whether this information will impact on the functional result of angioplasty,

as assessed by FFR measured after stent implantation in patients with NSTEMI-ACS.

References

1. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012;59:1058-72.
2. Habara M, Nasu K, Terashima M, et al. Impact of frequency-domain optical coherence tomography guidance for optimal coronary stent implantation in comparison with intravascular ultrasound guidance. *Circ Cardiovasc Interv* 2012;5:193-201.
3. Imola F, Mallus MT, Ramazzotti V, et al. Safety and feasibility of frequency domain optical coherence tomography to guide decision making in percutaneous coronary intervention. *EuroIntervention* 2010;6:575-81.
4. Templin C, Meyer M, Muller MF, et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J* 2010;31:1792-801.
5. Gonzalo N, Garcia-Garcia HM, Serruys PW, et al. Reproducibility of quantitative optical coherence tomography for stent analysis. *EuroIntervention* 2009;5:224-32.
6. Terashima M, Rathore S, Suzuki Y, et al. Accuracy and reproducibility of stent-strut thickness determined by optical coherence tomography. *J Invasive Cardiol* 2009;21:602-5.
7. Raber L, Radu MD. Optimising cardiovascular outcomes using optical coherence tomography-guided percutaneous coronary interventions. *EuroIntervention* 2012;8:765-71.
8. Prati F, Di Vito L, Biondi-Zoccai G, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention* 2012;8:823-9.
9. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial thrombus by optical coherence tomography. *Am J Cardiol* 2006;97:1713-7.
10. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
11. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J* 2010;31:2501-55.
12. Prati F, Guagliumi G, Mintz GS, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur Heart J* 2012;33:2513-20.
13. Prati F, Regar E, Mintz GS, et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J* 2010;31:401-15.
14. Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation* 2002;105:2950-4.

15. Mudra H, di Mario C, de Jaegere P, et al. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). *Circulation* 2001;104:1343-9.
16. Schiele F, Meneveau N, Vuilleminot A, et al. Impact of intravascular ultrasound guidance in stent deployment on 6-month restenosis rate: a multicenter, randomized study comparing two strategies—with and without intravascular ultrasound guidance. RESIST Study Group. *REStenosis after Icus guided STenting*. *J Am Coll Cardiol* 1998;32:320-8.
17. Biondi-Zoccai G, Sheiban I, Romagnoli E, et al. Is intravascular ultrasound beneficial for percutaneous coronary intervention of bifurcation lesions? Evidence from a 4,314-patient registry. *Clin Res Cardiol* 2011;100:1021-8.
18. Casella G, Klaus V, Ottani F, et al. Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: a meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. *Catheter Cardiovasc Interv* 2003;59:314-21.
19. Maluenda G, Lemesle G, Ben-Dor I, et al. Impact of intravascular ultrasound guidance in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2010;75:86-92.
20. Park SJ, Kim YH, Park DW, et al. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv* 2009;2:167-77.
21. Roy P, Steinberg DH, Sushinsky SJ, et al. The potential clinical utility of intravascular ultrasound guidance in patients undergoing percutaneous coronary intervention with drug-eluting stents. *Eur Heart J* 2008;29:1851-7.
22. de Jaegere P, Mudra H, Figulla H, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J* 1998;19:1214-23.
23. Gaster AL, Slothuus Skjoldborg U, Larsen J, et al. Continued improvement of clinical outcome and cost effectiveness following intravascular ultrasound guided PCI: insights from a prospective, randomised study. *Heart* 2003;89:1043-9.
24. Oemrawsingh PV, Mintz GS, Schlij MJ, et al. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses: final results of a randomized comparison with angiographic guidance (TULIP Study). *Circulation* 2003;107:62-7.
25. Parise H, Maehara A, Stone GW, et al. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. *Am J Cardiol* 2011;107:374-82.
26. Sels JW, Tonino PA, Siebert U, et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv* 2011;4:1183-9.
27. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
28. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;103:2928-34.
29. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;334:1703-8.
30. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
31. Fearon WF, Luna J, Samady H, et al. Fractional flow reserve compared with intravascular ultrasound guidance for optimizing stent deployment. *Circulation* 2001;104:1917-22.
32. Hanekamp CE, Koolen JJ, Pijls NH, et al. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment. *Circulation* 1999;99:1015-21.

Appendix. Definitions of end points

The following definitions of variables and features are based on available expert consensus documents.^{1,12-13}

For OCT guidance during angioplasty

Calcifications within plaques are identified by the presence of well-delineated, low back-scattering heterogeneous regions.

Thrombus

A thrombus is identified as an intraluminal mass, with no direct continuity with the surface of the vessel wall or as a highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing.

Thrombus appears as a mass attached to luminal surface or floating within the lumen (evidence level: high). When imaging without pullback, some thrombi may be seen to be moving in real-time. Optical coherence tomography is capable of discriminating 2 types of thrombus: red (red blood cell-rich) thrombus, which is highly backscattering and has a high attenuation (resembles blood), and white (platelet-rich) thrombus, which is less backscattering, is homogeneous, and has low attenuation.

Extent and area of thrombus are measured, and the ratio of thrombus to lumen area is calculated.

Plaque erosion and rupture

Erosions may be composed of OCT evidence of thrombus, an irregular luminal surface, and no evidence of cap rupture evaluated in multiple adjacent frames.

Acute plaque ulceration or rupture can be detected by OCT as a ruptured fibrous cap that connects the lumen with the lipid pool. These ulcerated or ruptured plaques may occur with or without a superimposed thrombus.

Dissection

Because of the similarity of OCT and IVUS appearance of dissections, definitions are adopted from the Consensus Document for IVUS of the American College of Cardiology.³³ For completeness, these definitions are presented below:

The classification of dissections into 5 categories is recommended:

- Intimal: Limited to the intima or atheroma and not extending to the media.
- Medial: Extending into the media.
- Adventitial: Extending through the EEM.
- Intramural hematoma: An accumulation of [blood or] flushing media within the medial space, displacing the internal elastic membrane inward and EEM outward. Entry and/or exit points may or may not be observed.

- Intrastent: Separation of intima or neointimal hyperplasia from stent struts.

The severity of a dissection can be quantified according to (1) depth into plaque, (2) circumferential extent (in degrees of arc) using a protractor centered on the lumen, (3) length using motorized transducer pullback, (4) size of residual lumen (CSA), and (5) CSA of the luminal dissection. Additional descriptors of a dissection may include the presence of a false lumen, the identification of mobile flap(s), the presence of calcium at the dissection border, and dissections in close proximity to stent edges.

Postangioplasty OCT

Residual or edge dissection

Dissections are frequent at the stent edges and are defined by their longitudinal extension (mm), circumferential extension (degrees or quadrants), and width.

Thrombus

As above.

Stent criteria

Prolapse. Prolapse is defined as the projection of tissue into the lumen between stent struts after implantation.

Malapposition. Malapposition is present when the axial distance between the strut's surface to the luminal surface is greater than the strut thickness (including polymer, if present).

Underexpansion. Underexpansion is deemed to be present when the ratio of in-stent MLA to average reference MLA is <80%.

Incomplete lesion coverage

Persistent lesion proximal or distal to stent edges, meeting the definition of a stenosis.

Instructions for operators using OCT

In the OCT arm of the study, OCT runs will be performed before coronary angiography and at the end of the angioplasty procedure, with additional runs allowed as necessary during the procedure. The operator should guide the procedure using the OCT images, taking into account the following elements in particular:

- Before angioplasty: Quantitative measures of the reference vessel diameter and lesion length to guide choice of stent size and length, presence and extent of thrombus, and presence and extent of calcifications.
- After stent implantation: Quantitative measure of the in-stent MLA and reference MLA, presence of thrombus, presence of edge dissection above or below the stent, tissue prolapse, optimal lesion

coverage by the stent, stent malapposition, and suboptimal stent deployment.

The choice of the stent size and length should be based on the quantitative measures of average reference vessel diameter and lesion length as evaluated by OCT. The evaluation of stent deployment should be based on the quantitative measure of in-stent MLA and reference MLA as defined above.

In the OCT group, the guidelines for procedural strategy incorporating OCT information are as follows:

1. The length and diameter of the stent to be implanted are to be chosen based on the quantitative measures of reference vessel diameter and lesion length by OCT.
2. Additional balloon inflations should be performed in case of stent malapposition or underexpansion. Evaluation of stent deployment must be performed based on quantitative measurement of the minimal lumen area and reference lumen area. Stent underexpansion is deemed to be present when the ratio of in-stent minimal lumen area to reference lumen area is $\leq 80\%$.
3. Additional stent implantation(s) should be performed to rectify incomplete lesion coverage (including edge dissection).
4. Use of GP IIb/IIIa inhibitors and/or thromboaspiration should be systematically considered in case of presence of thrombus.
5. Rotational atherectomy should be considered in case of circumferential calcifications.

Safety

The use of OCT to optimize the results of stenting implies repeated contrast injections, and this may significantly increase the total amount of procedural contrast medium and/or increase the total duration of the procedure, leading to an increase in the overall amount of radiation received by the patient.

Quantitative measures

As OCT depicts with high accuracy the interface between lumen and plaque, the definitions of "lumen," "lesion stenosis," and "reference segment" are consistent with those currently applied for IVUS.

- Stenosis. A stenosis is a lesion that compromises the lumen by at least 50% by cross-sectional area (CSA) compared with a predefined reference segment lumen.
 - Luminal area stenosis. The relative decrease in luminal area of the target lesion, in percent, when compared with a reference lumen area in the same vessel segment. The lumen area relative to the reference lumen area is analogous to the angiographic definition of diameter stenosis.
 - Minimal lumen area (MLA). Minimal lumen area along the length of the target lesion.
 - Maximum lumen diameter. The largest lumen diameter from one intimal leading edge to another along any line passing through the center of the lumen.
 - Minimum lumen diameter. The smallest lumen diameter from one intimal leading edge to another along any line passing through the center of the lumen.
 - Length of measurements. Lengths can be measured by the duration of the pullback and the pullback speed of the imaging fiber.
 - Proximal and distal reference lumen area. The site with the largest lumen either proximal or distal to a stenosis, but within the same segment (usually within 10 mm of the stenosis with no major intervening branches).
- At the end of the procedure, the following variables will be recorded:
- Lesion length
 - MLD
 - Reference diameter
 - % stenosis
 - Duration of the procedure
 - Total fluoroscopy time
 - Amount of radiation received
 - Total volume of contrast medium
 - Average of 3 consecutive measures of FFR.
- Creatinine and troponin at 24 hours will also be recorded. Periprocedural complications will be recorded, as follows:
- No reflow, defined as an acute reduction in coronary flow (TIMI grade 0-1) in the absence of evidence of persistent mechanical obstruction.³⁴
 - Perforation, defined as free perforations (free contrast extravasation into the pericardium) or contained perforations (localized rounded crater of contrast outside the contrast-filled lumen).³⁵
 - Dissection, defined angiographically according to the NHLBI classification.³⁶
 - Coronary spasm
 - PCI-related MI, defined according to the Third Universal Definition of MI.³⁷
 - Stent occlusion
 - Loss of collateral branch
 - Arrhythmia
 - Hemodynamic instability.
- Outcome events at 6 months will be recorded and are defined as the occurrence of any one or more of the following:
- Death
 - Recurrent MI
 - Stent thrombosis, defined according to the ARC definition³⁸
 - Target vessel lesion revascularization
 - Documented myocardial ischemia