shortreport

Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

OPTICAL COHERENCE TOMOGRAPHY TO GUIDE PERCUTANEOUS CORONARY INTERVENTION

n. 9

TECHNOLOGY

Intra-coronary frequency-domain optical coherence tomography (FD-OCT).

COMMERCIAL TECHNOLOGY NAME AND PRODUCER'S/SUPPLIER'S NAME

Two manufacturers presently produce systems performing FD-OCT, i.e. LightLab Imaging, Inc., USA and Terumo Corporation, Japan. Both systems are composed by a console and a catheter that, in case of LightLab Imaging, are called Ilumien™ and Dragonfly™, respectively, and in case of Terumo Corp., are named Lunawave® and FastView®, respectively. In Italy only the system produced by LightLab Imaging, Inc., is used and it is distributed by St. Jude Medical [Flusso Consumi].

USE

☐ therapeutic
■ diagnostic
☐ other: prognostic

CATEGORY

Medical device: invasive, intra-coronary imaging system.

THERAPEUTIC/DIAGNOSTIC FIELD OF APPLICATION

Cardiovascular.

DESTINATION OF USE

FD-OCT is used

1. for qualitative and quantitative evaluation of vascular morphology in the coronary arteries
2. as an adjunct to conventional angiographic procedure to provide an image of vessel lumen and wall structures
3. for the imaging of coronary arteries and for their suitability for patients who are candidates for transluminal interventional procedure.

The present short report assesses the third indication of FD-OCT, i.e. **use in patients needing intravascular imaging to guide percutaneous coronary intervention (PCI)**.

CLINICAL CONDITION

Coronary artery disease (CAD) is the development of stenoses in coronary arteries' walls caused by plaques of atheroma that, in time, leads to partial or complete obstruction of normal blood flow and the development of myocardial ischaemia. Atheroma of the coronary arteries presents in a variety of ways, from stable angina to acute myocardial ischemia (the latter including unstable

THE REPORT

A brief presentation of a technology, providing sufficient information to decide whether to undertake a comprehensive assessment process.

The reported information derives from:

> the consultation of web materials supplied by the producer and of current national and/or regional registries

> the search of secondary studies on HTA databases and of primary studies, indexed on Medline.

! The report does not represent a definitive assessment of the technology.

ISSUED

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angina - UA -, non ST-segment elevation myocardial infarction - NSTEMI -, ST-segment elevation myocardial infarction - STEMI - and sudden death) [Kumar 2009, NICE 2010]. Acute myocardial ischemia is mostly due to plaque rupture and partial or total coronary occlusion [NICE 2010] and is usually managed with revascularization (thrombolytic therapy or primary percutaneous coronary intervention, PCI). In very rare cases acute myocardial ischemia may be due to non-atherosclerotic spontaneous coronary artery dissection (NA-SCAD), a non-traumatic and non-iatrogenic separation of the coronary arterial wall; a definite diagnosis based on coronary angiography is difficult to achieve. In most cases conservative therapy with antithrombotic drugs is the preferred strategy, whilst revascularization is both technically challenging and associated with high failure rates or complications [Douglas 2016]. Symptoms compatible with acute myocardial infarction are indicated as acute coronary syndrome (ACS) and include chest pain or discomfort, dyspnea, nausea and vomiting, and unexplained fatigue [Kumar 2009].

Cardiovascular disease is the most common cause of death in Europe and is responsible for 45% of all deaths, equating to 4 million deaths per year [Townsend 2015]. In Europe, cardiovascular disease leads to a total estimated annual cost of 196 billion euros of which approximately 54% is due to direct health care costs and 24% is due to lost productivity [Ferreira-Gonzalez2014]. Over the total amount of cardiovascular disease, coronary heart disease is the most common single cause of death, resulting in 19% of deaths in men and 20% of deaths in women [Townsend 2015].

In Italy, the prevalence of coronary heart disease resulted of 9 per 1,000 for men of 40-44 years old and 52 per 1,000 for men of 75-79 years old; 4 per 1,000 for women of 40-44 years old and 24 per 1,000 for women of 65-69 years old. The incidence of coronary heart disease estimated by “CUORE” project (population’s age ranged from 35 to 69 years) is 59 per 10,000 person-years in men and 15 per 10,000 person-years in women [Giampaoli 2010]. In Italy, in 2010, standardized mortality rates of coronary heart disease were 44.9/100,000 and 20.4/100,000 for males and females, respectively [RSSP 2012-13].

STANDARD TREATMENT/PRACTICE

Invasive coronary angiography has been regarded as the reference standard for the detection and the assessment of the severity of CAD and for establishing the need for revascularization: in most cases, coronary artery stenoses that on coronary angiography appear as having more than 80% diameter reduction are associated with myocardial ischemia and need to be treated [Kern 2016]. Decisions regarding the need for revascularization - with either percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG) surgery - are based on information obtained from this procedure, as well as other clinical and noninvasive data [Regar 2016].

In addition to coronary angiography, other technologies may be used in specific circumstances.

When the coronary angiogram demonstrates intermediate severity stenoses, i.e. narrowing in the range of 40-80% diameter reduction or appearing hemodynamically “benign” obtaining coronary artery functional data such as coronary artery pressure and flow can facilitate clinical decision making on revascularization [Kern 2016]. Fractional flow reserve (FFR) is the current standard of care for the functional assessment of coronary arteries [ESC/EACTS 2014]. Fractional flow reserve (FFR) measurement is carried out by an intracoronary catheter and consists in the ratio between the pressures proximal to and distal to stenotic lesions at maximal blood flow. FFR normal value is 1 and values <0.80 are associated with ischemia with an accuracy of >90 percent [Kern 2016]. The deferral of revascularization in patients with FFR 0.80 appears instead safe [ESC/EACTS 2014]. FFR is presently recommended to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available; FFR-guided PCI is also recommended in patients with multivessel disease [ESC/EACTS 2014].

Coronary angiography provides information only about the contour of the vascular lumen and in some patients is not able to optimally visualize coronary arteries. An adjunctive invasive imaging tool for visualizing the coronary artery’s wall is coronary intravascular ultrasound (IVUS) [ESC/EACTS 2014]. IVUS allows visualization of the coronary arterial wall by utilizing ultrasound in the 10 to 40 MHz range. IVUS has become useful in delineating plaque morphology and distribution and in providing a rationale to guide PCIs [Regar 2016] and its use is recommended in selected patients to optimize stent implantation and to assess severity and optimize treatment of unprotected left main lesions [ESC/EACTS 2014].

Patients with CAD and needing revascularization may undergo percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG) surgery [NICE 2010, ESC/EACTS 2014]. PCI is a non-surgical technique

used to treat the stenotic coronary arteries with the aim of reducing the coronary stenosis making it no longer haemodynamically significant thus ameliorating both symptom relief and prognosis [ESC/EACTS 2014, NICE 2010]; it involves a team of physicians, nurses, radiologists and cardiac invasive specialist. PCI is performed under coronary angiography guidance and includes both non-stent procedures (such as balloon angioplasty or atherectomy) and stent interventions on one or more coronary arteries [ESC/EACTS 2014, Levin 2016]. Presently, angiography-guided PCI with stenting is the standard of care and balloon angioplasty alone is used only in situations where a stent cannot be delivered to the targeted lesion [Levin 2016]. Stents are delivered and positioned through balloon catheters and, once positioned, they are expanded to restore the vessel patency. There are a variety of types of intracoronary stents that can be characterized according to material composition (bare metal stents, bioabsorbable stents), thickness of struts, possibility of eluting drugs for local delivery (drug-eluting stents), dimensions, shapes and sizes [Levin 2016]. Achieving the full expansion of the arterial lumen (so-called optimal stenting) is the most important factor for a successful stenting [Levin 2016]; in this regard, it should be highlighted that the possibility to over-expanding a bioresorbable stent (BVS) is limited, necessitating more precise device sizing compared with other drug-eluting stents (DES) [Brown 2014]. Optimal stent's expansion is critical for reducing the risk of major stents' complications i.e. restenosis and stent thrombosis [Levin 2016]. Restenosis is a gradual re-narrowing of the stented segment occurring mostly between 3 to 12 months after stent placement and usually presenting as recurrent angina or, sometimes, also as acute myocardial infarction (10% of patients); management consists in repeating PCI. Stent thrombosis consists in a sudden thrombotic occlusion of a previously widely patent stent; it is a very severe complication causing sudden death or large myocardial infarction and requiring repeat revascularization. The cumulative rate of stent thrombosis at 2 years range from 1.5 to 2%; around 10% of cardiac deaths after stent placement are attributable to stent thrombosis, with disease progression being responsible for most of the remainder [Cutlip 2016]. Coronary angiography and PCI-related complications include chest discomfort, bleeding from the catheter's insertion point; most serious procedural risks (coronary artery dissections, vessel occlusion, intracoronary thrombosis, and coronary perforation) and the need for urgent surgery to manage PCI-related complications are uncommon [ESC/EACTS 2014].

TARGET POPULATION

FD-OCT is a high-resolution invasive coronary imaging technique aiming at guiding percutaneous coronary intervention (PCI).

Target population of FD-OCT imaging is represented by patients needing intra-coronary imaging:

1. to guide PCI in case of complex coronary anatomy (i. e. bifurcation, long coronary lesions);
2. to guide PCI when a Bioresorbable Vascular Scaffold (BVS) is used;
3. for suspicion of non-atherosclerotic spontaneous coronary artery dissection (NA-SCAD);
4. to evaluate unclear angiography imaging.

To estimate the number of patients eligible to FD-OCT for indications 1. and 4. the following methods and assumptions were used:

- we estimated the number of PCI performed in Emilia-Romagna region using administrative data from Emilia-Romagna's Hospital Discharge Records Database (SDO) using the following ICD9-CM procedures codes for extracting data: 00.66, 36.01, 36.02, 36.05, 36.06, 36.07;
- we hypothesized that patients with indication 1. and 4. are presently evaluated with IVUS imaging;
- we estimated the number of catheters used for intravascular ultrasound in the Emilia-Romagna region using administrative data from Emilia-Romagna's Medical Device Records Database (DIME 2015) selecting the "C0104010102" codes of classification system for medical devices (CND);
- we assumed that a proportion of patients presently evaluated with IVUS imaging could be shifted to FD-OCT imaging, due to the fact that it has an higher imaging resolution.

In 2015, in the Emilia-Romagna region approximately 11.700 PCIs were carried out and the number of intravascular ultrasound catheters used in 2015 resulted in 444 (3.8% of PCI).

For the year 2015, considering that a proportion of about 40%-50% of patients evaluated by IVUS imaging could be shifted to FD-OCT imaging (expert opinion) the number of patients eligible for FD-OCT for indication 1. and 4. ranged from 178 to 222.

To estimate the number of patients candidate for FD-OCT due to bioresorbable vascular scaffold (BVS) implantation (indication 2.), we used administrative data from Emilia-Romagna's Medical Device Records Database (DIME) selecting the "P0704020104" codes of classification system for medical devices (CND). The

number of BVS used in Emilia-Romagna region in 2015 resulted to be 291. Considering that the number of stent implanted per patient undergoing a PCI is 1.5 [GISE 2015], the number of patients candidate to BVS implantation and eligible to FD-OCT was estimated in 194.
To estimate the number of patients with SCAD (indication 3.), we used administrative data from the Emilia-Romagna's Hospital Discharge Records Database (SDO) and extracted the ICD9-CM Diagnosis Codes "414.12" (identifying "Dissezione dell'arteria coronarica"). The number of patients with SCAD in 2015 resulted to be 8.
To sum up, in 2015, for Emilia-Romagna region the number of patients eligible for FD-OCT imaging for the above reported indications ranged from 380 (3.2% of PCI) to 424 (3.6% of PCI).

TECHNOLOGY DESCRIPTION

Optical coherence tomography (OCT) is an invasive intravascular imaging modality, based on near-infrared light emission (approximately 1,300 nm wavelength): cross-sectional images are generated by measuring the echo time delay and intensity of light that is reflected or back-scattered from internal structures in tissue. The technology requires to clear the artery from blood during image acquisition. OCT improves the localization of the returned signal origin due to the much shorter wavelength of the imaging light when compared with ultrasound (IVUS); hence, OCT offers significantly improved axial resolution (15-20 μm) [Prati 2010].
First generation OCT employed a "time-domain" (TD) technology. However its use was limited by slow data acquisition that required to clear the artery from blood during image acquisition for a relatively long time. Since 2008, a new generation of OCT systems (frequency/Fourier domain, FD-OCT) has been available for clinical use. The main advantages of FD-OCT are the more rapid imaging of the coronary artery that allows a non-occlusive acquisition modality and the improved lateral resolution (axial resolution does not change) [Prati 2012, Regar 2016]. These features, together with reduced motion artifacts and an increased maximum field of view up to 11 mm, have significantly improved both the quality and the ease of use of OCT, even if the imaging depth of the FD-OCT is still approximately 1.0 to 1.5 mm within the coronary artery wall, thus inferior to that of IVUS [Regar 2016]. As FD-OCT is the presently available and used technology, the short report assesses only FD-OCT.
The system includes an OCT imaging system and a single-use catheter. The OCT imaging system provides in vivo images of tissues whilst the single-use catheter consists of two parts: the catheter body and the internal rotating fiber optic imaging core. During image acquisition, the fiber optic core of catheter rotates and is automatically retracted within the catheter to obtain a 360° image of the artery and a continuous pullback image of an arterial segment. The catheter is connected to OCT imaging system through the drive-motor and the optical connector (DOC). All fiber optical and translational pullback is driven by the DOC and occurs inside the catheter [Manuale d'istruzioni Dragonfly™]. Intracoronary OCT is performed by introducing the small (2.7 French) imaging catheter over a guide wire (0.014 inch = 0.36 mm) distally into the coronary artery using standard guide catheters (6F or larger). A motorized pullback is performed to scan the coronary artery segment. The pullback speed is typically 20 mm/sec with a frame rate of 100 frames per second or higher. The blood is temporarily cleared by an injection of radiograph contrast medium during the duration of the FD-OCT pullback (typical flush rate 3.0 ml/s). The time needed to image a 50 mm artery segment is typically three seconds with a total volume of radiograph contrast of 10 to 12 mL, which is comparable to the amount of radiograph contrast needed for a single angiographic run [Regar 2016]. The FDA indications for use report that C7 Dragonfly, Dragonfly DUO, or Dragonfly OPTIS Imaging Catheter are intended for use in vessels 2.0 to 3.5 mm in diameter [FDA 2014].

MAIN EXPECTED BENEFITS

Through an accurate acquisition of intravascular imaging, FD-OCT in addition to coronary angiography is expected to guide PCI in patients with complex and/or unclear lesions to coronary angiography (including patients with suspected SCAD). Through optimization of the coronary angioplasty in terms of stent's type, number, positioning and optimal expansion, FD-OCT is expected to lead to a reduction of both short- and long-term clinical events due to stents's malapposition and/or evolution of CAD.
In order to better assess the role of FD-OCT, an evidence profile of the technology was set up [Ballini 2010].
The evidence profile developed for FD-OCT is described in the following table:

<table>
<tr><th colspan="4">Rationale</th></tr>
<tr><td colspan="4">Through a better visualization of coronary artery walls and atherosclerotic lesions, FD-OCT is expected to guide PCI in patients with complex or unclear lesions by determining the need of the procedure (as for patients with suspected NA-SCAD) and by providing additional information useful for the choice of stent's type and number, for stent's positioning and optimal expansion, eventually leading to a reduction of both short- and long-term clinical events.</td></tr>
<tr><th>Population</th><th colspan="2">Intervention</th><th>Comparator(s)</th></tr>
<tr><td>Patients eligible for invasive coronary imaging to guide PCI, with unclear or complex[1] coronary lesions</td><td colspan="2">FD-OCT in addition to coronary angiography</td><td>• coronary angiography alone
• coronary angiography plus IVUS</td></tr>
<tr><th colspan="4">Domain: procedural outcomes and technical performance</th></tr>
<tr><td colspan="4">Study design: systematic reviews and randomized controlled trials, cohort and case-control studies, cross-sectional studies, prospective case series</td></tr>
<tr><th>Outcome 1</th><th>Outcome 2</th><th>Outcome 3</th><th>Outcome 4</th></tr>
<tr><td>Procedural success</td><td>In vivo intra- and inter-observer reproducibility of measurements</td><td>Procedural and fluoroscopy time</td><td>Diagnostic accuracy in measuring coronary arteries' parameters</td></tr>
<tr><th colspan="4">Domain: safety</th></tr>
<tr><td colspan="4">Study design: systematic reviews, randomized controlled trials (RCTs), cohort and case-control studies, cross-sectional studies, prospective case series, case reports</td></tr>
<tr><th colspan="2">Outcome 1</th><th colspan="2">Outcome 2</th></tr>
<tr><td colspan="2">Procedure-related complications</td><td colspan="2">Adverse events</td></tr>
<tr><th colspan="4">Domain: efficacy</th></tr>
<tr><td colspan="4">Study design: systematic reviews, randomized controlled trials (RCTs)</td></tr>
<tr><th colspan="4">Clinical outcomes</th></tr>
<tr><th>Outcome 1</th><th colspan="2">Outcome 2</th><th>Outcome 3</th></tr>
<tr><td>Incidence of MACE</td><td colspan="2">Incidence of stent restenosis</td><td>Incidence of stent thrombosis</td></tr>
<tr><th colspan="4">Surrogate outcomes</th></tr>
<tr><th colspan="2">Outcome 1</th><th colspan="2">Outcome 2</th></tr>
<tr><td colspan="2">Post-PCI FFR</td><td colspan="2">Stent's uncovered struts</td></tr>
<tr><th colspan="4">Domain: change in management</th></tr>
<tr><td colspan="4">Study design: systematic reviews, RCTs, cohort and case-control studies, cross-sectional studies, case series</td></tr>
<tr><th colspan="2">Outcome 1</th><th colspan="2">Outcome 2</th></tr>
<tr><td colspan="2">Pre-PCI OCT: treatment planning modification</td><td colspan="2">Post-PCI OCT: stent deployment optimization</td></tr>
</table>

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AVAILABLE EVIDENCE

Literature search

The search for primary studies and systematic reviews was carried out in Pubmed using keywords and Mesh descriptors that describes the device (FD-OCT, frequency domain, fourier domain, Optical Coherence Tomography, optis, lunawave, dragonfly, ilumien, fastview) and the condition (coronary artery disease, coronary stenosis, coronary thrombosis) and was restricted to studies on humans in English, French, Spanish and Italian language; no data limits were used. Literature search for HTA reports, horizon scanning and guidelines was performed on Google, HTA Agencies websites, National Guidelines Clearinghouse website. Ongoing trials were searched in the main clinical trial registries: Clinical Trials.gov, ISRCTN, EU Clinical Trials Register; NIH Clinical Research Studies; UK Clinical Trials Gateway: International Clinical Trials Registry Platform (ICTRP). All searches were performed in July 2016 (details on bibliographic search strategy are available upon request).

[1] type B1/B2/C lesions according to American College of Cardiology (ACC) and American Heart Association (AHA) classification.

Studies were assessed for risk of bias with the following checklists: AMSTAR checklist for systematic reviews [Shea 2007], QUADAS-2 checklist for diagnostic cross-sectional studies [Whiting 2011], criteria suggested by the Cochrane Handbook for Randomized controlled trials [Higgins 2009], New Castle-Ottawa checklist for case-control studies and cohort studies [New Castle-Ottawa checklist]; case series were assessed only for consecutiveness in patients' recruitment (prospective enrollment being a pre-requisite for inclusion).Studies were included only if including at least 10 patients.

Number and type of studies

The search of HTA reports retrieved six documents: three medical policies from a U.S. health care insurance company [AETNA 2015, BlueCross BlueShield 2015, Empire BlueCross BlueShield 2016], an horizon scanning report [Agenas 2010], an interventional procedure overview and related guidance [NICE 2014], and a consensus statement of the Society of Cardiovascular Angiography and Interventions [SCAI 2014]. Report by Agenas [Agenas 2010] assessed the use of FD-OCT for the study of vulnerable atherosclerotic plaques and was then excluded. The other five documents were included.
The literature search performed in Pubmed retrieved 1,539 records of which 78 were considered eligible. After full-text assessment, 1 systematic review [D'Ascenzo 2015] and 34 primary studies were finally included.

Secondary literature

D'Ascenzo and colleagues performed a systematic review to evaluate the accuracy of FD-OCT and intravascular ultrasound in identifying functionally significant coronary stenosis according to vessel diameter [D'Ascenzo 2015]. A total of 15 studies (including 2,581 patients) evaluating accuracy of IVUS/OCT in measuring minimal luminal area (MLA) and minimal luminal diameter (MLD) of hemodynamically significant lesions at FFR (i.e. presenting a FFR< 0.80) were included. The methodological quality, assessed by Amstar checklist, was judged as low. Based on their meta-analysis, Authors reported that FD-OCT and IVUS have modest diagnostic accuracy, even with specific cut-offs for different coronary artery diameters. Meta-analysis resulted in the following values:

- MLA measurement with FD-OCT: AUC of 0.80 (95%CI: 0.74-0.86), with a sensitivity of 0.81 (95%CI: 0.74-0.87) and specificity of 0.77 (95%CI: 0.71-0.83); for IVUS-MLA, AUC was 0.78 (95%CI: 0.75-0.81) for all lesions, 0.78 (95%CI: 0.73-0.84) for vessels with a diameter >3 mm, and 0.79 (95%CI: 0.70-0.89) for those with a diameter <3 mm;
- MLD measurement with FD-OCT: AUC of 0.85 (95%CI: 0.79-0.91), sensitivity of 0.74 (95%CI: 0.69-0.78), and specificity of 0.70 (95%CI: 0.68-0.73).

Based on these results, Authors stated that "Based on our meta-analysis of OCT, neither MLA nor MLD has adequate sensitivity or specificity to confidently guide decisions for revascularization".
Insurance companies that assessed FD-OCT decided against procedure reimbursement. Aetna considered FD-OCT experimental and investigational for any indications [AETNA 2015] . BlueCross and BlueShield of Alabama considered "FD-OCT investigational when used as an adjunct to PCI with stenting and in all other situations, including but not limited to, risk stratification of intracoronary atherosclerotic plaques and follow-up evaluation of stenting" [BCBS 2015]. Empire BlueCross BlueShield considered FD-OCT investigational and not medically necessary for all indications including, but not limited to, the assessment, treatment and follow-up of coronary disease [BCBS 2016].
NICE interventional procedure overview and corresponding guidance, assessed efficacy, safety and diagnostic outcomes of FD-OCT [NICE 2014]. Based on data retrieved by the interventional overview, NICE guidance states that "The evidence on the safety of OCT to guide PCI shows no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research".
A Consensus Statement of the Society of Cardiovascular Angiography and Interventions [SCAI 2013] concluded that "The appropriate role for OCT in routine clinical-decision making has not been established. FD-OCT is *probably beneficial* to determine the optimal stent deployment (sizing, apposition, and lack of edge dissection), with improved resolution compared with IVUS; *possibly beneficial* to assess plaque morphology, and *should be discouraged* (no proven value) to determine stenosis functional significance".

Primary studies

We included 34 studies: 3 RCTs, 3 cohort, 6 cross-sectional and 22 case-series studies, including a total of 4,445 patients (median number of patients 39, range 14-984). Twenty-three over 34 studies (67.6%) were industry-funded or reported conflict of interest for at least one of the Authors.

Among the included studies, 22 reported on FD-OCT's technical performance and seven (6 cross-sectional [Belkacemi 2013, Gonzalo 2012, Pyxaras 2013, Reith 2013, Reith 2015a, Zafar 2014b] and one RCT [Meneveau 2016]), enrolling a total of 535 patients (min-max: 27-240) assessed FD-OCT diagnostic accuracy versus FFR. Twenty-three studies (for a total of 2,819 patients, range: 15-984) reported data on safety of FD-OCT. Four studies (3 case-series [Allahwala 2015, Stefano 2013, Wijns 2015] and one RCT [Meneveau 2016]) analysed change in management (CIM) due to pre- or post-PCI FD-OCT findings in 827 patients (range: 19-418). Efficacy of FD-OCT-guided PCI compared with angio-guided-PCI was evaluated in two RCTs including 100 and 240 patients, respectively, followed-up for 6-months [Antonsen 2015, Meneveau 2016].

All the studies included patients candidate to PCI for suspected acute coronary syndrome (ACS) or stable angina not responding to optimal medical treatment. Two studies evaluated FD-OCT use in patients undergoing PCI with bioresorbable vascular scaffold [Allahwala 2015, Okamura 2010] and one [Antonsen 2015] in patients undergoing PCI with biolimus-eluting stent (BES).

Some of the studies assessed outcomes belonging to more than one domain.

Results

TECHNICAL PERFORMANCE

Three out of 34 studies [Antonsen 2015, Habara 2012, Menevau 2016] assessed length of procedure and fluoroscopy time of FD-OCT versus angiography alone [Antonsen 2015, Menevau 2016] or versus IVUS [Habara 2012]. Length of procedure ranged from 31.0 to 36.0 minutes for angiography-guided PCI, from 40.0 to 56.0 minutes for FD-OCT-guided PCI and was 47 minutes for IVUS-guided PCI. Corresponding values for fluoroscopy time ranged from 6.9 to 9.0 minutes (angiography-only PCI), from 9.9 to 20.4 minutes (FD-OCT-guided PCI) and was 24.8 minutes for IVUS-guided PCI.

Sixteen studies involving 2,145 patients reported data on OCT failure (intended as failure to cross lesion or obtain blood clearance, for technical problem, low quality image, patients compliance or problems of safety) [Amabile 2015, Antonsen 2015, Di Giorgio 2013, Fujino 2013, Imola 2010, Imola 2015, Kajander 2015, Kubo 2013, Okamura 2010, Okamura 2011, Paoletti 2016, Soeda 2015, Stefano 2011, Stefano 2013, Taniwaki 2015, Yoon 2012]. Median failure rate was 6.7%, ranging from 0.9% [Imola 2010] to 17.9% [Okamura 2011]. However, as failure was reported differently by study (per patients, per vessel, per pullback or per side branches) data should be read cautiously.

Twelve studies reported data on intra- and inter-observer reproducibility enrolling 1,272 patients (range: 14-786). Five studies evaluated pre-PCI reproducibility [Fedele 2012, Jamil 2013, Kubo 2013, Paoletti 2016, Pyxaras 2013], six studies evaluated post-PCI reproducibility [Abnousi 2013, Antonsen 2015, Gerbaud 2015, Liu 2014, Okamura 2011, Soeda 2015] and 1 study evaluated both [Kajander 2015]. Studies were heterogeneous in terms of variables and measures reported and it was not possible to summarize results.

Pre-PCI intra-observer reproducibility was measured as mean difference on MLA in two studies [Jamil 2013, Pyxaras 2013] reporting values of (0.08±0.15) mm^2 and (0.19±0.57) mm^2, respectively, and as root mean squared deviation on MLA in one study (0.16 mm^2) [Kubo 2013]; pre-PCI inter-observer reproducibility measured as mean difference on MLA and reported by two studies [Kubo 2013, Pyxaras 2013] was 0.01 (±1.96SD: 0.31-0.33) mm^2 and (0.02±0.08) mm^2, respectively. Pre-PCI intra- and inter-observer reproducibility measured as mean difference on MLD reported by one study [Pyxaras 2013] was (0.02±0.02) mm and (0.02±0.08) mm. One study [Paoletti 2016] reported that there was no significant difference in pre-PCI intra-observer reproducibility measured as mean on lumen area (7.63±(2.95) mm^2 vs 7.69 ±(2.98) mm^2, p=0.230). Pre-PCI intra and inter-observer reproducibility measured as mean difference on lumen area reported in one study [Fedele 2012] were 0.003 (95%CI: -0.002 – 0.009) mm^2 and 0.001 (95%CI: -0.012 – 0.009) mm^2. Pre-PCI intra- and inter-observer reproducibility reported in one study [Kajander 2015] and measured as mean absolute difference on lumen area were 0.03 (95%CI: -0.01 – 0.06) mm^2 and 0.13 (95%CI: 0.07 – 0.19) mm^2 while post-PCI intra- and inter-observer reproducibility measured as mean absolute difference on stent area were 0.00 (95%CI: -0.06 – 0.06) mm^2 and 0.13 (95%CI: 0.06 – 0.21) mm^2. One study [Abnousi 2013] reported data stratified for expert and beginner

observer on post-PCI reproducibility measured as mean difference on stent area (intra-: 0.00±0,04 mm^3/mm (expert); 0.04±0,06 mm^3/mm (beginner); inter: 0.09±0,08 mm^3/mm (expert) 0.24±0,26 mm^3/mm (beginner)).
Post-PCI intra-observer reproducibility measured as mean difference on mean stent area, MLA, MSA evaluated were 0.07±0.10 mm^2, 0.04±0.09 mm^2 and 0.04±0.10 mm^2, respectively [Jamil 2013]. Post-PCI intra- and inter-observer reproducibility measured as variance on lumen area reported by one study was 0.0016 mm^2 and 0.0003 mm^2 [Okamura 2011]. Post-PCI intra-observer reproducibility measured as mean difference on stent complete stent apposition (CSA) reported by one study was (0.05±0.26) mm^2 [Gerbaud 2015]. Post-PCI intra- and inter-observer reproducibility measured as mean difference on length stent reported by one study was -0,04 mm and 0,04 mm [Liu 2014]. One study evaluated post-PCI inter-observer reproducibility in terms of K statistics for smooth protrusion (K=0.93), disrupted fibrous tissue protrusion (K=0.93), irregular protrusion (K=0.88), thrombus (K=0.86) [Soeda 2015] and another study for strut coverage (K=0.88 (95% CI, 0.85–0.91; P<0.01)) and strut malapposition (K=0.73 (95% CI: 0.60–0.85; P<0.01)) [Antonsen 2015].
One RCT [Menevau 2016] and 6 cross-sectional studies [Belkacemi 2013, Gonzalo 2012, Pyxaras 2013, Reith 2013, Reith 2015a, Zafar 2014b], including a total of 535 patients (range 27-240), assessed diagnostic accuracy of FD-OCT using functional flow reserve (FFR) as a reference standard. Diagnostic accuracy was assessed in measuring minimal lumen area (MLA), minimal lumen diameter (MLD) and intra-stent percent of area stenosis (AS%); none of the included studies used a pre-specified cut-off values for the investigated parameters but specific cut-off values aimed at optimizing FD-OCT's accuracy (best cut-off).
The cross sectional study were of poor quality: two out of six cross-sectional studies [Belkacemi 2013, Zafar 2014b] were judged at "unclear" risk of bias in patients selection domain, while all studies presents "unclear" risk of bias about index test and reference standard (no pre-specified threshold and blindness). The RCT by Meneveau was of moderate quality (risk of bias was judged as high and unclear for performance and detection bias, respectively). The six cross-sectional studies evaluated FD-OCT parameters measured by OCT against a reference validated value of FFR ≤ 0.8 whilst the RCT by Menevau tested FD-OCT versus a reference value of FFR ≤ 0.9. Best **MLA** cut-off ranges from 1.59 mm^2 [Reith 2013] to 5.44 mm^2 [Menevau 2016]. MLA sensitivity was reported to be in the range of 70-91.3% (best cut-off of 1.62 mm^2 [Zafar 2014b] and >5.44 mm^2 [Menevau 2016], respectively), while specificity fell in the range 60.2-97% (best cut-off >5.44 mm^2 [Menevau 2016] and of 1.62 mm^2 [Zafar 2014b], respectively). Cut-off for best **MLD** ranged from 1.23 mm [Zafar 2014b] to 1.77 mm [Belkacemi 2013]. MLD sensitivity and specificity were in the range 70-87.9% (minimum at best cut-off of 1.23 mm [Zafar 2014b], maximum at best cut off of 1.31 mm [Reith 2013]) and 67-87% (minimum at best cut-off of 1.34 mm [Gonzalo 2012] and maximum at 1.23 mm [Zafar 2014b]), respectively. OCT accuracy in determining **AS%** was reported in 3/6 cross-sectional studies [Reith 2015a, Reith 2013, Gonzalo 2012]. OCT's sensitivity ranged from 70 to 87.9% and specificity from 55 to 72.4%, depending on the best cut-off chosen in the study. The study by Reith [Reith 2015a] specifically aimed at comparing OCT's accuracy in diabetic versus non-diabetic patients. Whilst sensitivity was lower in diabetic patients for both MLA and AS% (sensitivity: 76.6% versus 78.8% and 59.6% versus 78.8%, respectively), OCT's accuracy in measuring MLD resulted always better in diabetic versus non-diabetic patients (sensitivity: 93.6% versus 84.8%, specificity: 66.7% versus 65.6%, respectively).
In summary, data on procedural success, procedural and fluoroscopy time reassure on procedure feasibility and success. Both data on procedure's reproducibility and diagnostic accuracy suffer from heterogeneity in measured parameters and cut-off values leading to a very difficult interpretation of results.

CHANGE IN MANAGEMENT

Change in management (CIM) was assessed in one RCT [Meneveau 2016] and three case-series [Allahwala 2015, Stefano 2013, Wjins 205], for a total of 827 patients. All the four studies assessed CIM due to post-PCI FD-OCT findings whilst 3/4 CIM due to pre-PCI FD-OCT findings.
The studies investigated CIM due to **post-PCI OCT** in terms of post-stent deployment optimization (overdilation, additional stent implantation, scaffold optimization) due to malapposition, under-expansion and edge dissection. In the RCT by Meneveau [Meneveau 2016] including 240 patients, the use of OCT (carried out immediately after stent implantation) led the operator to optimize the procedural strategy in 60/120 patients (50%), compared to 27/120 patients (22.5%) in the angiography-guided group (P<0.0001); this change led to a significantly lower stenosis diameter at the end of PCI (7.0±4.3% versus 8.7±6.3%, p=0.01). The three case-series [Allahwala 2015, Wijns 2015, Stefano 2013], including a total of 587 patients, reported change in management due to post-PCI

OCT in 8/29 (28%) [Allahwala 2015], 106/418 (25%) [Wijns 2015] and 54.8% [Stefano 2013] patients, respectively.
Change in management due to **pre-PCI OCT** was assessed measuring treatment planning modifications (change in stent length, diameter and number) in one RCT [Meneveau 2016] and two case series [Stefano 2013, Wjins 2015]. The study by Menevau reported that no significant difference in procedural strategy between the 2 groups was registered, except for more frequent use of GP IIb/IIIa inhibitors in the OCT-guided group, due to the significantly higher rate of thrombus visualized by OCT. The two case series reported that pre-stent OCT findings led to changes in stent length and/or diameter and in number of implanted stents in 55% (230/418) [Wijns 2015] and 81.8% [Stefano 2013] patients, respectively.
From the available data on CIM, FD-OCT before or after PCI seems to lead to optimization of the procedure itself; however data on improvement of clinical outcomes due to change in clinical strategy are not provided.

SAFETY

Safety of OCT imaging was assessed in 23/34 studies for a total of 2,819 patients. Among the 23 studies reporting on safety, 15 declared that no procedural and peri-procedural complications related to FD-OCT occurred [Allahwala 2015, Amabile 2015, Belkacemi 2013, Cervinka 2014, Fedele 2012, Fujino 2013, Imola 2015, Jamil 2013, Liu 2014, Okamura 2011, Paoletti 2016, Pyxaras 2013, Reith 2013, Reith 2015a, Reith 2015b].
Of the eight remaining studies reporting procedural/peri-procedural complications and including a total of 1,699 patients undergoing FD-OCT, two are RCTs [Habara 2012, Menevau 2016] and six are controlled [van der Sijde 2016, Taniwaki 2015] or uncontrolled [Yoon 2012, Imola 2010, Parodi 2010, Stefano 2013] case series. Controlled studies compared OCT-guided versus IVUS-guided PCI except for the RCT by Meneveau comparing angio- and FD-OCT-guided PCI versus ango-guided PCI alone [Menevau 2015].
Excluding a very small study [Parodi 2010] reporting a procedural complication rate of 26.7% (4/15), procedural complication rate for patients undergoing FD-OCT ranged from 0.6% [van der Sijde 2016] to 11.4% (4/35) [Habara 2012]. Incidence of comparators' adverse events reported by four studies (two RCTs and 2 case-control studies) ranged from 0.5% [van der Sijede 2016] to 28.6% [Habara 2012]. The two RCTs assessing IVUS-guided versus FD-OCT-guided PCI [Habara 2012] and angio- plus FD-OCT-guided PCI versus angio-only guided PCI [Menevau 2016] reported a non-statistically significant difference in complications' incidence between the arms of the study. A large prospective case series study [van der Sijde 2016], enrolling 984 patients and undergoing FD-OCT imaging to guide PCI (1,142 procedures) and controlled with 2,054 patients undergoing 2,476 IVUS procedures reported complications in 7/1,142 (0.6%) and in 12/2,476 (0.5%) patients ($p<0.6$), respectively.
The RCT by Habara [Habara 2012] reported non–Q-wave MI observed for 1 patient in the FD-OCT group and in 4 patients in the IVUS group (all of them were attributed to distal embolus) and Q-wave MI observed in 1 patient in both groups. Additionally, the RCT by Menevau [Menevau 2016] reported a non-statistically significant difference in type 4a myocardial infarction between angio-guided (33%) and angio plus FD-OCT-guided arm (40%) ($p=0.28$); no difference in acute kidney injury rate between the two arms (1.6% for both groups) was reported. Pulmonary edema was reported only by one study [Stefano 2013] at a rate of 0,7%; proportion of transient ST segment (depression/elevation) was reported by two studies with very different rates i.e. in 3/1142 (0.3%) and in 4/15 (27%) patients in van der Sijde [van der Sijde 2016] and in Parodi [Parodi 2016], respectively.
Coronary artery dissection was reported in 2 controlled case series [van der Sijde 2016, Taniwaki 2015] comparing FD-OCT versus IVUS: whilst Taniwaki reported that coronary artery dissection occurred in 1 out of 103 patients undergoing FD-OCT and no cases were registered in those undergoing IVUS, van der Sijede reported coronary artery dissection in 3 out of 2,476 procedures with IVUS and no cases in 1,142 procedures with FD-OCT. Two studies [Parodi 2010, Yoon 2012] reported transient chest pain/discomfort in 2/15 (13%) and 5/47 (10.6%) of patients, respectively.
In summary, incidence and type of procedural adverse events seem to be comparable to those occurring during angio-guided or IVUS plus angio-guided PCI.

EFFICACY

Two RCTs [Antonsen 2015, Menevau 2016] (for a total of 340 patients) assessed clinical efficacy of FD-OCT plus angiography versus angiography alone in guiding PCI.
Studies were of moderate quality: the study by Meneveau [Menevau 2016] was judged at low risk of bias for all domains, except for performance and detection bias (rated as high and unclear, respectively) and the study by

Antonsen [Antonsen 2015] was judged at "unclear" risk of bias only for selection bias (random sequence generation).
The RCT by Antonsen [Antonsen 2015] included 100 patients (mean age around 62 years, around 70% of men, diabetes 10-16% of patients, 56% hypertension, 26% with lesion type classified as "A" according to the AHA/ACC classification, i.e. the lowest level of risk) and assessed the percentage of uncovered struts at 6 months as primary end-point. Also Major Adverse Cardiac Events (MACE) incidence at 6 months was investigated. Patients with left main coronary artery disease, narrowed, calcified or tortuous culprit vessels unsuitable for intravascular imaging, long lesions (>45 mm), bifurcation lesions, reference vessel diameter(s) >3.5 mm were excluded. At 6-month follow-up percentage of uncovered struts (primary end-point) was significantly lower in the OCT-guided group (4.3% [interquartile range -IQR-: 1.2–9.8%] versus 9.0% [IQR: 5.5–14.5%]; P<0.01) and a higher number of patients undergoing OCT-guided PCI had completely covered stents (17.5% versus 2.2%, p=0.02). During the 6-month follow-up only 2/50 (4%) patients from the angio-guided group experienced a MACE whilst no cardiac events were registered in the OCT-guided group.
The study by Meneveau [Meneveau 2016] is a two-arms RCT (OCT-guided versus angio-guided PCI) including 240 patients (age: 60.5±11.4 years, 77.5% men, 18.8% with diabetes mellitus, 63.3% obese, 69.2% with only one vessel disease, 28.3% with lesion type classified as "A"). Patients with left main disease, in-stent restenosis, presence of coronary artery bypass grafts, cardiogenic shock or severe hemodynamic instability, severely calcified or tortuous arteries were excluded. Study compared PCI-guided by both angiography and FD-OCT imaging versus by angiography alone. Study's primary efficacy endpoint was post-PCI fractional flow reserve (FFR) value; also MACEs at 6-month follow-up were investigated but the study was not powered to demonstrate improved long-term clinical outcomes. Results of the study indicated that post-PCI FFR values were slightly better in the OCT-guided group compared to angio-guided group: 0.94±0.04 versus 0.92±0.05 respectively (p=0.005) however the clinical significance of this difference is unclear. No statistically significant difference between groups at 6 months was reported for MACEs (7 versus 4 cases in in the OCT-guided arm and the angio-guided PCI, respectively).
The comparison of presently available data against the evidence profile highlights that RCTs enrolled > 70% of patients having type B1/B2/C lesions (thus comparable to those eligible according to our evidence profile) but were primarily focused on demonstrating FD-OCT's superiority for surrogate outcomes measured at a short follow-up instead of being powered to test superiority in improving the incidence of patient-important clinical outcomes (such as stent restenosis or stent thrombosis) at longer follow-up (12 months or more).

COSTS

The system produced by LightLab Imaging Inc consists of two units: a console for imaging acquisition (Ilumien™), processing and display and a single-use catheter (Dragonfly Imaging Catheter).
FD-OCT imaging system can be acquired in two different ways: by purchasing the console at a price of 150,000.00€+VAT [Agenas 2010] and single-use catheters costing from 1,464€ to 2,415€ (Flusso Consumi 2015); otherwise the console may be rented at a cost of 2,988€+VAT/year and single-use catheters purchased at a cost of 1,200.00€+VAT (the price is established for a volume of 900 catheters over a 3 years period [ESTAV 2014]).

PRESUMED IMPACT

Clinical

To date, the evidence on presumed clinical impact is limited in terms of quality and quantity of available studies: most of the studies are non-randomized and assess surrogate outcomes. Available evidence reports that FD-OCT use to guide PCI does not show any impact on reducing post-PCI incidence of cardiac events. FD-OCT shows a statistically significant effect on surrogate outcomes (uncovered struts and post-PCI FFR) nevertheless the clinical relevance of such an effect is unclear.

Economic

The use of the FD-OCT system to guide PCI leads to an additional cost to angiography-guided PCI due to the cost of the device. As for IVUS and FFR technology, the increase of costs due to FD-OCT technology is presently

not covered by any increase on the diagnosis-related group (DRG) reimbursement related to the coronary angioplasty procedure

Organizational
FD-OCT procedure extends the duration of the angiography-guided PCI procedure from a minimum of 7 to a maximum 20 minutes and fluoroscopy time from a minimum of 3 to a maximum 4.4 minutes.
The use of this technology does not require the employment of extra personnel with respect to habitual angiography procedures. The appropriate use of this technology requires centers specialized in coronary procedures and specifically trained staff (a learning curve for training has to be taken into account).

Ethical-social-legal
Presently no ethical or social issues have been considered relevant.

ONGOING STUDIES

The following registries of ongoing studies were searched (last access: 1 July 2016): Clinical Trials (www.clincaltrial.gov); ISRCTN (http://www.isrctn.com); EU Clinical Trials Register (www.clinicaltrialsregister.eu); NIH Clinical Research Studies (http://clinicalstudies.info.nih.gov/); UK Clinical Trials Gateway (https://www.ukctg.nihr.ac.uk/clinical-trials/search-for-a-clinical-trial) and International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)
Finally, 15 clinical trials – 10 RCTs and 5 non-RCTs - were retrieved.

Randomized controlled Trials (RCT)
Among the 15 eligible studies, 10 are RCTs of which 9 open label and 1 single blind (NCT02683356).
Seven studies are currently ongoing (1 manufacturer-sponsored: NCT02471586) and 2 have been completed (NCT02466282, NCT01873027-OPINION study) but results are not available; for one study (NCT01824030) status is unknown.
Only two studies (NCT01873027; NCT02237456) refers specifically to FD-OCT; all other studies refers generically to OCT, but they probably investigate FD-OCT as it is the newest technology. All the studies assess OCT-guided strategy for stent implantation. Seven compare OCT-guided interventions with coronary angiography alone; 2 (NCT02471586, NCT01873027) compare OCT with IVUS, only 1 with FFR (NCT01824030).
Seven out of ten RCTs assess technical performance and diagnostic accuracy: minimal stent area, rate of struts coverage, minimal luminal area, minimal in-scaffold lumen area, malapposition in the main vessel bifurcation segment facing the side-branch ostium. Three studies assess clinical endpoints, i.e. angina at 13 months follow-up (NCT01824030), Target Vessel Failure at 12 months post-PCI (TVF) (NCT01873027) and Target lesion revascularization at 5 years post-PCI in patients with stent failure (NCT02337348).

Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
NCT02466282	Patients with ischemic heart disease eligible for PCI; significant coronary de novo lesion treated by single BVS ≤ 25mm; reference vessel diameter of 2.5 to 3.5 mm by operator assessment; ≥19 years old (N=13)	RCT Angiography-guided PCI *vs* OCT-guided PCI (with BVS[2])	Percentage of **uncovered scaffold struts** [Time Frame: 6 months] Percentage of uncovered scaffold struts between OCT guidance vs. angiography-only guidance PCI on 6 month OCT	July 2016 Completed, no results available

[2] BVS = bioresorbable vascular scaffold

Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
NCT01743274	Patients aged 18-80 years, admitted for ACS; AND at least 1 of the following 2 criteria: new ST segment depression ≥1 mm or transitory ST segment elevation (<30 minutes) (≥1 mm) on at least 2 contiguous leads of the ECG OR Elevation (>upper limit of normal, ULN) of cardiac enzymes (CK-MB, Troponin I or T) (N=230)	RCT Angioplasty procedure guided by traditional fluoroscopy *vs* angioplasty procedure guided by OCT	Functional result of the angioplasty procedure as assessed by fractional flow reserve (**FFR**) [Time Frame: at the end of the angioplasty procedure] The average of three consecutive FFR measures will be recorded.	October 2016 Ongoing, but not recruiting participants
NCT01824030 (FORZA)	≥18 years; single vessel disease with an intermediate coronary artery stenosis; multivessel disease with multiple intermediate coronary artery stenosis only; multivessel disease with already treated angiographically critical stenosis and at least one intermediate coronary artery stenosis) (N=400)	RCT PCI FFR-guided *vs* PCI OCT-guided	Occurrence of **angina** defined as Seattle Angina Questionnaire score < 90 in angina frequency scale, at 13 month follow up from index procedure* [Time Frame: 13 months] *In case of MACE rate absolute difference of >1% between the two study arms, the primary end-point will be: "Occurrence of Major Cardiovascular Event and angina defined as Seattle Angina Questionnaire score < 90 in angina frequency scale, at 13 months follow up from index procedure"	April 2013 Unknown
NCT02471586 (ILUMIEN III)	≥ 18 years patient with an indication for PCI including: angina (stable or unstable), silent ischemia (a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or fractional flow reserve (FFR) ≤0.80 must be present), Non-ST segment elevation myocardial infarction (NSTEMI), or recent ST segment elevation myocardial infarction (STEMI) (>24 hours from initial presentation and stable). (N=450)	RCT coronary PCI guided by IVUS *vs* coronary PCI guided by OCT *vs* coronary PCI guided by angiography (drug-eluting stents)	Primary Efficacy Endpoint (powered) [Time Frame: Time of PCI Procedure]: **Post-PCI MSA**[3] assessed by OCT in each randomized arm. Testing will be done in a hierarchal manner as follows (all analyses powered): 1. Non-inferiority of OCT guided stenting to IVUS guided stenting 2. Superiority of OCT guided stenting to angiography guided stenting 3. Superiority of OCT guided stenting to IVUS guided stenting Primary Safety Endpoint (non-powered) [Time Frame: Time of PCI Procedure]: Procedural MACE defined as procedural complications requiring active interventions	May 2017 Ongoing, but not recruiting participants

[3] MSA = minimal stent area

Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
NCT02683356	Age ≥18 years; de novo native coronary artery disease with lesions that have a distal and proximal reference vessel diameter in the range between 2.25mm and 3.8mm. Single or multi vessel disease. Full revascularization of all lesions should be achievable (staged PCI not recommended). Elective or ad hoc PCI, stable angina and acute coronary syndrome (NSTE-ACS and STEMI). Angiographically significant (>50% visual estimation) stenosis present in at least one native coronary artery and evidence of ischemia. (N=270)	RCT OCT-guided PCI *vs* Angiography-guided PCI (with bioresorbable vascular scaffolds)	**Minimal in-scaffold lumen area** (mm^2) as assessed by OCT [Time Frame: 6 months]	March 2021 Not yet open for participant recruitment
NCT01873027 (OPINION)	20 - 85 years old with a de novo lesion (in the native coronary circulation) and planned to undergo drug-eluting stent implantation for indications according to the Japan and USA guidelines. (N=829)	RCT OFDI[4]-guided PCI and assessment by OFDI at pre-PCI and post-PCI *vs* IVUS-guided PCI and assessment by IVUS at pre-PCI and post-PCI	Target Vessel Failure (**TVF**), composite endpoint of cardiac death, target vessel-related myocardial infarction (MI) and clinically-driven TVR [Time Frame: 12 months after PCI]	July 2016 Completed, no results available
NCT02337348 (PROCTOR)	≥18 years with a clinical indication for coronary angiography and intervention due to stent failure (stent restenosis or stent thrombosis in stable patients or unstable patients with ACS) (N=200)	RCT OCT-guided coronary intervention *vs* Conventional angiography-guided coronary intervention	Target **lesion revascularisation** [Time Frame: 5 years]	December 2021 Currently recruiting participants.
NCT01869842	≥20 years old with a single lesion in a single vessel. Reference vessel diameter 2.5 - 3.5 mm. Lesion length ≤ 34 mm and ≤ 34 mm stent length. Stable angina requiring revascularization, patients with unstable angina, with no difficulty to enforce the follow-up angiography. (N=115)	RCT Traditional PCI *vs* OCT-guided PCI (with Resolute zotarolimus-eluting stent)	Ratio of the **stent strut** [Time Frame: Angiographic follow-up with OCT at 6 month]	December 2016 Currently recruiting participants
NCT02234804 (DOCTOR Recross)	>18 years with stable or unstable AP or silent AP, de novo coronary bifurcation lesions at "LAD/diagonal", "Cx/obtuse marginal", "right coronary artery (RCA)-posterior descending artery (PDA)/posterolateral branch" or "left main (LM)/Cx/LAD".All Medina classes except Medina 0.0.1; diameter of side branch ≥2.5 mm; diameter stenosis >50% by operator's visual assessment. (N=60)	RCT non-blinded, multicenter OCT-guided *vs* angiography-guided (two investigated stents: Medtronic Resolute Integrity, Xience Prime)	Cross sectional **stent strut malapposition** in the main vessel bifurcation segment facing the side-branch ostium [Time Frame: Baseline]	February 2017 Currently recruiting participants.

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Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
ISRCTN22628285 (OCTIMISE)	30 -90 years who are undergoing either: a. elective PCI for the treatment of CAD or b. urgent PCI for the treatment of ACS. Patients who are anticipated to have at least a 20 mm stent length in at least one lesion (N=128)	RCT Angiographically guided stent placement *vs* OCT guided stent placement	To estimate the difference in **MLA** immediately after the completion of PCI between the OCT-guided and the angiographically guided PCI groups. This outcome will be assessed by processing the digitally stored OCT images.	May 2018 Ongoing, currently recruiting participants

Non-RCTs

Among non-randomized trials, 3 are observational prospective cohort studies (NTR5376 manufacturer-sponsored, NCT02237456, NCT02486861) and 2 interventional open label single group studies (NCT01288105, ACTRN12615001234505). One out of 5 studies (NCT02237456) comparing two different FD-OCT systems (Lunawave and Optis) in assessing surrogate outcomes is completed but results are not available. One study (NCT01288105) assessing MACEs at 30 days has been terminated (no reasons reported).

The other three studies (NCT02486861, ACTRN12615001235405, NTR5376) are registries assessing: correlation of FD-OCT findings with MACEs at 12 months (NCT02486861), correlation between pathogenesis of the plaque measured on CT scan within 30 days post-OCT and MACEs (5 years post OCT), prognostic accuracy of OCT as a predictor of future MACE risk (at 18 months) in DM patients with any indication for angiography (NTR5376).

Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
NCT02237456 (DOCTOR)	Consecutive patients undergoing PCI (N=11)	Observational [Patient Registry] Prospective Lunawave, Terumo *vs* OPTIS,St. Jude Medical	Comparison of quantitative and semi-quantitative tissue analysis obtained with OCT images; characteristics of thrombic mass (average thickness of signal-rich area, shade degree), of fibrous tissue (maximum scan penetrance), of lipid plaque (signal intensities under the fibrous cap); of calcium plaque (matched calcium plaques that can be quantified for sizes), of vessel dissection (exploratory), of the fibrous cap (minimum thickness);	March 2015 Completed, no results available
NCT02486861	All consecutive patients that perform OCT on culprit and not culprit plaque in any subset in patients with ACS. (N=100)	Observational [Patient Registry] Cohort OCT	Correlation of OCT characteristics with incidence of MACEs and clinical baseline characteristics [Time Frame: 12 months]	June 2015 Currently recruiting participants

Study ID (acronym)	Patients (N)	Study design and comparator	Primary outcomes	Study deadline and status
NCT01288105	≥ 18 years ,need for major non-cardiac surgery requiring discontinuation of dual antiplatelet therapy. (N=107)	Observational OCT (OCT will be performed to determine the stent strut coverage. Patients in whom >95% of stent struts are covered will not receive perioperative bridging with a glycoprotein IIb/IIIa inhibitors, whereas those with <95% stent strut coverage will receive perioperative bridging).	Major adverse cardiac events [Time Frame: 30-days post surgery] composite of cardiac death, myocardial infarction, coronary revascularization	February 2014 Terminated
ACTRN12615001234505 (MOTIVATOR)	≥ 18 years presenting to hospital with: NSTEMI proceeding to in-patient angiography, STEMI proceeding to non-emergency in-patient angiography (late presentation or reperfused without PCI). All major epicardial coronary arteries suitable for for OCT prior to stenting (intervention). The time point is during that hospital admission for the MI event. Simply in-patient angiography. (N=100)	Non-randomised trial, open (masking not used), single group. OCT	Major Adverse Cardiac Events (Cardiovascular disease, death, MI, revascularisation). Via telephone follow-up and hospital records.[5 years post OCT.] Pathogenesis of plaque progression measured on CT scan within 30 days from OCT. [Within 30 days post OCT]	Not specified Not yet recruiting
NTR5376 (COMBINE Registry)	≥18 years, history of diabetes mellitus with any indication for angiography (Stable Angina (SA) or any type of Acute Coronary Syndrome (ACS) including ST-Elevation MI); coronary angiography, including FFR and OCT imaging of at least one coronary de novo stenosis in a native not-grafted vessel with a visually estimated diameter stenosis (DS) of 40 - 80% (target lesion). Target lesion should be other than the culprit lesion(s) in patients presenting with MI (STEMI or non-STEMI). (N=500)	Observational (Prospective, open label natural history registry) OCT, FFR	The per patient incidence of the target lesion(s) related composite MACE (cardiac death, MI, clinically-driven target lesion revascularisation or hospitalization due to unstable or progressive angina at 18 months in the FFR-negative No-TCFA (Group A) and FFR-negative TCFA (Group B).	February 2018 Currently recruiting participants

AUTHORIZATION

Two manufacturers (Lightlab Imaging Inc, Terumo Corporation) produce FD-OCT technology systems.
In the Italian medical devices repertoire the Lightlab Imaging Inc system has three codes for the console (227068, 435759, 809628) and six codes for the catheter (65243, 65223, 104083, 1273755, 809630, 809631) that have received the CE mark in 2010.
Terumo Corporation system has one code for the console (600622) that has received the CE mark in 2009 and one code for the catheter (600645). In the following table information regarding the different products are reported.

Manufacturer	Commercial Name	Repertoire code	CND Code	CE mark	CE mark expiration date
LIGHTLAB IMAGING INC	DRAGONFLY DUO KIT BOX	65243	Assembled		
LIGHTLAB IMAGING INC	DRAGONFLY CATHETER KIT	65223	Assembled		
LIGHTLAB IMAGING INC	DRAGONFLY OPTIS KIT	104083	Assembled		
LIGHTLAB IMAGING INC	DRAGONFLY OPTIS	1273755	C0104010101	CE565565	05/08/2018
LIGHTLAB IMAGING INC	DRAGONFLY DUO	809630	C0104010101	CE565565	05/08/2018
LIGHTLAB IMAGING INC	DRAGONFLY DUO KIT BOX	809631	C0104010101	CE565565	05/08/2018
LIGHTLAB IMAGING INC	C7XR - OPTICAL COHERENT TOMOGRAPHY IMAGING SYSTEM	227068	Z119099	CE565562	02/10/2018
LIGHTLAB IMAGING INC	ILUMIEN	435759	Z119099	CE565562	02/10/2018
LIGHTLAB IMAGING INC	ILUMIEN OPTIS	809628	Z119099	CE565562	02/10/2018
TERUMO CORPORATION	FASTVIEW	600645	C0104010101	Unavailable in repertoire	
TERUMO CORPORATION	LUNAWAVE	600622	Z119099	HD600263440001/expiration date 12/08/2014	

DIFFUSION/DIFFUSION PREDICTION

The diffusion of FD-OCT was evaluated through data from the database of activity data held by the Italian Society of Interventional Cardiology (Società Italiana di Cardiologia Interventistica) [GISE 2014]. We use this data instead that from Italian's Medical Device Database (Flusso Consumi) because the rate of coverage of this database over CE Models is quite variable between region from a minimum value of 62% for Provincia autonoma di Trento to the maximum value of 95% for Emilia-Romagna region with a national mean value of 82% (http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=2367 last access 16/09/2016).
In 2014, FD-OCT was used by 16 region (Veneto, Toscana, Sicilia, Sardegna, Puglia, Piemonte, Molise, Marche, Lombardia, Liguria, Lazio, Friuli Venezia Giulia, Emilia Romagna, Calabria, Campania, Abruzzo) and FD-OCT use presented the higher values for 3 Italian regions that are Sicilia with 456 catheters (about 4.3% of PCI), Lazio with 462 catheters (about 4.0% of PCI) and Toscana with 280 catheters (about 3.5% of PCI) .
From 2011 to 2014, national use of FD-OCT catheters increased from 1,173 catheters (1% of PCI) to 2,098 (1.7% of PCI), whilst for Emilia Romagna Region a decrease from 74 (0.7% of PCI) to 19 (0.2% of PCI) was registered.

BRIEF SUMMARY

The short report assessed the use of FD-OCT imaging in guiding percutaneous coronary intervention (PCI).
The reference diagnostic procedure for guiding PCI is coronary angiography; however it provides information only on the contour of the vascular lumen and in some patients is not able to optimally visualize coronary arteries. In these patients invasive coronary imaging may support clinicians in guiding PCI.
Optical coherence tomography (OCT) is an invasive intravascular imaging modality, based on near-infrared light emission (approximately 1,300 nm wavelength). The system includes two components, a single-use intracoronary catheter consisting of the catheter body and the internal rotating fiber optic imaging core and an OCT imaging system. The technology requires to clear the artery from blood during image acquisition. Two main technologies can be used to obtain OCT images: time domain (TD-OCT) and frequency/Fourier domain (FD-OCT). The main advantage of FD-OCT is that offers a shorter data acquisition time (using a non-occlusive acquisition modality), an increased maximum field of view and an increased resolution. Two manufactures presently produce systems performing FD-OCT, i.e. LightLab Imaging, Inc., USA and Terumo Corporation, Japan. In Italy only the system produced by LightLab Imaging, Inc., is used and distributed by St. Jude Medical; it can be acquired in two different ways: by purchasing the console at a price of 150,000.00€+VAT and single-use catheters costing from 1,464€ to 2,415€; otherwise the console may be rented at a cost of 2,988€+VAT/year and single-use catheters purchased at a cost of 1,200.00€+VAT (the price is established for a volume of 900 catheters over a 3 years period). The use of FD-OCT system does not require employment of extra personnel with respect to routine angiography procedures but requires specialised centres and specifically trained staff in coronary procedures (a learning curve for training has to be taken into account). Besides FD-OCT, intravascular ultrasound (IVUS) may

be an option: IVUS allows visualization of the coronary arterial wall by using ultrasound, it has an higher tissue penetration than FD-OCT but a lower resolution of coronary artery walls.
The target population of FD-OCT imaging could be represented by patients needing invasive coronary imaging to guide PCI due to complex coronary anatomy or unclear imaging at coronary angiography (including patients with suspected non-atherosclerotic spontaneous coronary dissection, NA-SCAD) or implantation of bioresorbable vascular scaffolds (BVS). Considering that, in 2015, the total number of PCIs in Emilia-Romagna region was approximately 11,700, the estimated number of patients eligible for FD-OCT imaging in the same year was ranges from 380 (3.2% of PCI) to 424 (3.6% of PCI).
An evidence profile defining rationale, eligible population, critical outcomes to be investigated and eligible trial designs was set up to guide the literature search in order to answer the research question. The literature search retrieved 1,539 records of which 78 were considered eligible; finally 35 papers were included: 1 systematic review, 3 RCTs, 3 cohort, 6 cross-sectional and 22 case-series studies. None of the included studies assessed the use of FD-OCT to guide PCI in suspected NA-SCAD; two studies evaluated its use in patients undergoing PCI with bioresorbable vascular scaffold and 1 study in those implanted with biolimus-eluting stent (BES).
The median failure rate was 6.7%, ranging from 0.9% to 17.9%. FD-OCT extended the duration of the angiography-guided PCI procedure from a minimum of 7 to a maximum 20 minutes and fluoroscopy time from a minimum of 3 to a maximum 4.4 minutes.
Diagnostic accuracy of FD-OCT versus FFR was assessed in one systematic review of low quality, 7 cross-sectional studies of poor quality and 1 RCT of moderate quality. All primary studies chose different threshold parameters for FD-OCT to optimize diagnostic accuracy (best cut-off) leading to heterogeneous and incomparable results among studies.
Using FD-OCT before PCI did not affect the procedural strategy in the only included RCT, while two case series reported change in decision regarding stent length and/or diameter in 55% and 81.8% of patients. The three case-series evaluating the impact of FD-OCT performed after PCI reported a post-stent deployment optimization due to FD-OCT findings ranging from 25% to 54.8% of patients.
The rate of procedural complications for patients undergoing FD-OCT ranged from 0.6% to 11.4, thus comparable to that of angio-guided or IVUS plus angio-guided PCI.
Efficacy of FD-OCT-guided PCI was evaluated in two RCTs of moderate quality assessing FD-OCT plus angiography versus angiography alone in guiding PCI; they included patients mostly with type B1/B2/C lesion (from moderate to high severity) and were powered to investigate surrogate outcomes (post-PCI fractional flow reserve, uncovered struts both at 6 months) as primary endpoints. The clinical value of the statistically significant difference in surrogate outcomes in favour of FD-OCT is unclear; incidence of MACEs at 6-month follow-up resulted in a non-statistically significant difference between intervention and control groups but studies were not powered for this purpose. One of the RCTs excluded patients with long lesions (>45 mm), bifurcation and lesions with reference vessel diameter > 3.5 mm.
Presently available evidence, if reassuring on the safety of FD-OCT, is not considered sufficient to yet claim on clinical efficacy: the two included RCTs were not powered to demonstrate improvement of long-term patient-important outcomes such as stent thrombosis and restenosis and MACEs. Moreover, studies evaluating diagnostic accuracy of FD-OCT in guiding PCI would benefit from adopting clinically relevant and validated thresholds for measuring coronary arteries' parameters.
Three out of ten of the presently ongoing RCTs are powered to investigate patient-important outcomes with follow-ups ranging from 12 months to 5 years and will probably solve some of the uncertainties regarding FD-OCT's clinical value in guiding PCI.

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