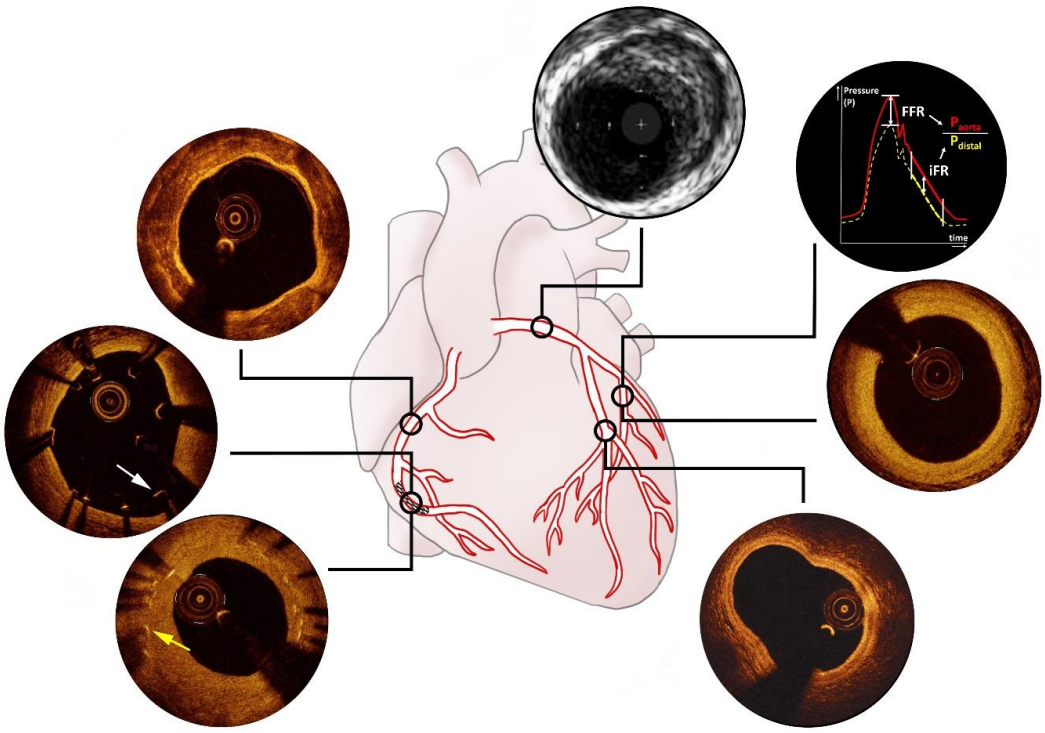
Master's Thesis

Invasive Coronary Artery Imaging using Optical Coherence Tomography: A Cost-effectiveness and Implementation Process Analysis

T.T.M. Oosterveer

Technical Medicine | Imaging & Intervention | TU Delft
Leiden University Medical Center | Sep 2019 – Jul 2020



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By

T.T.M. Oosterveer

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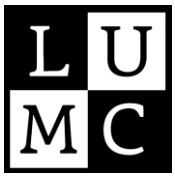

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"All models are wrong, but some are useful"

George Box (1919-2013)
Statistician

Timo Oosterveer
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PREFACE

After graduating high school I was searching for my passion. After three years, including a short career at the police and a job as day care host for elderly who suffer from the early stages of dementia, I decided to enroll for the bachelor's program Clinical Technology. The bachelor's program Clinical Technology and subsequent master's program Technical Medicine at the TU Delft are new joint-degree programs together with Leiden University and Erasmus University Rotterdam and their academic medical centers (LUMC and Erasmus MC). The programs are multidisciplinary, linking science and technology with clinical practice. As a result, technical physicians (or clinical technicians) are trained to combine their knowledge about the functioning of the human body and disease processes with their understanding of medical technology in clinical practice.

The final two years of the master's program consisted of clinical internships at the LUMC and Erasmus MC. During these internships I had the opportunity to put the theory into practice. For me, it especially was a great opportunity to discover my passion. A recurring theme during my internships was the constant communication and coordination between different professionals. During my internship at the Center of Pain Medicine at the Erasmus MC I really enjoyed working on a machine learning algorithm to diagnose patients based on imaging data. Especially explaining the concepts of machine learning to medical professionals was something I found really enjoyable and valuable. At that point I realized that the added value of technical physicians is not limited to the creation, application or optimization of new solutions in clinical practice, but also motivating and educating professionals, and bringing professionals together. That being said, I think I have found my passion!

Carrying out implementations of innovative techniques is one of the fields where I see the added value of technical physicians, as we oversee both medical and technical implications, and are able to connect all stakeholders. During the search for a graduation project, I was looking for such an implementation project. I want to thank Roderick for his input during this search and for providing the opportunity to carry out the implementation project at the department of interventional cardiology. I want to thank my supervisors, Sander and Roderick, for their extensive feedback and support throughout the whole project. In addition, a special thanks to Sander, Roderick and Wouter Jukema for the feedback and support while writing the literature review, which has been published two days before finishing this report! Also a special thanks to Elske for sharing her knowledge about cost-effectiveness analyses and providing extensive feedback and support during the thesis project. Furthermore, I want to thank everyone at the department for their enthusiasm, interest and support throughout the project. I also want to thank all external parties, including Jurgen Lighthart, Joost Damen, Kees-Jan Royaards, Paul Bloemen and Xavier Attendu, who have taken the time and effort to welcome me at their departments and cathlabs. Finally, thanks to Mirjam Sptizers for the cooperation during the implementation of optical coherence tomography at the department.

I am looking forward to start my career as a technical physician and to discover what the future has in store!

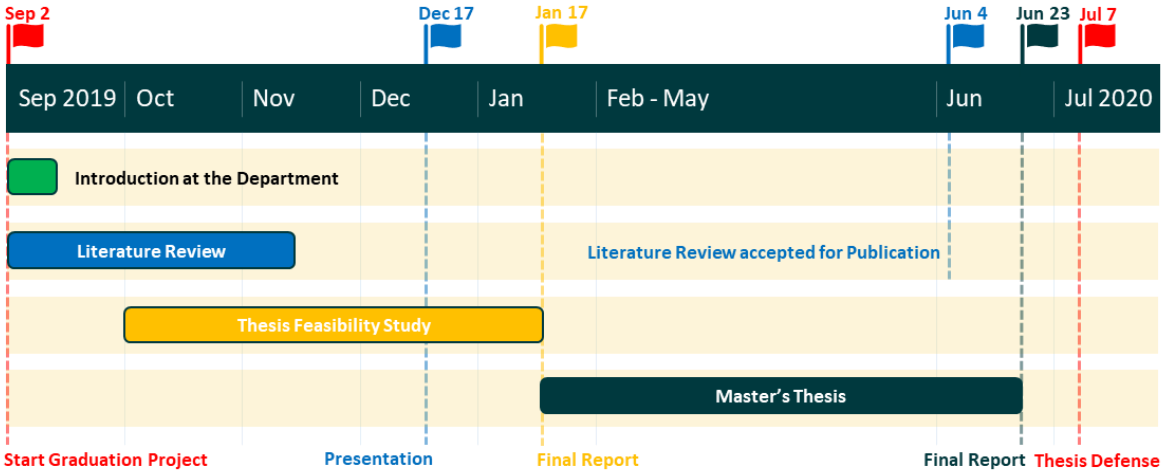
T.T.M. Oosterveer
Leiden, June 2020

SUMMARY

This report represents the master's thesis for the graduation project of the Technical Medicine master (track Imaging and Intervention). The project has been carried out at the Hart Lung Center of the Leiden University Medical Center (LUMC). The aim of this project was the implementation of optical coherence tomography (OCT), an invasive intracoronary imaging (ICI) tool used for the visualization of coronary arteries. The implementation was performed in a structured manner by:

(1) A literature review into the current applications of OCT in relation to current standards;
(2) A thesis feasibility study into clinical practices, professional views and other processes regarding ICI;
(3) A Master's thesis including a cost-effectiveness analysis (CEA) and the actual implementation of OCT at the department.

The timeline below provides an overview of the project set-up.



The project started with a literature review about the current applications of OCT in relation to intravascular ultrasound (IVUS) and coronary angiography (CAG). The literature review has been published in *Cardiology and Therapy*.[1] In general, OCT-guidance seems to contribute to favorable clinical outcomes compared with CAG-guidance alone. However, OCT-guidance results in similar clinical outcomes as IVUS-guidance. OCT could be considered for lumen assessment and stent related morphology in more complex cases in which CAG interpretation remains uncertain. Since OCT and IVUS have distinct characteristics, these techniques are complementary and should be considered carefully for each patient case based on the benefits and limitations of both techniques.

The thesis feasibility study aimed at acquiring insights into the clinical practices, the different views, and other processes (data, training, etcetera) related to ICI at the LUMC and other medical centers. This was achieved by observing clinical practices at the LUMC and other medical centers, and by interviewing clinicians and technicians at those centers. Both the literature review and the feasibility study provided extensive insights in current practices and controversies regarding ICI. Such insights were essential before implementation of OCT. These insights were used to carefully execute the implementation, while accounting for the interests

of all stakeholders as much as possible. In addition, the knowledge gained from the literature review and feasibility study were used as input for the master's thesis.

The master's thesis included a health economic evaluation comparing cost-effectiveness of OCT with IVUS and CAG, and the actual implementation of OCT at the department. The CEA was performed using the concept of Markov modelling. In general, OCT along with CAG was a more cost-effective intracoronary treatment strategy than IVUS along with CAG for patients with CAD. However, the gain in QALYs and reduction in costs were limited. Both IVUS and OCT outperform CAG alone in terms of cost-effectiveness.

With this thesis the current applications of OCT in relation to IVUS and CAG were identified, insights into different views and practices regarding ICI in the interventional cardiology domain were obtained and the cost-effectiveness of OCT-guided PCI compared with IVUS-guided PCI and PCI solely guided by CAG was assessed. In addition, OCT was implemented at the department of interventional cardiology of the LUMC. The processes, procedures and considerations around the implementation of OCT at the department of interventional cardiology were identified and described. Finally, the thesis was concluded with an argument about the added value of the technical physician as a new healthcare professional.

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AMC	Amsterdam University Medical Center, location AMC
BMS	Bare metal stents
CABG	Coronary bypass grafting
CAD	Coronary artery disease
CAG	Coronary angiography
CEA	Cost-effectiveness analysis
CPI	Consumer price index
CTO	Chronic total occlusion
CVD	Cardiovascular diseases
DES	Drug eluting stents
DSA	Deterministic sensitivity analysis
EACTS	European Association for Cardio Thoracic Surgery
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ESC	European Society of Cardiology
FFR	Fractional flow reserve
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICI	Intracoronary invasive imaging
ICMJE	International Committee of Medical Journal Editors
iFR	Instantaneous wave-free ratio
IGJ	Dutch Health Inspectorate (Inspectie gezondheidszorg en jeugd)
IQR	Interquartile range
IVUS	Intravascular ultrasound
LDL	Low density lipoproteins
LUMC	Leiden University Medical Center
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MLA	Minimum lumen area
MSA	Minimum stent area
NSTEMI	Non-ST elevation myocardial infarction
NURD	Non-uniform rotational disorders
OCT	Optical coherence tomography
OMT	Optimal medical treatment

PACS	Picture archiving and communication system
PCI	Percutaneous interventions
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCA	Right coronary artery
RCT	Randomized controlled trial
SCAD	Spontaneous coronary artery dissections
SD	Standard deviation
STEMI	ST elevation myocardial infarction
TAVI	Transcatheter aortic valve implantation
TLR	Target lesion revascularization
TVF	Target vessel failure
TVR	Target vessel revascularization
VBHC	Value based healthcare
WHO	World Health Organization
WTP	Willingness to pay

1. GENERAL INTRODUCTION

1.1 Medical Context

1.1.1 Coronary Artery Disease

Cardiovascular diseases (CVD) include all diseases of the heart and blood vessels.[2] Coronary artery disease (CAD) is considered a subgroup of CVD. CAD is a condition which results in narrowing of the coronary arteries. CAD is an inflammatory disease characterized by atherosclerosis. In more advanced stages of the disease, vessel narrowing and plaque formations cause reduction or interruption of blood flow to the heart muscle. Reduced flow to the heart muscle causes symptoms like shortness of breath and chest pain. CAD is often manifested by chest pain, myocardial infarction (MI) or sudden cardiac death.[3] Common risk factors for CAD are hypercholesterolemia, hypertension, diabetes, obesity, smoking, family history and aging.[4, 5]

1.1.2 Epidemiology of Coronary Artery Disease

CVD are the leading cause of death in both Europe and other continents around the world.[6] CVD accounts for approximately 40 to 50% of the total mortality in Europe. However, the mortality rates differs per country. In 10 European countries, including The Netherlands, only cancer causes more deaths than CVD. CAD accounts for 20% of the total mortality in Europe.[7] In the Netherlands, the mortality related to CVD has declined gradually since the mid-90s. Since then, the number of procedures has increased. The number of percutaneous interventions (PCI) increased more than surgical procedures, especially since the early 2000s with the introduction of drug eluting stents (DES). The prevalence of CAD in The Netherlands lies around 730,000 patients.[8] These statistics emphasize the importance of adequate treatment of patients with CAD.

1.1.3 Atherosclerosis in Coronary Artery Disease

Coronary arteries are composed of a three-layered circumferential structure (Figure 1-1).[9]

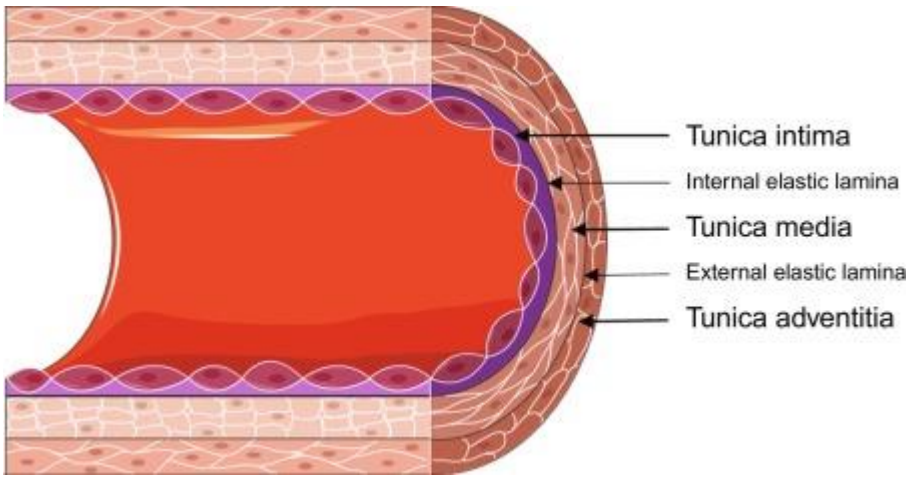

***Figure 1-1**. Schematic of a coronary artery. Adopted from Brown et al. (2017).*

The tunica intima consists of a thin layer of endothelial cells and a subendothelial extracellular matrix composed of collagen and elastin. The intima forms a physical barrier between the

blood and the vessel wall, preventing the blood from clothing on the vessel wall surface. The tunica media is formed by a layer of smooth muscle cells between the tunica intima and adventitia. The adventitia forms a connective tissue layer with micro-vessels, which supply oxygen and nutrients to the vessel wall.[9]

Atherosclerosis starts with thickening of the tunica intima. Macrophages and extracellular matrix accumulate. The risk factors mentioned earlier trigger endothelial dysfunction. As a result, low density lipoproteins (LDL) are captured inside the tunica intima, initializing a cascade of chemical reactions which trigger an inflammatory response. This response results in the accumulation of plaque and the arteries becoming less flexible. The macrophages and LDL particles interact and form a lipid-rich plaque. Smooth muscle cells from the tunica media infiltrate in the tunica intima and encapsulate the lipid-rich plaque. This way a fibrous cap with a lipid-pool is formed. Subsequently, the plaque grows into the vessel lumen, hampering blood flow. The fibrous cap becomes thinner with time and a necrotic core is formed inside the lipid pool, resulting in vulnerable plaque. Rupture of a vulnerable plaque results in thrombus formation inside the vessel lumen, eventually resulting in the occlusion of the coronary artery (Figure 1-2).[10] Roughly three types of plaque can be distinguished (Figure 1-3).[11]

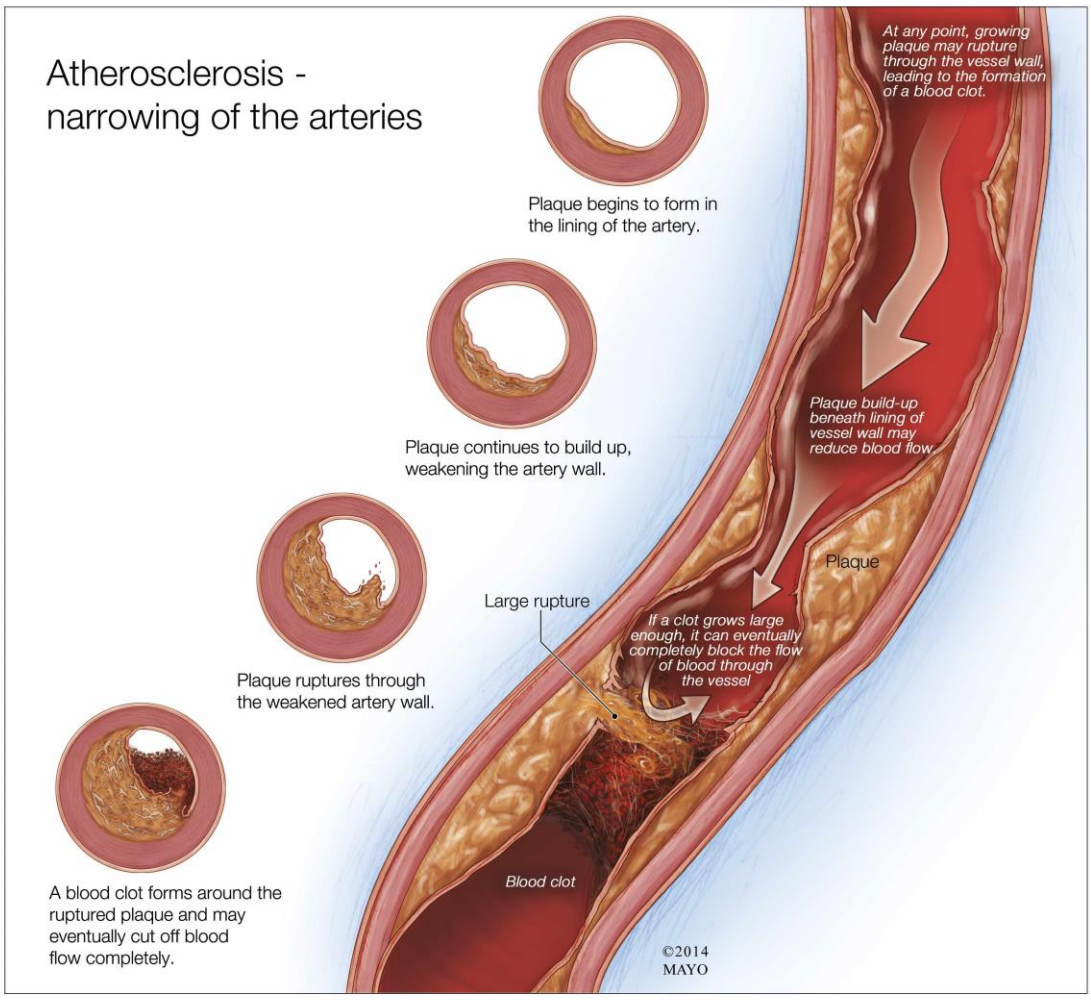

***Figure 1-2**. Different stages of plaque formation. Image adopted from mayoclinic.org.*

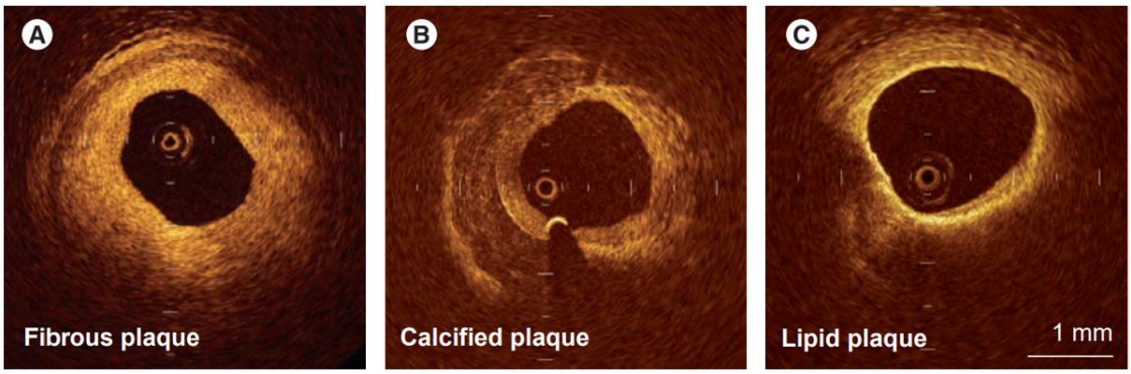

***Figure 1-4**. OCT images presenting different type of plaques. (A) Fibrous plaque presented as a homogeneous signal-rich region; (B) Calcified plaque presented as a sharply delineated signal-poor heterogeneous region; (C) Lipid-rich plaque presented as a diffusely bordered signal-poor region. Images adopted from Shinke et al. (2010).*

1.1.4 Treatment of Coronary Artery Disease

Treatment of patients with CAD exists of lifestyle changes on the one hand and optimal medical treatment (OMT) on the other hand. In addition, invasive treatment, such as percutaneous interventions (PCI) and coronary artery bypass grafting (CABG), should be considered when OMT is insufficient. As said before, especially the number of PCI are rapidly increasing.[8, 12] During PCI a stent is guided into the narrowing segment of the coronary artery by means of a heart catheterization. The stent is then expanded with a balloon to elevate the narrowing. Figure 1-4 shows a coronary angiogram before (left) and after (right) successful PCI.[13]

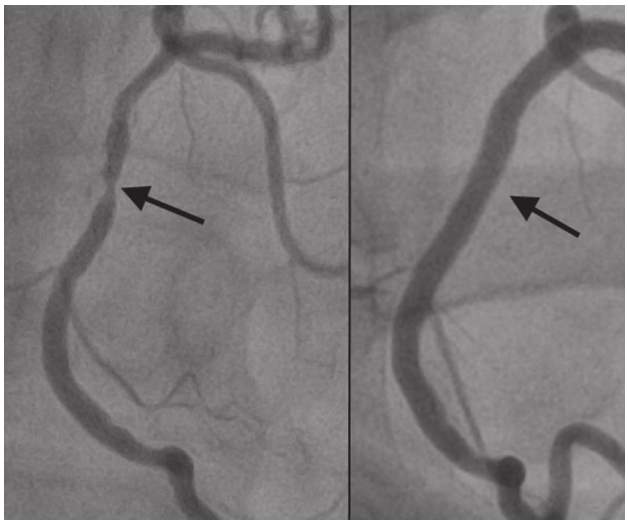

***Figure 1-3**. A coronary angiogram after successful PCI of the right coronary artery (RCA). Left: RCA before PCI; Right: RCA after PCI. The narrowing is indicated by the black arrows. Image adapted form Pachowicz et al. (2014).*

1.1.5 Invasive Coronary Artery Imaging during Percutaneous Interventions

Coronary angiography (CAG) is the standard modality for the invasive assessment of coronary anatomy and function, and the intraprocedural guidance of PCI (Figure 1-4).[14] However, CAG has well recognized limitations. CAG results in a two-dimensional luminogram of a complex three-dimensional structure. CAG only shows luminal dimensions and is limited in characterization of tissue or plaque and assessing features associated with suboptimal stent deployment.[14-16]

Intracoronary invasive imaging (ICI) can potentially overcome these limitations of CAG. According to the recent guidelines on myocardial revascularization from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), ICI should be considered for optimizing stent implantation and detecting stent-related mechanical problems leading to restenosis (Class IIa evidence). In addition, ICI can be used for the assessment of stenosis severity, lesion morphology, and the characterization of plaque composition.[17] Intracoronary ultrasound (IVUS) and optical coherence tomography (OCT) are the most common modalities for ICI and both modalities provide high resolution cross-

sectional images of the vessel wall.[18, 19] The benefits of IVUS-guidance on clinical outcome and stent optimization has been reported in multiple meta-analyses.[20-24] Despite growing evidence, the adoption of ICI in clinical practice remains limited.[25]

1.2 Intracoronary Imaging

1.2.1 Intravascular Ultrasound

IVUS first prototype was developed in de mid-1950s for the measurement of intracardiac dimensions in a dog.[26] The first clinical experience with IVUS for intravascular imaging as applied nowadays, was described in 1988.[27] Since then, IVUS is the most widely used clinical tool for intravascular imaging, when visual assessment of the angiogram is not clear.[28] There are two types of IVUS catheters, the solid state and mechanical scanning catheters. Solid state catheters have a circular array of transducers mounted at the tip of the IVUS catheter. The transducers are activated sequentially, resulting in an ultrasonic beam that sweeps the vessel wall. Mechanical IVUS catheters include a single transducer element that rotates inside the tip of the IVUS catheter. Both techniques are used in clinical practice. However, mechanical catheters have higher center frequencies resulting in higher resolutions. A drawback of mechanical catheters is that the guidewire is located outside the catheter, resulting in a shadowing artefact. Solid state IVUS has a higher depth penetration, due to the lower frequencies. In addition, solid state catheters have no moving parts, which prevents non-uniform rotational image distortions (NURD).[28] Box 1-1. provides a short explanation of the principles of ultrasound.

> Ultrasound waves are generated by piezoelectric crystals, which are the transducer elements. The crystals are excited by electrical pulses, resulting in mechanical oscillations. These oscillations form an ultrasonic beam. The beam then propagates into the vessel wall. Part the beam "echoes" while interacting with the tissue, as the rest of the beam propagates further. These echoes are dependent on the acoustic impedances of adjacent tissues. The acoustic impedance is defined as the multiplication of the density of a tissue with the speed of sound in that tissue. Higher acoustic impedance differences between two adjacent tissues result in more reflection and less propagation. These reflections or echoes are detected by the piezoelectric crystals and converted back into electrical pulses. The echo time delay is used to calculate the location of the reflection.

***Box 1-1**. The principles of ultrasound.*

1.2.2 Optical Coherence Tomography

OCT was first described in 1991 for the visualization of the retina.[29] Nowadays, applications of OCT have broadened to other disciplines such as gastroenterology and cardiology.[28] OCT is often defined as analogous to IVUS, as both techniques result in high resolution cross-sectional images by measuring the echo time delay and magnitudes of backscattered waves. However, with OCT near-infrared light pulses, instead of ultrasound, are used to acquire the images. Reflection of light is dependent on the differences between refraction indices of two tissues. These indices are in turn dependent on the speed of light in those tissues. Because light travels at a speed of $3x10^8$ m/s, the echo time delay cannot be measured directly. Therefore, OCT utilizes an interferometer (Figure 1-5).[30] The emitted light is split into a reference beam and a sample beam. The sample beam propagates into the wall of the coronary artery. Part of the beam backscatters while interacting with the tissue. The reference beam is sent to a mirror at

a known distance and is almost fully reflected. The backscattered beam in the sample arm and reflected beam in the reference arm interfere. The resultant waves are then detected by a detector. By applying a Fourier transform to the resultant waves, the frequencies comprising the signal can be calculated. From those frequencies the axial depth and intensity can be calculated. A mathematical explanation behind OCT is given in Appendix A.

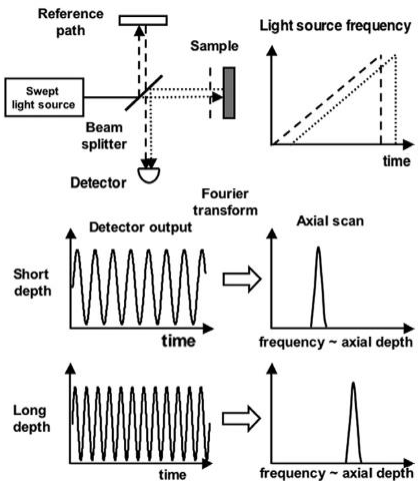

***Figure 1-5**. Schematic of OCT. Adopted from Lowe et al. (2011).*

1.2.3 Technical Implications of OCT and IVUS

The technical specifications of OCT and IVUS are summarized in Table 1-1. OCT provides an axial spatial resolution of 10 to 20 µm, whereas IVUS provides an axial spatial resolution of 100 to 200 µm. Lateral resolutions are typically 20 µm and 200 µm for OCT and IVUS respectively. In contrast, IVUS has a maximum penetration depth of 10 mm, where OCT has a penetration depth of only 1 to 2.5 mm. These differences are mainly caused by the differences in wavelength. OCT uses a near-infrared light source, which has a smaller wavelength (higher frequency) than ultrasound.[31-34] Due to its higher resolution, OCT is able to reveal more detail than IVUS. However, image interpretation should be performed carefully as it is not clear whether small detailed abnormalities are clinically relevant.[35] Also image acquisition speed of OCT is much faster than IVUS. A major drawback of OCT imaging is the need for a contrast agent for blood clearance, as near infrared light is fully attenuated by red blood cells. Especially for patients with renal disfunction, this extra use of contrast might increase the risk of contrast nephropathy.[32] Another drawback of OCT, is the inability to image ostial lesions as sufficient blood clearance is hampered, if not impossible.[33, 36]

***Table 1-1**. Technical specifications of OCT and IVUS as reported in different publications.[32-34]*

	OCT	**IVUS**
Image source (wavelength)	Near infrared light (1.3 µm)	Ultrasound (35-80 µm)
Minimum guide catheter size	6 Fr	5 Fr
Axial resolution	10-20 µm	100-200 µm
Lateral resolution	20-40 µm	200-300 µm
Penetration depth	1-2.5 mm	4-10 mm
Acquisition speed	Up to 25 mm/s	0.5 mm/s
Contrast for blood clearance	10-15 mL per pull-back	Not required
Distal catheter diameter*	2.7F (0.9)	3.5F (1.2 mm)
Largest catheter diameter*	3.2F (1.1 mm)	3.5F (1.2 mm)
Maximum guide wire diameter*	0.014” (0.36 mm)	0.014” (0.36 mm)

Abbreviations: IVUS, intravascular ultrasound; OCT, optical coherence tomography. *Based on manufacturer specifications: the Dragonfly™ Imaging Catheter for OCT and the Eagle Eye Platinum ST Catheter for IVUS.

1.3 Thesis Overview

1.3.1 Thesis Motivation

At the moment there is no standard implementation strategy for the introduction of new medical devices at the department of interventional cardiology of the Leiden University Medical Center (LUMC). As a result, some implementations resulted in barely used expensive medical devices. The increase of chronic conditions, such as CVD, and technological

advancements are key factors driving the increase of healthcare costs.[37] It is therefore especially of interest for the technical physician to develop skills to assess the added value of technology utilized in clinical practice and to be able to guide implementations of novel techniques efficiently to prevent waste of resources.

At the LUMC, IVUS along with CAG is currently the standard modality for the invasive assessment of coronary anatomy when CAG interpretation remains uncertain. IVUS is used in approximately 10% of all patients undergoing either diagnostic CAG or PCI. Compared with IVUS, OCT has high potential due to its higher resolution, high image acquisition speed and easy image interpretation. The department of interventional cardiology at the LUMC intended to implement OCT. The aim of this project was to implement OCT in a structured manner by assessing the added value of OCT for the department, assessing the cost-effectiveness of OCT in comparison with IVUS and CAG, and by assessing the implementation processes at the department. The long term goal is to improve the treatment of patients with CAD and to contribute to efficient implementations in the future.

1.3.2 Central Research Questions

(1) Which method for intracoronary invasive imaging, intravascular ultrasound or optical coherence tomography, is more cost-effective, in terms of quality of life and costs, for the assessment of coronary lesions in the context of percutaneous interventions?
(2) What are the processes around implementations of medical technologies at the department of interventional cardiology?

1.3.3 Goals and Objectives

Goals and objectives can be divided into research goals, clinical goals and professional development goals. The research goals were:

(1) Assessing the cost-effectiveness of OCT compared with IVUS and/or CAG.
(2) Identification and evaluation of the processes around implementations of medical devices at the department of interventional cardiology.
(3) Assess the role of the technical physician in implementation processes and health economic research.

The clinical goals were:

(1) Acquiring medical knowledge in the field of interventional cardiology, with emphasis on:
    a. Coronary angiography;
    b. Percutaneous interventions;
    c. Invasive intracoronary imaging.
(2) Assisting at procedures, assessment of intracoronary images, clinical reasoning and medical skills.

Professional development goals:

(1) Acquiring knowledge about Implementation of medical devices and the interventional cardiology domain.
(2) Performing the implementation of OCT at the department of interventional cardiology.
(3) Acquiring knowledge about health economic research.

1.3.4 Thesis Outline

The purpose of Chapter 1 was to provide the reader with background information on CAD, PCI and ICI. Other concepts related to specific chapters will be introduced per chapter.

In preparation of the master's thesis a literature review and thesis feasibility study were performed. The literature review aimed to identify the current applications of OCT in relation to IVUS and CAG. This literature review has been accepted for publication in *Cardiology and Therapy* and is presented in Chapter 2.[1] The thesis feasibility study aimed at acquiring insights into the clinical practices, views, and processes related to ICI at the LUMC and other medical centers. The thesis feasibility study is presented in Chapter 3.

The literature review and thesis feasibility study were followed by the master's thesis. The thesis included a health economic evaluation comparing the cost-effectiveness of OCT with IVUS and CAG, and the actual implementation of OCT at the department. The health economic evaluation was performed using the concept of Markov modelling. This analysis is discussed in Chapter 4, written as a scientific article, hence providing the answer to the first central research question.

The initial aim for Chapter 5 was to assess the conditions which determine the success of implementations of medical devices at the department of interventional cardiology and providing a general implementation strategy or improvement plan based on these conditions. Successful implementation cases would have been compared with less successful cases. Unfortunately, due to the current corona crisis, this analysis was not performed. Instead, Chapter 5 provides an overview of the department's implementation processes in relation to local and Dutch guidelines for the implementation of medical devices. Hence, providing the answer to the second central research question. This chapter concludes with a paragraph describing the aspects that play a role while considering the implementation of ICI.

Chapter 6 concludes this thesis with an argument about the added value of technical physicians as a new healthcare professional. Figure 1-6 provides an overview of the project timeline with references to corresponding chapters in this report.

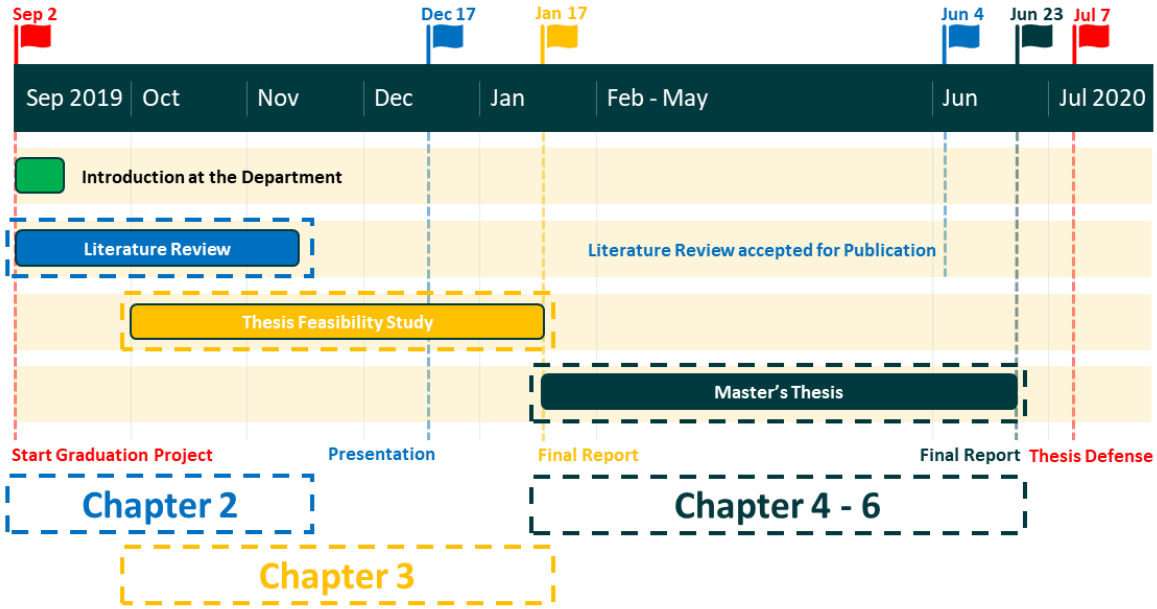

***Figure 1-6**. Project timeline.*

2. OPTICAL COHERENCE TOMOGRAPHY: CURRENT APPLICATIONS FOR THE ASSESSMENT OF CORONARY ARTERY DISEASE AND GUIDANCE OF PERCUTANOUS CORONARY INTERVENTIONS

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2.1 Abstract

Background

Coronary angiography (CAG) is the standard modality for assessment of coronary stenoses and intraprocedural guidance of percutaneous coronary interventions (PCI). However, the limitations of CAG are well recognized. Intracoronary imaging (ICI) can potentially overcome these limitations. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the main ICI techniques utilized in clinical practice.

Aim

This narrative literature review addresses the current clinical applications of OCT, in relation to IVUS and CAG in patients with coronary artery disease (CAD). Items reviewed are: technical implications of OCT and IVUS, lesion characterization and decision making, stent optimization criteria, post-stenting results, safety in terms of procedural complications, clinical outcomes and indications.

Main findings

OCT is able to reveal more detail than IVUS due to its higher resolution. However, this higher resolution comes at the cost of a lower penetration depth. Pre-stenting OCT results in procedural change in more than 50% of the cases in terms of stent length and diameter. Post-stenting OCT resulting in stent optimization is reported in at least 27% of the cases. Malapposition and under-expansion are treated with post-dilatations, while edge-dissections are treated with additional stent placement. Stent expansion, stent apposition, distal stent edge dissections and reference lumen areas seem to be the most important stent optimization criteria for both decision making and for reducing the risk of adverse events during follow-up. Both OCT and IVUS are superior in terms of post-stenting results compared with CAG alone. However, there is no consensus about whether OCT-guidance results in better stent expansion than IVUS-guidance. OCT, IVUS and CAG are safe procedures with few reported procedural complications. In general, OCT-guidance seems to contribute to favorable clinical outcomes compared with CAG-guidance only. However, OCT-guidance results in similar clinical outcomes as with IVUS-guidance. OCT could be considered for lumen assessment and stent related morphology in more complex cases in which CAG interpretation remains uncertain. Since OCT and IVUS have distinct characteristics, these techniques are complementary and should be considered carefully for each patient case based on the benefits and limitations of both techniques.

Keywords: Coronary artery disease; Percutaneous coronary interventions; Intracoronary imaging; Optical coherence tomography; Intravascular ultrasound.

2.2 Introduction

Coronary angiography (CAG) is the standard modality for the assessment of coronary stenoses and intraprocedural guidance of percutaneous coronary interventions (PCI).[14] However, CAG has some well recognized limitations. CAG results in a two-dimensional luminogram of a complex three-dimensional structure, which mainly shows luminal dimensions. CAG is limited in characterization of tissue or plaque (except for calcium, coarse ulcerations or large dissections) and assessing features associated with suboptimal stent deployment.[14-16, 38] However, these characteristics all contain important prognostic information, necessitating more advanced visualization.

Intracoronary imaging (ICI) can potentially overcome these limitations of CAG. According to the recent guidelines on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio Thoracic Surgery (EACTS), ICI can potentially be used during the diagnostic process of the evaluation of stenosis severity, lesion morphology and the characterization of plaque composition.[17] The guideline states that ICI should be considered for (1) optimizing stent implantation and (2) detecting stent-related mechanical problems leading to restenosis.

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the most common techniques for ICI and provide cross-sectional images of the vessel wall with a high resolution.[18, 19] The benefits of IVUS-guidance on clinical outcome and stent optimization have been reported in multiple meta-analyses.[20-24] However, the benefits of OCT in relation to IVUS are not always clear. Despite growing evidence, the adoption of ICI in clinical practice remains limited.[25]

This narrative literature review aimed to assess current clinical applications of OCT, in relation to IVUS and CAG in patients with coronary artery disease (CAD). This review addresses:

(1) A short comparison of technical implications of OCT and IVUS;
(2) Lesion characterization and decision making;
(3) Stent optimization criteria;
(4) Post-stenting results;
(5) Safety in terms of procedural complications;
(6) Clinical outcomes;
(7) Indications.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

2.3 Technological Implications

OCT is often defined as analogous to IVUS, as both techniques result in cross-sectional images by measuring the echo time delay and magnitudes of backscattered waves. However, the optical aspect of OCT compared to ultrasound has certain implications. First, OCT provides an axial spatial resolution of 10 to 20 µm whereas IVUS provides an axial spatial resolution of 100 to 200 µm. Lateral resolutions are typically 20 µm and 200 µm for OCT and IVUS respectively. In contrast, IVUS has a maximum penetration depth of 10 mm, where OCT has a penetration depth of only 1 to 2.5 mm.[31-34] OCT is able to reveal more detail than IVUS due to its higher resolution. However, image interpretation should be performed carefully as it is not clear whether small detailed abnormalities are clinically relevant.[35]

With the introduction of Fourier domain OCT, high image acquisition speeds can be acquired with OCT (up to 25 mm/s). A major drawback of OCT imaging is the need for a contrast agent for blood clearance, as near infrared light is fully attenuated by blood. Especially for patients with renal dysfunction, this extra use of contrast increases the risk of contrast induced nephropathy (CIN).[32] Another drawback of OCT is the inability to image ostial lesions as blood clearance is hampered, if not impossible.[33, 36] The technical specifications of OCT and IVUS are summarized in Table 2-1.

***Table 2-1**. Technical specifications of OCT and IVUS as reported in different publications.[32-34]*

	OCT	**IVUS**
Image source (wavelength)	Near infrared light (1.3 µm)	Ultrasound (35-80 µm)
Minimum guide catheter size	6 Fr	5 Fr
Axial resolution	10-20 µm	100-200 µm
Lateral resolution	20-40 µm	200-300 µm
Penetration depth	1-2.5 mm	4-10 mm
Acquisition speed	Up to 25 mm/s	0.5 mm/s
Contrast for blood clearance	10-15 mL per pull-back	Not required
Distal catheter diameter*	2.7F (0.9)	3.5F (1.2 mm)
Largest catheter diameter*	3.2F (1.1 mm)	3.5F (1.2 mm)
Maximum guide wire diameter*	0.014" (0.36 mm)	0.014" (0.36 mm)

Abbreviations: IVUS, intravascular ultrasound; OCT, optical coherence tomography. *Based on manufacturer specifications: the Dragonfly™ Imaging Catheter for OCT and the Eagle Eye Platinum ST Catheter for IVUS.

2.4 Lesion Characterization and Decision Making

Plaque rupture is one of the main causes of myocardial infarction (MI). The most vulnerable plaques are those with a large lipid core and a thin fibrous cap.[39, 40] A thin fibrous cap (< 65 µm), large lipid core (lipid in ≥ 2 quadrants in any image) and activated macrophages (multiple punctate signal-rich regions) near the fibrous cap were identified as characteristics of vulnerable plaques in OCT autopsy studies.[41-45] Future clinical trials should demonstrate whether OCT can definitively distinguish vulnerable from stable plaques. Recently, spontaneous coronary artery dissection (SCAD) gained recognition as a cause of acute coronary syndrome (ACS), specifically in women. The exact pathophysiology of SCAD remains fairly unknown. Nonetheless, ICI can help to identify the false lumen and intramural hematoma between the intima and media resulting in vessel occlusion, as it is difficult to distinguish SCAD from atherosclerotic lesions with conventional CAG.[46] OCT studies suggest the presence of a crescent-shaped false lumen and the presence of fenestrations between the true lumen and false lumen as characteristics of SCAD.[47-50] Most experts recommend OCT over IVUS to assess SCAD, due to its better spatial resolution.[51] Furthermore, ICI provides insight in the composition of coronary arterial thrombus and stent thrombosis. Especially OCT seems suitable for assessing thrombus, due to the higher resolution and the attenuation of the OCT signal by red blood cells.[52, 53] Thrombus is characterized as an irregular mass (≥ 250 µm) protruding into the lumen.[52, 54] Red thrombus (erythrocyte-rich) is visualized by OCT as a high-backscattering projection with signal-free shadowing. White thrombus (platelet-rich) is visualized as a signal-rich, low-backscattering projection.[52]

Pre-stenting OCT results in procedural change in 57% to 71.4% of the lesions. Most changes include changes in stent length and diameter.[55-57] Wijns et al. (2015) found no change in the number of stents implanted.[55] Leistner et al. (2018) found that changes in strategy occurred more frequently in complex lesions (60.7% in complex lesions vs. 10.7% in simple lesions, p=0.01).[56] Remarkably, Meneveau et al. (2016) reported no differences in stent length or diameter. However, Meneveau et al. reported an increase of glycoprotein inhibitors as OCT was able to visualize a significant higher rate of thrombus.[57] Differences in outcome can be

explained by the different patient characteristics between the studies. More than 80% of the patients in the study by Leistner et al. are characterized as stable CAD, Meneveau et al. only included patients with non-ST elevation MI (NSTEMI), whereas Wijns et al. included patients with stable CAD, unstable CAD and NSTEMI.

Multiple studies report on the effect of post-stenting OCT on decision making.[55-59] Stent optimization was performed in 27% to 52.2% of the lesions. Decisions were mainly based on stent malapposition, under-expansion or edge-dissections. Malapposition and under-expansion resulted in post-dilatation, while edge-dissections resulted in additional stent placement. Meneveau et al. (2016) reported post-stenting optimization based on OCT in 50% of the patients compared with 22.5% in the CAG-group ($p<0.0001$).[57]

2.5 Stent Optimization Criteria

IVUS or OCT should be considered for stent optimization, according to recent guidelines and consensus documents.[17, 25, 60, 61] Most studies included in this review used stent optimization criteria derived from the MUSIC study by De Jaegere et al. (1998).[62] De Jaegere et al. were the first to establish criteria for optimal stent expansion by IVUS-guidance. Under-expansion, malapposition and edge-dissections are the most important optimization criteria. Although small variations occur, under-expansion was mostly defined by an minimal stent area (MSA) or minimal lumen area (MLA) < 90% of the average reference lumen area.[16, 56-59, 63-66] Malapposition was defined as a stent lumen distance > 200 µm. Malapposition was indicated for optimization when present in at least five consecutive frames or in three consecutive struts.[55, 56, 58, 64, 67, 68] Edge-dissection was defined as a linear rim of tissue ≥ 200 µm, 5 mm proximal or distal from the stent edge. Edge-dissections were optimized when present in more than 5 consecutive frames.[55, 58, 59, 64, 68] Most studies used more optimization criteria, such as the presence of thrombus, tissue protrusions and complete lesion coverage. However, these criteria differed considerably between studies. Full criteria used by the OCT studies are provided in Appendix B.

2.6 Post-stenting Results

Numerous studies have demonstrated that IVUS-guidance compared with CAG-guidance, results in larger luminal dimensions and, thus, reduce the incidence of major adverse cardiovascular events (MACE) during follow-up. Stent expansion after PCI is the most compelling predictor of early stent thrombosis and restenosis.[16, 20, 21, 24, 69-72] However, Wijns et al. (2015) reported a decrease in stent diameter in 31% of the lesions based on pre-stenting OCT.[55] According to a randomized controlled trial (RCT) by Habara et al. (2012), comparing OCT-guidance with IVUS-guidance in 70 patients, OCT-guidance was associated with a smaller stent expansion compared with IVUS-guidance. Nonetheless, strong correlations were found between MSA and mean stent area comparing OCT with IVUS ($r=0.96$ and $r=0.95$ respectively, $p<0.0001$). Habara et al. mentioned the low penetration depth of OCT as a potential factor driving under-expansion.[63]

Prati et al. (2015) retrospectively analyzed end-procedural OCT findings and the risk of MACE in 832 patients. MACE was defined as a composite of all-cause mortality, myocardial infarction (MI) and target lesion revascularization (TLR). In-stent MLA <4.5 mm^2 (HR 1.64 (1.1-2.6), $p=0.040$), distal dissection >200 µm (2.54 (1.3-4.8), $p=0.004$), distal reference lumen area <4.5 mm^2 (HR 4.65 (2.5-8.8), $p<0.001$) and proximal reference lumen area <4.5 mm^2 (HR 5.73 (2.2-14.6), $p<0.001$) were independent predictors of MACE. The absence of at least 1 significant

criterion for optimal OCT stent deployment was also an independent predictor of MACE (HR 3.53 (2.2-5.8), p<0.001).[68]

An RCT by Ali et al. (2016) found that OCT-guidance was non-inferior to IVUS-guidance in terms of MSA. However, OCT was not superior. Compared to CAG-guidance, OCT resulted in significant higher minimum and mean stent expansions (p=0.02 and p=0.001, respectively). No significant differences in MSA were found between OCT, IVUS and CAG.[16] Maehara et al. (2015) found similar results as Ali et al.[35, 55, 73] However, malapposition, tissue prolapse and edge-dissections were detected more often with OCT than with IVUS.

Since the introduction of drug-eluting stents (DES), the rate of in-stent restenosis declined.[74] Incomplete endothelial strut coverage is a predictor of late in-stent restenosis.[75, 76] Antonsen et al. (OCTACS, 2015) conducted an RCT on whether OCT-guided stenting resulted in improved stent strut coverage at 6 months compared with CAG-guidance only. In total, 85 patients were included in a single center in Denmark. The percentage of uncovered struts was significantly lower in the OCT group (4.3% (1.2-9.8) vs. 9.0% (5.5-14.5), p<0.01). In addition, OCT-guidance led to completely covered struts in 17.5% of the cases vs. 2.2% for CAG-guidance (p=0.02). OCT-guidance led to a significant reduction in the total malapposition area, volume and the percentage of malapposed struts directly after stenting. However, no differences were observed in stent malapposition or MSA after 6 months.[64] An RCT by Lee et al. (2018) found similar results.[77] An RCT by Meneveau et al. (2016) compared post-procedural fractional flow reserve (FFR) after OCT-guidance and CAG-guidance. OCT-guidance was performed both before and after stent placement. Multiple OCT runs could be performed until satisfactory results were acquired. As a result, FFR values of the OCT-group were significantly higher (0.94±0.04 vs. 0.92±0.05, p=0.005). In addition, the number of patients with an FFR >0.90 at the end of the procedure was significantly higher in the OCT-group (82.5% vs. 64.2%, p=0.0001).[57] Gatto et al. (2018) retrospectively analyzed 125 lesions in patients who experienced MACE during one-year follow-up. 57 lesions (54%) of 105 optimal CAG results showed suboptimal stenting results on OCT. Stent MLA <4.5 mm^2 and narrowing of the references were the most common features of suboptimal stent deployment identified with OCT.[78]

Thus, OCT-guided stenting improves strut coverage and stent apposition, while reducing tissue protrusions compared with CAG-guidance. OCT is non-inferior, but not superior to IVUS-guidance. However, there is no consensus about whether OCT-guidance or IVUS-guidance results in better stent expansion. Full results of post-stenting results are provided in Appendix C.

2.7 Procedural Complications

To establish whether OCT-guided PCI is a safe procedure, studies which addressed safety in the form of procedural complications after OCT-guided PCI were identified.[16, 55, 57-59, 66, 79] In general, the incidences of procedural complications, including contrast induced nephropathy (CIN), were low and not different from either IVUS-guided or CAG-guided stenting. One propensity-matched cohort (1134 pairs) by Jones et al. (2018) found that OCT-guided stenting was associated with even a lower in-hospital MACE compared with CAG-guidance alone (0.80% vs. 2.00%, p=0.01).[79] Full results of procedural complications are provided in Appendix D.

2.8 Clinical Outcomes

To establish whether OCT-guided stenting results in favorable clinical outcomes, studies which addressed clinical outcomes after OCT-guided stenting were identified.[55, 57-59, 64, 66, 79, 80] Although the evidence is scarce and follow-up times are short, clinical outcomes in terms of MACE seem favorable for OCT-guided stenting over CAG-guided stenting. However, no differences were observed between OCT-guided and IVUS-guided stenting. Full results are discussed below and an overview is provided in Appendix E.

Imola et al. (2010) prospectively performed pre-PCI OCT in 40 patients with ambiguous lesions. Post-PCI OCT was performed in 74 patients for post-stent assessment. Clinical follow-up was available in 88 patients with mean follow-up of 4.6±3.2 months. No deaths, MI or stent thrombosis were observed. Angina recurrence was observed in 3 patients with restenosis, leading to one coronary artery bypass grafting (CABG) and one re-PCI.[58]

Prati et al. (CLI-OPCI, 2012) retrospectively compared 335 matched patient pairs undergoing either OCT-guidance plus CAG-guidance or CAG-guidance only. 12-Months follow-up showed a significantly lower risk of cardiac death for the OCT-group (4 (1.2%) vs. 15 (4.5%), p=0.010). MI occurred in 18 (5.4%) vs. 29 (8.7%) patients in the OCT-group and CAG-group respectively (p=0.096). The incidence of the composite of cardiac death and MI was significantly lower in the OCT-group (P=0.006). After multivariable logistic regression analysis, propensity score-adjusted analysis and Cox proportional hazard analysis OCT remained associated with a significantly lower risk of cardiac death or MI. No differences were observed in stent thrombosis or TLR.[59]

An RCT by Antonsen et al. (OCTACS, 2015) compared OCT-guided PCI with CAG-guided PCI in 85 patients with NSTEMI. During 6-months follow-up, 2 patients (4%) from the CAG-group had MACE (one subacute stent thrombosis and one cardiac death). No cardiac events were reported in the OCT-group.[64]

Wijns et al. (ILUMIEN I, 2015) reported on the occurrence of cardiac events in patients with unstable or stable angina or NSTEMI in a large intercontinental prospective trial. The data was analyzed based on four optimization groups: PCI without optimization based on OCT (N=137), optimization based on pre-PCI OCT only (N=163), optimization based on post-PCI OCT only (N=40) and optimization based on both pre-PCI and post-PCI OCT (N=65). In general, all rates of cardiac events were low. Device-oriented MACE after 30 days follow-up were observed in 8.8%, 8%, 12.5% and 1.5% respectively. Patient-oriented MACE after a 30 days follow-up were observed in 10.9%, 9.8%, 12.5% and 1.5% respectively. Rates of periprocedural MI after 30 days follow-up were significantly lower when procedural changes were made based on pre-PCI and post-PCI OCT (p=0.029). Other events, such as revascularization and stent thrombosis, rarely occurred.[55]

An RCT by Meneveau et al. (DOCTORS, 2016), including 240 patients with non-ST elevation ACS (NSTE-ACS), reported similar rates of MACE for OCT-optimization vs. CAG-optimization groups after 6-months follow-up. There was 1 death in the OCT-guided group and 1 recurrent MI in each group. No stent thrombosis was observed and no significant difference in the rate of target vessel revascularization (TVR).[57]

Iannaccone et al. (FORMIDABLE, 2017) retrospectively analyzed 270 propensity matched patient pairs with ACS, comparing OCT-guided PCI with CAG-guided PCI. After a mean follow-up of 700 days no differences in MI (6% vs. 6%, p=0.86) were observed. MACE (11% vs. 16%, p=0.06), TVR (2% vs. 4%, p=0.15) and stent thrombosis (0% vs. 2.7%, p=0.26) were numerically lower for OCT, but not significant.[80]

An RCT by Kubo et al. (OPINION, 2017) aimed to demonstrate non-inferiority of OCT-guided PCI compared with IVUS-guidance in terms of clinical outcome. The primary outcome was target vessel failure (TVF), defined as a composite of cardiac death, target-vessel related MI and ischemia-driven TVR. Secondary outcomes were cardiac death, MI, vessel revascularization, lesion revascularization, MACE, stent thrombosis, restenosis, stroke and CIN. In total, 791 patients were analyzed in a per-protocol analysis. Within 12 months, TVF was observed in 21 patients (5.2%) in the OCT-guided group vs. 19 patients (4.9%) in the IVUS-guided group, p=0.042 for non-inferiority testing. No differences in secondary outcomes were observed. Most noteworthy, no cases of CIN occurred in both groups, although OCT led to a significant higher amount of contrast used during PCI (164±66 mL vs. 138±56 mL).[66]

Jones et al. (Pan-London PCI registry, 2018) analyzed the occurrence of all-cause mortality in a cohort of 87,166 patients who received PCI between 2005 and 2015. OCT was used in 1,149 patients, IVUS in 10,971 patients and CAG alone in 75,046 patients. A significant difference in mortality was found after a median follow-up of 4.8 years: 7.7% vs. 12.2% vs. 15.7% (p<0.0001), respectively. This difference was observed for both elective as ACS subgroups. This difference persisted for OCT vs. CAG after multivariate Cox analysis and propensity score matching. No differences were found between matched OCT and IVUS cohorts.[79]

Currently two large RCTs are initiated to demonstrate the superiority of OCT-guided stent implantation compared to CAG-guided stenting in terms of MACE after two years follow-up. The ILUMIEN IV trial is a multi-center RCT in 125 countries across the globe.[81] They aim to include 3,656 patients. The first results are expected mid-2021, while the estimated completion date is mid-2022. The OCTOBER trial is a European RCT which aims to demonstrate the superiority of OCT-guided stenting in bifurcations lesions.[82] They aim to include 1200 patients. The first results are expected in May 2021.

2.9 Indications

In a web-based survey among 1,105 interventional cardiologists, stent optimization (88.5%), preprocedural strategy guidance (79.6%) and left-main interventions (77.0%) were the main indications for ICI. High costs (65.9%) and prolongation of the procedure (35.0%) were mentioned as the main factors limiting the use of ICI.[25]

A recent consensus document by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) appraised current evidence on clinical indications for ICI.[61] Pre-PCI strategy guidance and stent optimization are the main clinical applications of both OCT and IVUS.[17, 25] Patients with ACS and complex lesions, including left-main, bifurcation, chronic total occlusion (CTO) and long lesions, benefit the most from ICI regarding all-cause mortality and MACE.[24, 69] Two RCTs showed that OCT is non-inferior to IVUS regarding post-optimization results and clinical outcomes.[16, 66] The expert consensus group stated that IVUS and OCT are equivalent and both superior to CAG-guidance. However, an extensive RCT that addresses

superiority of OCT-guidance in terms of clinical outcome is currently still missing. Therefore, the benefits and limitations of both techniques as mentioned earlier (*see Technological Implications*) should be considered carefully when selecting patients.

OCT has a limited penetration depth, especially in lipid-rich plaques. In contrast, calcified plaques can be visualized well with OCT, whereas IVUS is not capable of penetrating calcified plaques. Therefore, IVUS should be preferred for assessing plaque burden and vessel size in patients presenting with lipid rich plaques, whereas OCT should be preferred for assessing calcified plaques. This is especially relevant in a research setting, as in clinical practice you might not know what type of plaque is present before assessment with ICI. In clinical practice IVUS is mostly indicated for assessing ostial lesions of the left-main. OCT is not suitable in left-main lesions, due to the need for blood clearance. In addition, IVUS can be considered in patients presenting with CTO lesions after opening the vessel, as blood clearance by contrast injections may be challenging in these patients. In patients with renal dysfunction, IVUS is recommended as no contrast injections are required. OCT has a much higher resolution compared with IVUS and should therefore be considered for lumen assessment and stent related morphology, such as thrombosis, restenosis, edge dissections, expansion and malapposition.[61] Interpretation of small abnormalities should be considered carefully, as the clinical impact of such abnormalities is unknown.[35]

Prati et al. (2010) mentioned that CAG for suspected CAD results in normal angiograms in approximately 10 to 15% of the patients.[33] Yamamoto et al. (2019) found abnormal OCT findings in approximately 25% of the patients presenting insignificant lesions by CAG.[83] IVUS and OCT can both confirm the findings by CAG or indicate the subclinical lesion formation, resulting in an optimal therapeutic strategy for primary prevention. In general, ICI should be considered for the evaluation of intermediate stenoses and ambiguous lesions. Especially in cases of uncertain severity, very short lesions, pre-aneurysmal or post-aneurysmal lesions, ostial or left-main stenoses, branching sites, sites with focal spasm or angiographically hazy lesions. OCT should not be performed in cases where the expected plaque thickness exceeds the penetration depth.[33]

2.10 Discussion

With this review, the clinical applications of OCT in patients with CAD were identified. OCT stenting optimization criteria were described. Both pre-PCI as post-PCI OCT affected physician decision making. Pre-PCI OCT mainly affected the choice of stent length and stent diameter in patients with complex lesions. Post-PCI OCT resulted in post-procedural changes in 27% to 52.2% of the lesions. Post-procedural changes were mainly based on stent malapposition, under-expansion or edge dissections and resulted in additional stent deployment, post-dilatation or both. Stent expansion, stent apposition, distal stent edge dissections and reference lumen areas seem to be the most important stent optimization criteria for both decision making as reducing the risk of adverse events during follow-up. In general, the incidence of procedural complications is low and not different from IVUS-guided or CAG-guided stenting. Also, clinical outcomes are comparable between OCT-guidance and IVUS-guidance. Both OCT and IVUS result in favorable clinical outcomes compared with CAG-guidance alone. OCT-guided PCI improved strut coverage and stent apposition, and reduced tissue protrusions compared with CAG-guidance only. OCT was non-inferior, but not superior,

to IVUS-guidance. There is no consensus about whether OCT-guidance or IVUS-guidance results in better stent expansion.

OCT results in a higher resolution than IVUS at the cost of a lower penetration depth. The penetration depth of OCT is an important disadvantage of OCT. Large lipid-rich plaques disable the ability to image the vessel border with OCT, due to signal attenuation. However, lumen dimensions can still be assessed. In addition, the presence of red thrombus results in signal-free shadowing, complicating image interpretation by OCT. The need for a contrast agent and the potential risk of CIN is another drawback of OCT. However, multiple OCT studies have shown low risks of CIN in patients treated with OCT. Thus, OCT can reveal more detail, where IVUS provides more insight in deeper layers of the coronary arteries. However, small abnormalities should be interpreted carefully. OCT and IVUS are complementary and should be considered depended on the case characteristics.[53, 84]

The number of PCI is rapidly increasing compared to surgical procedures.[8] Nowadays, PCI are increasingly performed in more complex lesions and multivessel coronary disease. In addition, patients tend to be older with more calcifications. For example, many patients assigned to undergo transcatheter aortic valve implantation (TAVI) need prior revascularization. Due to the increasing complexity of the patient population and the limitations of CAG, ICI is becoming increasingly important. Hospitals with a large number of these complex patient cases potentially benefit the most from ICI. The patient population which should be assessed with ICI comprises patients with intermediate, complex or ambiguous lesions. There is an unmistakable role for IVUS in left-main lesions and in patients with large lipid-rich plaques. OCT should especially be considered for lumen assessment and stent related morphology. Especially OCT-guided stent optimization seems to result in better clinical outcomes. Table 2-2 and Figure 2-1 show the situations and considerations in which ICI should be considered.

For some years, there is discussion about the influence of gender on CAD. Men more frequently develop the disease and earlier in life. The incidence of CAD has been relatively low before the menopause, thereafter it increases rapidly. Munnur et al. (2016) reviewed current literature on various subgroups and provided an overview of differences in clinical manifestations between genders.[85] Differences are especially seen in patients under the age of 65, whereafter plaque characteristics become more similar. In addition, women seem to benefit more from lipid-lowering therapy, in terms of plaque regression.[86, 87] Although differences in plaque characteristics exist between men and women, the occurrence of MACE seems similar.[88] As ICI provides more insight in plaque characteristics it should be considered, regardless of gender. In addition, ICI is an essential tool when conducting research into CAD morphology in relation to gender and patient outcome.

2.11 Future Directions

In anticipation of the ILUMIEN IV trial and the OCTOBER trial, OCT is expected to improve clinical outcomes. However, it is still unknown which patients benefit the most from ICI. Further research should focus on which patients benefit the most from ICI, ideally differentiating between OCT and IVUS. Utilizing large datasets might support researchers. Luckily, large datasets of CAG and laboratory data already exist. New data is stored each day during treatment of patients with CAD. In addition, an increasing amount of ICI data is acquired. Such datasets might be used in the future for all kinds of research purposes.

***Table 2-2**. Situations where ICI should be considered. (#) denotes to Figure 2-1.*

Situation	Rationale
Pre-PCI stent sizing (1)	Both OCT and IVUS can be considered to determine the appropriate stent size. However, OCT provides a higher resolution which may result in a more accurate size. This is especially important in complex lesions or lesions with uncertain morphology.
Pre-PCI identification of exact deployment site (1)	Both OCT and IVUS can be considered to determine the deployment site. However, OCT provides a higher resolution which may result in a better determination of the most appropriate landing zone.
Pre-PCI lesion characterization (1)	OCT better distinguishes between various types of plaques and lesion characteristics compared to IVUS.
Ostial left-main lesion assessment and guidance (2)	Only IVUS should be considered, as blood clearance, needed for OCT, may be challenging, if not impossible.
Uncertainty about severity or composition of lesions (3)	Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) seems to be the most appropriate technique for assessing lesion severity. However, both OCT and IVUS can provide insight in composition of lesions and may result in a different stenting strategy.
Bifurcation lesions assessment and guidance (4)	OCT might support bifurcation guidance by assessment of plaque composition and distribution, stent sizing and deployment sites and positioning of the re-crossing wire. An RCT by Holm et al. (OCTOBER, 2018) comparing clinical outcomes after OCT-guidance compared with CAG-guidance in bifurcation lesions is currently running.[82]
Post-PCI stent assessment and optimization (5)	OCT provides detailed insight in how the stent is positioned inside the coronary artery (apposition, expansion and edge-dissections). Optimization may result in improved clinical outcomes.
Assessment of stent failure (5)	OCT provides detailed insight in mechanisms associated with stent failure (thrombosis, in-stent restenosis, malapposition, under-expansion, edge-dissections, tissue-protrusions).
Patients with impaired kidney function	Only IVUS should be considered, as contrast injections are needed with OCT.

Abbreviations: CAG, coronary angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; RCT, randomized controlled trial.

Although speculative, ICI data might contribute to the development and training of prediction models, such as machine learning algorithms, to assess which patients benefit the most from ICI or to support physicians in deciding whether lesions should be stented or not. OCT could be more suitable for the development of such models, as OCT provides much higher resolutions than IVUS. Multiple studies already showed the potential of automatic interpretation of OCT images.[89-91] Other applications of OCT data might be in the further optimization of stent design. OCT can help to provide insight in the effects of different stent designs on in-stent restenosis or thrombosis. To conclude, the added value of OCT, in comparison with IVUS, probably lies especially in the optimization of PCI, both in a clinical as a research setting.

2.12 Conclusion

In conclusion, OCT is a safe procedure with few reported procedural complications. In general, OCT-guidance seems to contribute to favorable clinical outcomes compared with CAG-guidance only. However, in general, OCT-guidance results in similar clinical outcomes as with IVUS-guidance. Stent expansion, stent apposition, distal stent edge dissections and reference lumen areas seem to be the most important stent optimization criteria for both decision making and reducing the risk of adverse events during follow-up. OCT could be considered for lumen assessment and stent related morphology in more complex cases in which CAG interpretation remains uncertain. Since OCT and IVUS have distinct characteristics, these techniques are complementary and should be considered carefully for each patient case based on the benefits and limitations of both techniques.

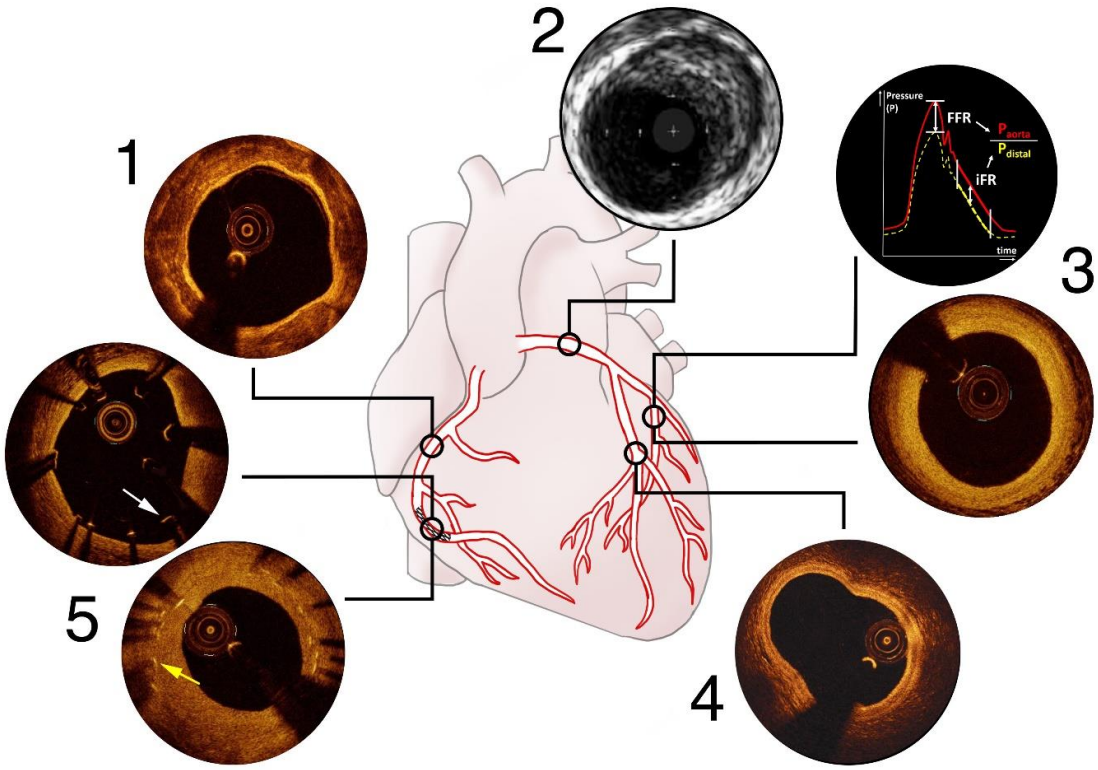

***Figure 2-1**. Summarizing figure for situations where intracoronary imaging should be considered (Table 2-2). (1) OCT or IVUS for pre-PCI stent sizing and identification of deployment site, OCT for lesion characterization: OCT image showing severe calcifications. (2) IVUS for ostial left-main lesion assessment and guidance: IVUS image showing left-main plaque. (3) Functional measurement (FFR/iFR) for uncertainty about severity of distal lesions and OCT for composition: iFR/FFR and OCT image showing intimal thickening. (4) OCT for bifurcation lesion assessment and guidance: OCT image showing a bifurcation with high resolution. (5) OCT for post-PCI stent assessment and optimization and assessment of stent failure: OCT images demonstrating malapposition (white arrow shows an intraluminal stent strut) and in-stent restenosis (yellow arrow shows a stent strut covered by neointima hyperplasia).*

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Tables and Figures

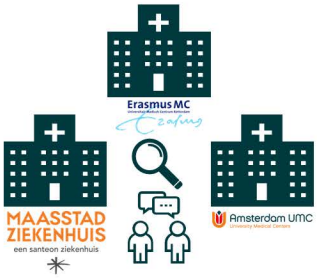
All Tables and Figures are original and have been produced by the authors for this particular publication. Figure 1 was designed by C.L.H. Broekmeulen in favor of the authors. OCT images were provided by Abbott Medical Nederland B.V.

3. THESIS FEASIBILITY STUDY: A STRUCTURED IMPLEMENTATION OF OPTICAL COHERENCE TOMOGRAPHY

3.1 Summary

Methods

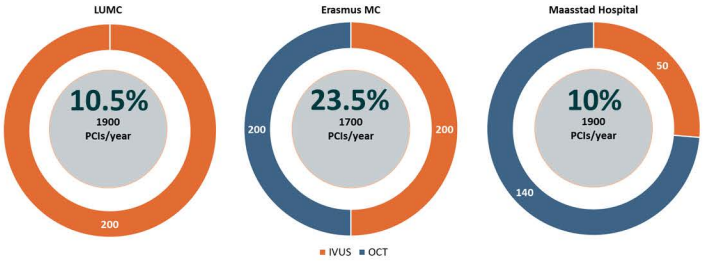
IVUS vs. non-IVUS



Site Visits

Survey

Results



PCI Characteristics

63 – 68 years

3 : 1

IVUS Procedures

PCI in medical history
Elective procedures
Fluor times ↑

OCT Applications

Strategy guidance
Stent optimization
Stent failure

OCT or IVUS?

90% operator preference
IVUS: left-main lesions
OCT: stent optimization and stent failure

Personal Opinions

- ✓ ICI is an essential tool
- ✓ OCT and IVUS are complementary techniques
- ✓ OCT is desired in addition to IVUS
- ✓ Automated pullback is preferred, especially in a research setting

Major Benefits

Better outcomes, assessment of vessel/plaque morphology, reliable measurements

Major Drawbacks

Time, patient risks, costs, association with prognosis is not always clear

Considerations for OCT Implementation

Data management: raw OCT data needed for research purposes | user-friendly data storage
Research program: getting experienced | literature is scarce
Adequate training: in-depth clinical training | clear instructions and protocols | benefits and pitfalls of IVUS and OCT

3.2 Introduction

The underlying purpose of the thesis feasibility study was to obtain input for the implementation of OCT, eventually resulting in a structured implementation supported by the department. This input was acquired by visiting other hospitals (site visits) experienced in the field of ICI, obtaining input from local cathlab employees (LUMC), and evaluation of the patient population with CAD treated with PCI at the LUMC.

Three goals were defined:

(1) Evaluation of the characteristics of the patient population with CAD treated with PCI at the LUMC;
(2) Acquire insights into OCT (ICI) implementations and clinical practice regarding OCT (ICI) at other hospitals;
(3) Evaluate the views on ICI within the department of interventional cardiology at the LUMC.

3.3 Overview of the Methods, Results and Discussions

Each goal was achieved by a different approach. This paragraph is therefore divided into three sections, one section for each goal as described in the Introduction.

3.3.1 The LUMC Patient Population

Methods

In order to evaluate the patient population with CAD treated at the LUMC, data of PCI and diagnostic CAG procedures were extracted from the electronic patient files (EPD-V). All procedures between the first of January 2018 and the twentieth of December 2019 were included. In total, 3,932 procedures were extracted from EPD-V. However, 324 patients received two or three treatments. When these additional treatments occurred within 31 days after the first treatment, the procedure was considered to be one procedure. These procedures were therefore merged into one record. The indication of the first procedure was leading. The merged record was considered to be a PCI when one of the procedures was registered as such. In total, 135 procedures were excluded after merging, resulting in 179 patients occurring multiple times in the dataset. Eleven patients were excluded based on the uncertainty whether IVUS was used or not. Five patients were excluded as they were younger than 18 years old. In total, 3781 procedures were included in this study (Figure 3-1).

As can be seen in Figure 3-1, the procedures were divided into four groups: (1) PCI without IVUS, (2) PCI with IVUS, (3) CAG without IVUS and (4) CAG with IVUS. This division allowed for a comparison between PCI groups, CAG groups and an overall comparison between IVUS and non-IVUS procedures. We were especially interested in the difference in patient characteristics and procedure characteristics between PCI groups, as this is the main application of ICI according to the literature (Chapter 2).

Continuous variables were described by median and quartile ranges (IQR) as all continuous data were not normally distributed. Categorical variables were described by frequencies (N) and percentages (%). The Mann-Whitney U test was used to compare continuous variables between groups and the Chi-square test was used to compare the distributions of categorical data between groups. For variables with an expected cell count less than 5, the Fisher's Exact test was used. Unknown data were excluded from statistical testing. A p-value <0.05 was considered statistically significant.

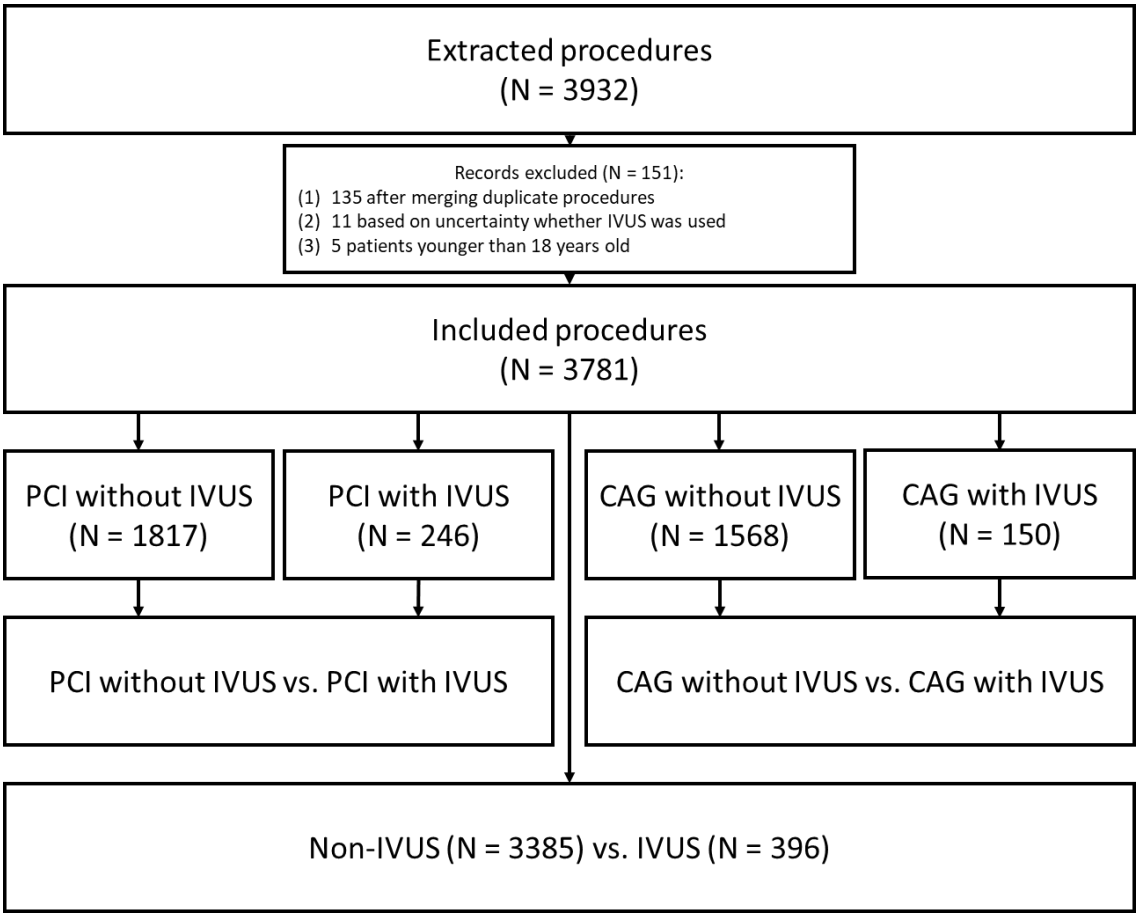


***Figure 3-1**. Flowchart illustrating the inclusion process and the different comparisons.*

Results

Table 3-1 shows the differences between PCI groups. In total, 1817 PCI were performed without IVUS and 246 PCI with IVUS (11.9%). There were no significant differences in age, gender, or BMI distributions. The age and gender distributions were in line with the studies included in the literature review (Chapter 2). PCI in the medical history was more prevalent in the IVUS group (32.5% vs. 26.5%, p=0.018). This was expected as stent failure was one of the indications for ICI according to the literature review and site visits (Paragraph 3.3.2). IVUS was used more frequently during elective procedures and less frequently during urgent procedures (p<0.001). Also, more stents were placed during IVUS procedures (2 (IQR: 1-4) vs. 2 (IQR: 1-3), p=0.003). Although few complications were reported for both groups, the number of reported complications were significantly higher in the IVUS group (9.8% vs. 3.7%, p<0.001). However, most complications were either dissections (13) or perforations (2) related to wire positioning or dilatations in heavily calcified lesions or chronic total occlusions (CTO). Only 1 dissection was reported as related to IVUS catheter positioning. In the cases where complications occurred, IVUS was mainly used to assess the dissection, the vascular wall prior to stenting or the final stenting result. Other complications were also not IVUS related. These findings regarding complications might indicate that IVUS was used in more complex lesions. This was also indicated in the literature. The total amount of fluor time was significantly higher in the IVUS group (18 (IQR: 11-29) vs. 11 (IQR: 7-19) min, p<0.001). Although it seems that there was a significant difference in the presence of heart failure in the medical history, in most patient records this field was not completed.

***Table 3-1**. Characteristics of PCI with and without IVUS. Bold p-values indicate significant differences between groups.*

Characteristics	PCI without IVUS (N=1817)	PCI with IVUS (N=246)	p-value
Age [years], median (IQR)	68 (58-76)	66 (57-75)	0.125
Gender, N (%)			0.132
Male	1290 (71.0)	186 (75.6)	
Female	527 (29.0)	60 (24.4)	
BMI [kg/m²], median (IQR)	26.7 (24.3-29.5)	26.9 (24.5-29.4)	0.799
Medical history, N (%)			
Heart failure	90 (5.0)	4 (1.6)	**0.020**
Coronary artery bypass grafting	137 (7.5)	17 (6.9)	0.810
Previous PCI	482 (26.5)	80 (32.5)	**0.018**
Myocardial infarction	436 (24.0)	62 (25.2)	0.403
Chronic kidney failure	100 (5.5)	16 (6.5)	0.576
Dialysis	17 (0.9)	4 (1.6)	0.295
Smoking, N (%)			0.055
Current smoker	288 (15.9)	27 (11.0)	
Used to smoke	487 (26.8)	66 (26.8)	
Never smoked	337 (18.5)	57 (23.2)	
Smoking unknown	705 (38.8)	96 (39.0)	
Risk factors, N (%)			
Hypertension	634 (34.9)	70 (28.5)	0.079
Diabetes	337 (18.5)	42 (17.1)	0.988
Hypercholesterolemia	497 (27.4)	57 (23.2)	0.610
PCI status, N (%)			**<0.001**
Urgent	837 (46.1)	80 (32.5)	
Elective	903 (49.7)	150 (61.0)	
Unknown	77 (4.2)	16 (6.5)	
PCI indication, N (%)			**<0.001**
Elective	634 (34.9)	120 (48.8)	
STEMI	585 (32.2)	53 (21.5)	
NSTEMI	244 (13.4)	25 (10.2)	
Post ACS	185 (10.2)	22 (8.9)	
Unstable AP	80 (4.4)	10 (4.1)	
Unknown/Other	89 (4.8)	16 (6.6)	
Number of stents, median (IQR)	2 (1-3)	2 (1-4)	**0.003**
Complications, N (%)			**<0.001**
Yes	67 (3.7)	24 (9.8)	
No	1595 (87.8)	201 (81.7)	
Unknown	155 (8.5)	21 (8.5)	
Total fluor time [min], median (IQR)	11 (7-19)	18 (11-29)	**<0.001**

Abbreviations: *ACS, acute coronary syndrome; AP, angina pectoris; IQR, interquartile range; IVUS, intravascular ultrasound; (N)STEMI, (non)-ST-elevation myocardial infarction; PCI, percutaneous intervention.*

Comparisons between the CAG groups resulted in similar results. IVUS was less frequently used during CAG (8.7%) and patients were slightly younger than in the PCI groups. Remarkably, IVUS was used more frequently in patients with a medical history of MI (36.7% vs. 15.2%,

p<0.001). This can be explained by the fact that MI is usually treated with PCI. CAG with IVUS might be used to access post-stenting results during follow-up in MI patients with recurring symptoms. In contrast to the PCI groups, IVUS was more frequently used during urgent procedures. This might be explained by the higher proportion of previous PCI in medical history. IVUS might be used to assess in-stent restenosis in those patients. However, the CAG status (elective or urgent) was unknown in more than 50% of the procedures. The comparison between the CAG groups and the overall comparison between IVUS and non-IVUS procedures are reported in Appendix F.

Discussion

In conclusion, IVUS was used in approximately 10% of the PCI or CAG procedures. In general, IVUS is more often used during elective procedures and less frequently during urgent procedures. Fluor time increased when IVUS was used. Complications were more prevalent in IVUS PCI. This was mainly caused by dissections due to wire positioning or dilatation in heavily calcified lesions or chronic total occlusions. In those cases, IVUS was used to assess the dissection, the vascular wall prior to stenting, or the final stenting result. Patients who underwent IVUS tend to be slightly younger and were more often male compared to the patients who did not undergo IVUS.

Not all characteristics were available for all procedures. For example, out of 3781 procedures, for 814 procedures it was unknown whether the patients had heart failure in their medical history. These missing data were not taken into account during statistical testing. Therefore, the results might show a distorted view. Furthermore, each procedure was tested twice, namely in a comparison between non-IVUS and IVUS for PCI or CAG and in a general comparison between non-IVUS and IVUS for all procedures combined. Therefore, a correction for multiple testing (e.g. Bonferroni correction) would be appropriate with a resulting α of 0.003. However, such a correction avoids type I errors (false positives) at the expense of type II errors (false negatives). As we were interested in all characteristics that might be associated with the use of IVUS, we decided not to perform a correction for multiple testing.

3.3.2 Intracoronary Imaging Implementations and Clinical Practices at Other Hospitals

Methods

The cathlab of the Erasmus Medical Center (Erasmus MC), Maasstad Hospital, and Amsterdam University Medical Center location AMC (AMC) were visited. In addition, OCT trainings given by Abbott (OCT manufacturer) were attended at the Maasstad Hospital and the AMC. Information was obtained by observations, and discussions with interventional cardiologists and cathlab technicians at the different locations. Findings were summarized in appropriate tables and figures.

We were especially interested in:

(1) The number of procedures;
(2) The field of application of ICI;
(3) Image interpretation;
(4) Clinical and data management processes;
(5) OCT training.

Results

Figure 3-2 shows the average number of CAG and PCI at the Erasmus Medical Center (Erasmus MC) and Maasstad Hospital according to local cardiologists. In addition, the number of ICI procedures are presented. From the first of January up till the 17th of October 2019, 349 patients underwent PCI with either IVUS or OCT at the Erasmus MC. IVUS was used in 205

cases, whereas OCT was used in 152 cases. At the Erasmus MC, ICI was used in more than 20% of the cases. In contrast, at the Maasstad Hospital, OCT was used more often than IVUS. ICI was used in approximately 10% of the cases at the Maasstad Hospital. This is consistent with the number of ICI procedures at the LUMC.

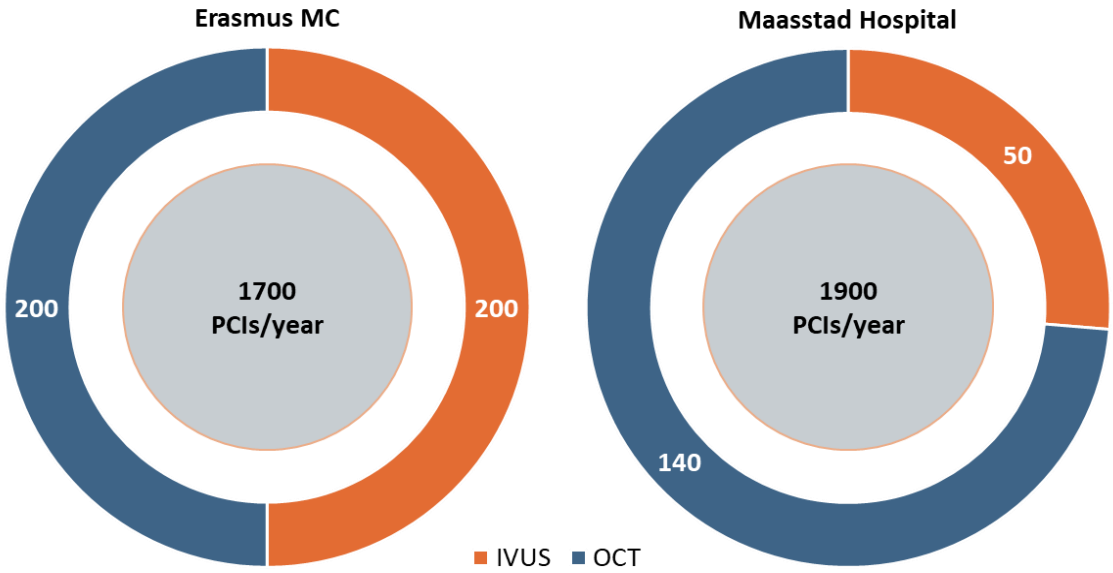


Figure 3-2. ICI in numbers at the Erasmus MC and the Maasstad Hospital. Blue indicates OCT. Orange indicates IVUS.

Table 3-2 shows the field of application of OCT at the Erasmus MC, Maasstad Hospital and Isala Zwolle according to local cardiologists and cathlab technicians. The applications of OCT at the Erasmus MC and Maasstad Hospital were based on site visits at both cathlabs, whereas the applications of OCT at Isala Zwolle were based on discussions with cathlab technicians present at an OCT training. Most notable are the numerous applications at the Erasmus MC compared to the other centers. These differences are probably caused by the extensive research programs at the Erasmus MC regarding ICI. No clear indications for OCT were mentioned by cardiologists at the AMC.

***Table 3-2**. The field of application regarding OCT at other hospitals.*

Erasmus MC	Maasstad Hospital	Isala Zwolle
Assessment of stent apposition and expansion	Assessment of stent apposition and expansion	Assessment of stent apposition and expansion
Stent sizing	Stent sizing	Stent sizing
Assessment of stent failure	Doubt about the landing zone	Doubt about the landing zone
Degree of stenosis		
Degree of calcification		
Thrombus visualization		
Doubt about the culprit		

Abbreviations: OCT, optical coherence tomography.

Remarkably, the choice between OCT and IVUS at the Erasmus MC is for 90% based on operator preferences. Nevertheless, according to Joost Daemen, there are some clear indications where you should use either IVUS or OCT. OCT is superior in assessment of the PCI result and thrombus visualization, and should therefore be considered for stent optimization and assessment of stent failure. IVUS is superior in the assessment of ostial left-main lesions. In those lesions it is impossible to achieve enough blood clearance for optimal OCT image quality. To the question whether you should use ICI or a functional test (i.e. fractional flow

reserve (FFR) or instantaneous wave-free ratio (iFR)) to assess the significance of stenoses, Joost Daemen (interventional cardiologist) responded that functional tests help to decide *what* should be treated, whereas ICI can be used to determine *how* lesions should be treated.

During the site visits at the cathlab of the Erasmus MC, the processes around ICI were observed and discussed with Joost Daemen and Jurgen Ligthart (senior technician invasive imaging). Two processes were identified, namely the clinical process and the data management process. Three different kind of professionals play a role in these processes. The interventional cardiologists and the cathlab nurses are inside the room and involved with direct patient care. In addition, five imaging technicians are employed, which is unique in the Netherlands. They are involved in operating the different imaging modalities, image interpretation, supporting researchers and maintaining a database concerning ICI. Figure 3-3 shows a schematic overview of the clinical process at the Erasmus MC. Besides the specific role of the imaging technicians, the clinical processes around ICI at the Maasstad Hospital and AMC were similar to Erasmus MC.

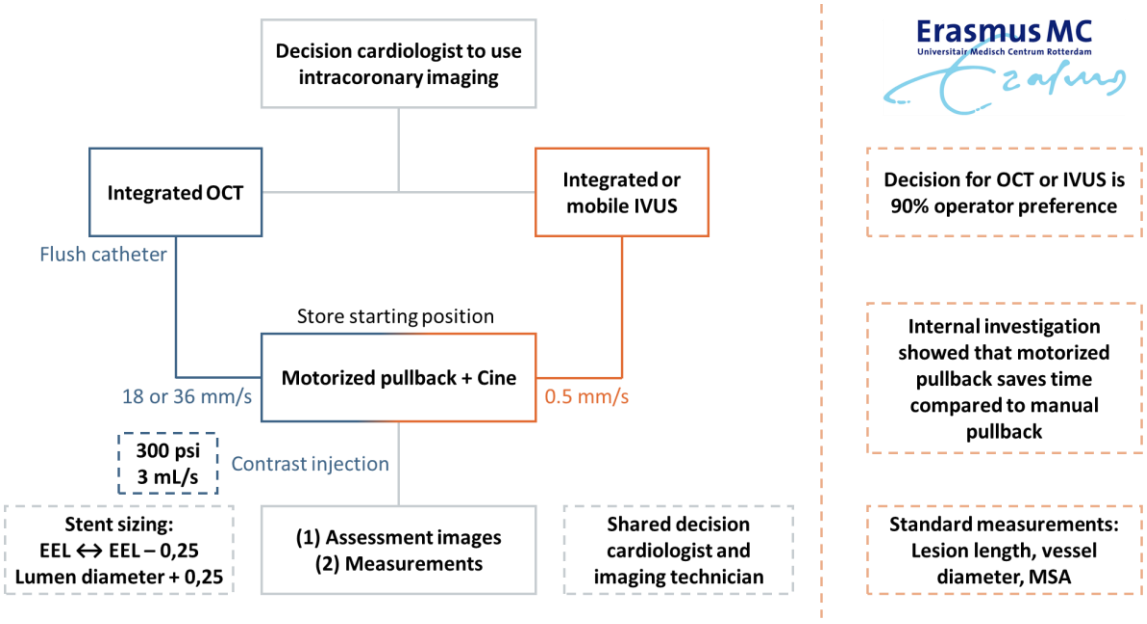


***Figure 3-3**. Clinical process regarding ICI at the Erasmus MC. Blue indicates processes related to OCT. Orange indicates processes related to IVUS. Abbreviations: EEL, external elastic lamina; MSA, minimal stent area; ICI, intracoronary imaging; IVUS, intravascular ultrasound; OCT, optical coherence tomography.*

Both the Maasstad Hospital and Erasmus MC use automated contrast injections during OCT acquisition. In contrast, at Isala Zwolle mainly manual contrast injections are used. At the AMC both automated and manual contrast injections are used depending on operator preferences.

Figure 3-4 shows a schematic overview of the data management processes at the Erasmus MC. When ICI is used, the imaging technicians fill out a form with the details about the procedure (i.e. patient characteristics, imaging modality, vessel, which wire was used, which device, pullback speed and the amount of contrast injected). An example form is provided in Appendix G. The imaging technician exports the data over the network (IVUS) to the picture archiving and communication server (PACS) or manually to an external USB-drive (OCT). Jurgen Ligthart then stores those images in an in-house developed database and annotates the images based on the forms and the images. In contrast to the Erasmus MC, the AMC stores their data on external drives (DVDs). These differences between exporting IVUS and OCT data is caused by the necessity to store the raw OCT data for research purposes. Without the raw data it is only

possible to perform standard measurements. The raw OCT data can not be transferred over the network.

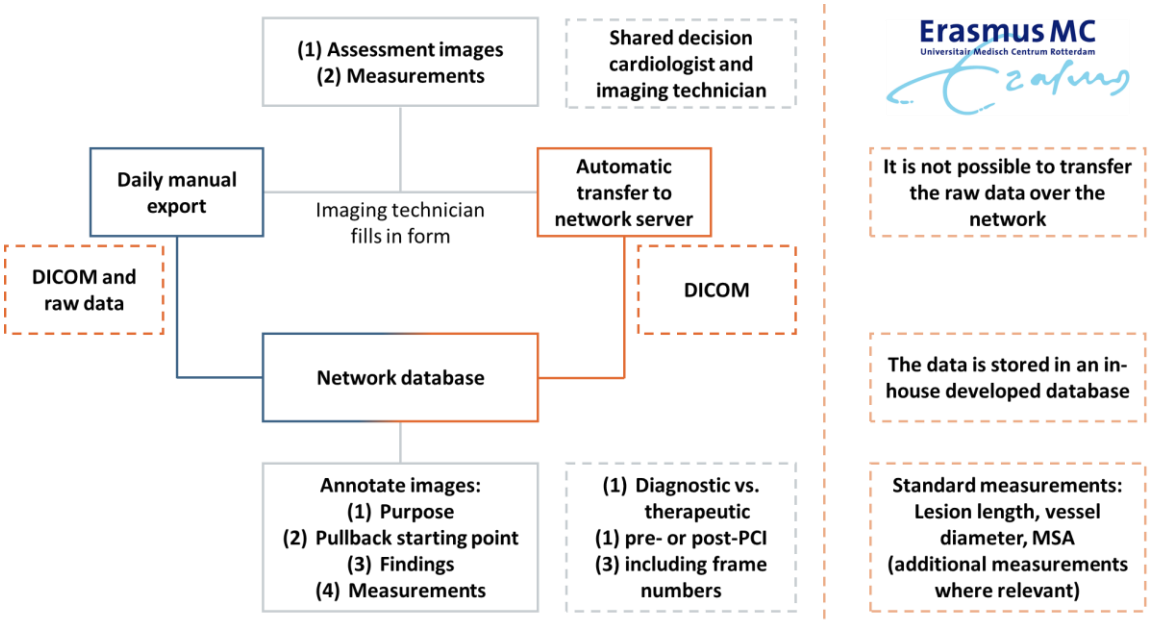


***Figure 3-4**. Data management process regarding ICI at the Erasmus MC. Blue indicates processes related to OCT. Orange indicates processes related to IVUS. Abbreviations: MSA, minimal stent area; PCI, percutaneous intervention; ICI, intracoronary imaging; IVUS, intravascular ultrasound; OCT, optical coherence tomography.*

Two types of OCT training were attended during this project, namely an advanced OCT workshop and a refreshment workshop. The advanced OCT workshop was organized by Abbott in cooperation with the Maasstad Hospital. The workshop was specifically designed for cathlab technicians from different hospitals, who are eager to extend their knowledge about OCT. Figure 3-5 (A) shows the content and learning goals of this training. After hospitals start using OCT, Abbott provides refreshment trainings upon request. The content and learning goals of these refreshment trainings are shown in Figure 3-5 (B). The two types of training overlap considerably. However, the advanced OCT workshop is much more detailed with room for extensive discussions. In addition, participants may bring their own cases up for discussion. The refreshment training consists of a short theoretical slideshow followed by hands-on demo cases and/or support during live cases at the cathlab.

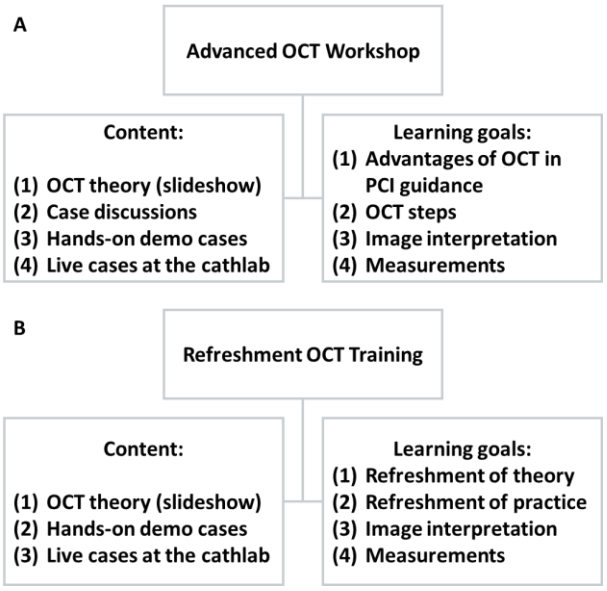


***Figure 3-5**. (A) Overview of the content and learning goals of the Advanced OCT Workshop; (B) Overview of the content and learning goals of the Refreshment OCT Training OCT.*

Before hospitals start with OCT, Abbot also provides an initial training for all interventional cardiologists and cathlab technicians. This training comprises the same elements as the refreshment training. However, more time is reserved to elaborate on each aspect of the training. In addition, interventional cardiologists and cathlab technicians are trained in how to

operate the OCT system. The standard and refreshment trainings are part of the service contract and are provided at hospital locations.

Discussion

During the site visits the number of ICI procedures, clinical and data processes, indications for ICI and different OCT trainings were identified. Besides the findings reported in this paragraph, the site visits contributed to obtaining knowledge about OCT image interpretation. Furthermore, insight in the practices at other hospitals resulted in some concrete considerations for the implementation of OCT:

(1) It is important to consider data handling, as the raw OCT data cannot be transferred over the network. The raw OCT data is necessary for research purposes.
(2) Indications and preferences for ICI modalities are largely operator dependent. Operators should be well instructed about the benefits and pitfalls of IVUS and OCT to achieve optimal use of ICI. In addition, the department should consider initiating a research program regarding OCT in relation to IVUS as current literature is scarce. This could also enable physicians into getting more experienced with applying ICI in routine clinical practice, and with the benefits and pitfalls of both modalities.
(3) OCT trainings included in the service contract with Abbott should be considered for the training plan.

3.3.3 Intracoronary imaging survey

Methods

To evaluate the views on ICI within the department, a survey was conducted among cathlab technicians and interventional cardiologists at the LUMC. Separate questionnaires were designed for the interventional cardiologists and cathlab technicians (Appendix H and I). The questionnaires were designed in compliance with practical survey guidelines by Dijkstra et al (2014).[92] The survey was carried out as semi-structured personal interviews. All participants were interviewed by the author of this thesis. The participants were asked about: (1) their experience with ICI, (2) their personal views on ICI, (3) the problems they encounter while using ICI, (4) the field of application of ICI and (5) what they think is important to keep in mind during the implementation process. Only the cardiologists were specifically asked about the field of application of ICI. Categorical data were described by frequencies (N). Continuous data were described by both means ± standard deviation (SD), and medians and interquartile ranges (IQR). Answers to open questions were summarized in appropriate tables and figures.

Results

Table 3-3 shows the demographic profile of the questionnaire respondents. In total seven interventional cardiologists and fifteen cathlab technicians were interviewed. As OCT is not yet used at the LUMC, none of the respondents had any experience with OCT.

Figure 3-6 shows the extend of agreement of the interventional cardiologists on statements about ICI. All interventional cardiologists agreed that ICI is an essential tool for interventional cardiology. All cardiologists agreed on the fact that OCT and IVUS are complementary techniques rather than interchangeable. In addition, all cardiologist would like OCT as a novel imaging technique at the LUMC. The need for an automatic contrast injector would resist four out of seven cardiologists from using OCT. This emphasizes the importance of this questionnaire. The clinical process must be structured in such a way that there are no obstacles for using OCT when necessary.

***Table 3-3**. Demographic profile of the survey respondents.*

Characteristics	Values
Respondents, N	
Interventional Cardiologists	7
Cathlab technicians	15
Experience in years	
Interventional Cardiologists	
Mean ± SD	15 ± 9
Median (IQR)	15 (7 - 23.5)
Minimum	3
Maximum	28
Total	107
Cathlab technicians	
Mean ± SD	8 ± 10
Median (IQR)	3 (0.5 - 13.5)
Minimum	0
Maximum	27
Total	116
Number of CAG/PCI per year, N	
Interventional Cardiologists	
< 50	0
> 50 & < 100	0
> 100	7
Cathlab technicians	
< 50	4
> 50 & < 100	6
> 100	5
Number of IVUS per year, N	
Interventional Cardiologists	
< 50	4
> 50 & < 100	3
> 100	0
Cathlab technicians	
< 50	14
> 50 & < 100	0
> 100	1

Abbreviations: CAG, coronary angiography; IQR, interquartile range; IVUS, intravascular ultrasound; SD, standard deviation.

Figure 3-7 shows the responses of cathlab technicians on whether they feel comfortable using ICI and whether they are aware of the purposes and benefits of ICI. One cathlab technician was not always comfortable using ICI and answered this question with both *yes* and *no*. Although all cathlab technicians are aware of the purposes of ICI, two cathlab technicians stated that it is not always clear how patients actually benefit from ICI.

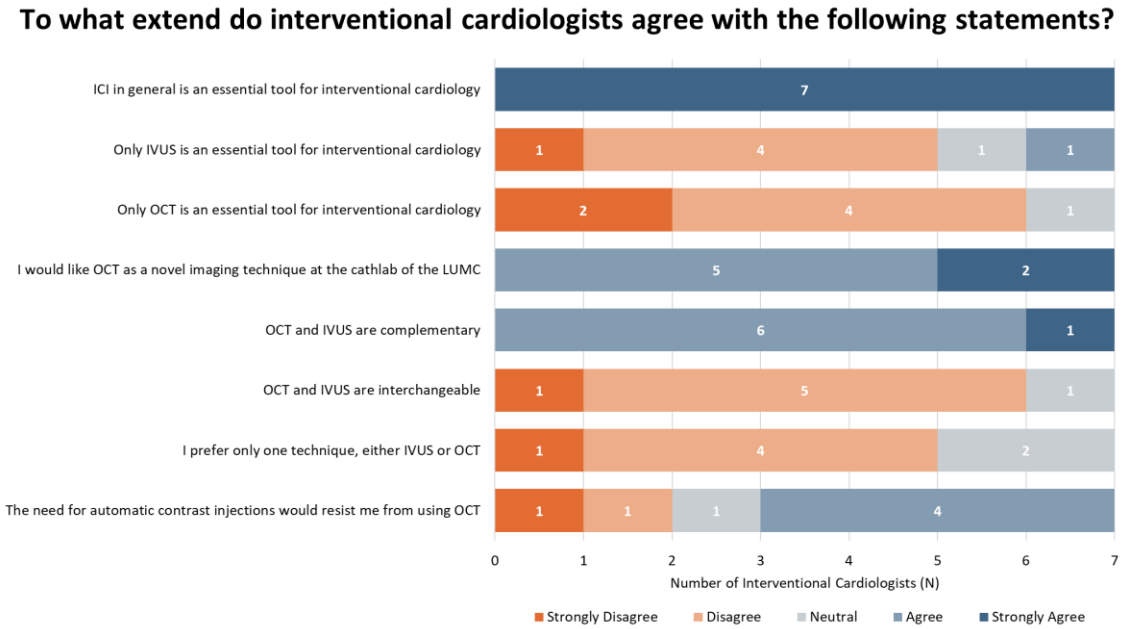


***Figure 3-6**. The extend of agreement of the seven interventional cardiologists on statements regarding ICI.*

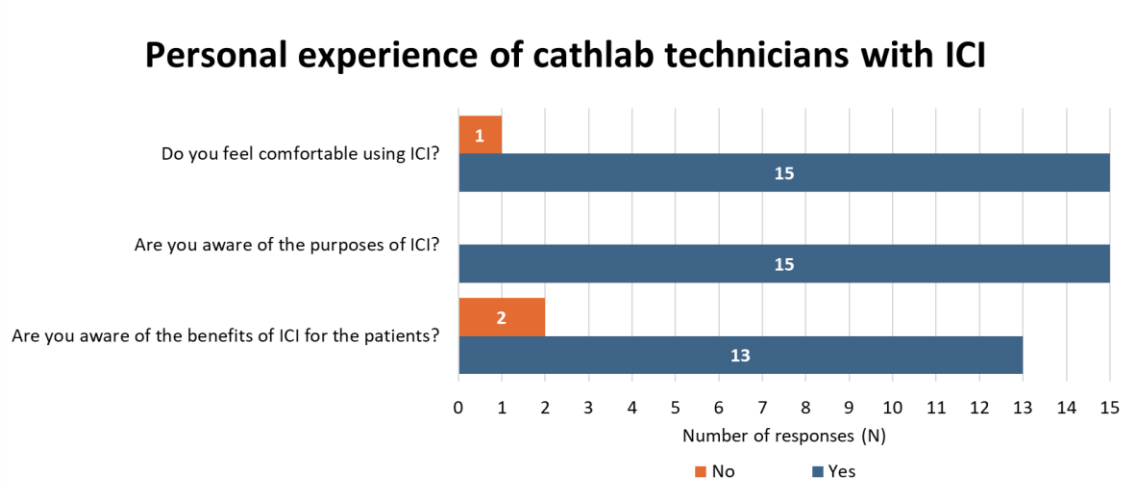


***Figure 3-7**. The personal experience of the fifteen cathlab technicians regarding ICI. One cathlab technician answered the question "Do you feel comfortable using ICI?" with both yes and no.*

All interventional cardiologists were asked how much extra time would be acceptable for using ICI during procedures (Figure 3-8). Responses varied from 3 to 15 minutes. As three cardiologists responded with a time range, the mean extra acceptable time was calculated including only the lower limits or upper limits of the time ranges. The mean extra acceptable time varied from 8 to 10 minutes (SD = 4 minutes). Five out of seven cardiologists found 10 or 15 minutes of extra time acceptable. In addition, the cardiologists were asked which pullback method they prefer (Figure 3-9). Five out of seven cardiologists preferred the automatic pullback method. Four cardiologists commented that an automatic pullback provides more accurate data which can be used for research purposes. One cardiologist commented that the automatic pullback method is only preferred if there is a clear image quality improvement. Another cardiologist stated that the manual pullback method is faster, simpler and results in

less hassle. One cardiologist stated that depending on the purpose you can do both. In conclusion, for research purposes the automatic pullback is required. For clinical purposes both pullback methods are possible. Furthermore, the cardiologists were asked whether they think co-registration between ICI and the angiogram is important. All cardiologists rated co-registration as an important tool. The benefits of co-registration are: time saving, more reliable image fusion and directly knowing where you are in the vessel.

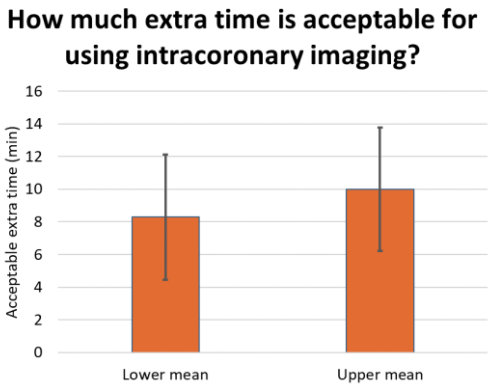


***Figure 3-8**. The acceptable amount of extra time for using ICI during procedures according to the interventional cardiologists.*

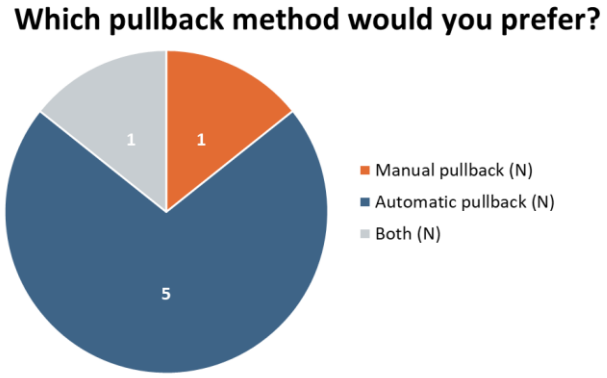


***Figure 3-9**. The preferred pullback method of the interventional cardiologists. Only applies to IVUS.*

Furthermore, the cardiologists were asked about the major benefits and drawbacks of ICI. Table 3-4 provides an overview of the major benefits and drawbacks as mentioned by the cardiologists. All cardiologists mentioned at least one benefit of ICI. Two cardiologists specifically stated that in their opinion there are no major drawbacks of ICI.

Some of the arguments seem to be contradictory. On the one hand a better outcome for patients is mentioned as one of the major benefits, mainly caused by the other benefits of ICI as mentioned in Table 3-4. On the other hand, extra patient risks is frequently mentioned as a major drawback. These risks arise due to the introduction of an extra catheter inside the vessel, the need for extra contrast injections with OCT, and longer fluor times. However, as shown in the literature review (Chapter 2) and the analysis of the LUMC patient population, (Paragraph 3.3.1) these risks are limited and not different from regular treatment guidance by CAG alone.

***Table 3-4**. Major benefits and drawbacks of ICI according to the interventional cardiologists.*

Major benefits	Major drawbacks
Better outcome	Extra time
Higher quality procedures	Extra patient risks
Assessing vessel (wall) morphology and characteristics	Extra costs
Reliable measurements (vessel diameter)	Association with prognosis is not always clear
The ability to determine stent lengths	
Additional information besides angiography alone	
Knowing what you are treating	

The cathlab technicians were asked what they experience as major drawbacks of ICI (i.e. IVUS). Difficult to interpret was most frequently mentioned (n=3). Other drawbacks were mainly associated with the logistics around ICI: extra time (n=2), manual data storage on a DVD (n=2) and the need to enter the patient data before connecting the catheter (n=2). Other drawbacks mentioned by the cathlab technicians were: not being involved in the measurements, difficult

to explain to patients, unable to cross lesions with the IVUS catheter and a higher risk of complications.

The cardiologists were asked to specify the situations where they would rate the use of ICI appropriate (Figure 3-10). For each case, they were asked to specify which modalities (i.e. IVUS, OCT or both) are appropriate. In some cases the cardiologist responded with *don't know*. These responses were added to both categories. For the sake of visualization, stent sizing, stent deployment, stent apposition, stent edge dissections and lesion coverage were combined in the category *optimization of PCI result*. Assessment of plaque erosion, plaque burden, vessel wall pathology, lesion symmetry and thrombus aspect were combined in the category *plaque morphology and composition*. In-stent restenosis and thrombosis were combined in the category *mechanisms of stent failure*. Other applications of ICI, which were only mentioned once, are: measurement of reference diameter, guidance in bifurcation lesions, guidance in CTO lesions after elevation of the occlusion, mechanisms of plaque rupture in patients with ACS and determining the significance of proximal lesions.

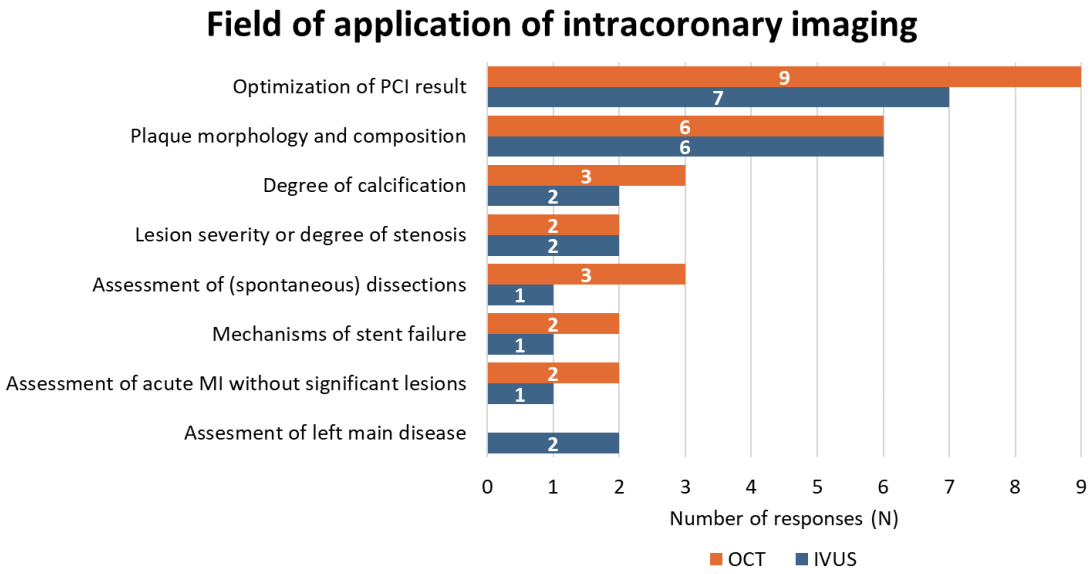


***Figure 3-10**. The field of application of ICI as indicated by the interventional cardiologists.*

Furthermore, the cardiologists were asked to specify which techniques they would rate appropriate in pre-specified situations (Figure 3-11). One cardiologist mentioned that ICI can provide extra information in a lot of cases, but that it is not feasible to use it always. The cardiologists who rated IVUS and OCT as appropriate for guidance in CTO lesions, interpreted this situation as guidance after elevation of the occlusion. One cardiologist mentioned an additional case, namely OCT assessment of stent fracture in patients with ACS or stent failure.

Currently, there is no protocol on when (i.e. in which patients) to use ICI. Each case needs to be assessed individually. Although a strict protocol is not desired, a consensus about the cases where you should consider ICI is preferred. At the moment there is a cathlab protocol on how to use IVUS. Before OCT can be used in clinical practice, such a protocol must be written and published on iProva (quality management system of the LUMC).

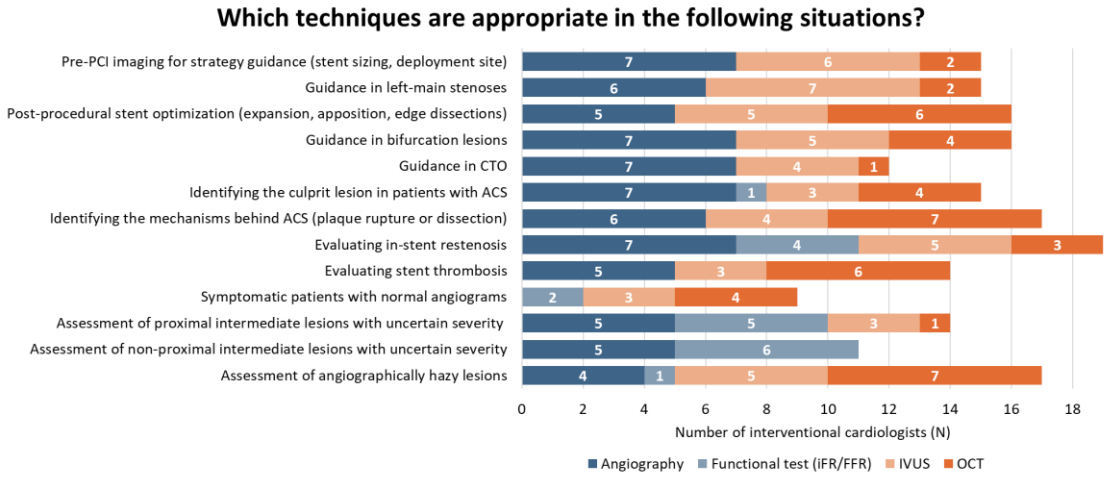


***Figure 3-11**. Techniques rated as appropriate in pre-specified situations. Abbreviations: ACS, acute coronary syndrome; CTO, chronic total occlusions; FFR, functional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention.*

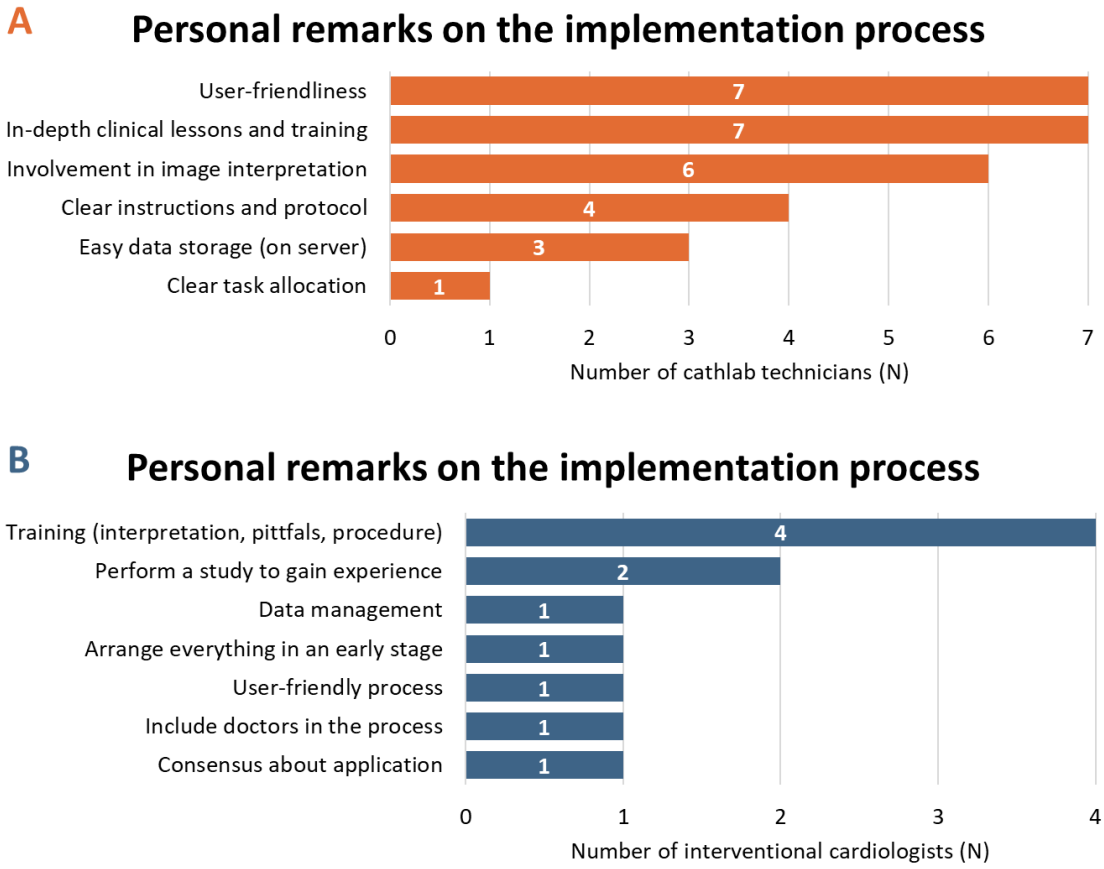


***Figure 3-12**. Personal remarks by the cathlab technicians (A) and the interventional cardiologists (B) for the implementation of OCT.*

All respondents were asked about problems they encounter while working with IVUS. These issues are important to consider for the implementation of OCT. Most respondents rarely experience problems. The main issue for the cardiologists was the inability to cross severe stenoses, which is inherent to the diameter and stiffness of ICI catheters. Cathlab technicians mainly experience technical problems with the IVUS system (Vulcano), catheter, software or server. Especially problems with data storage on external drives (DVDs) are important to consider for the implementation of OCT. Other problems are mainly device specific. Finally, all respondents were asked to give any remarks on what they find important to consider for the implementation of OCT (Figure 3-12). Six cathlab technicians specifically mentioned that they want to be more involved in or learn about the image interpretation to get a better feeling with ICI.

Discussion

In total seven interventional cardiologists and fifteen cathlab technicians were interviewed. All cardiologists agreed that ICI is an essential tool for interventional cardiology. All cardiologists rated OCT and IVUS as complementary, rather than interchangeable. All cardiologists want OCT as a novel imaging technique at the department. The need for automatic contrast injections would resist four cardiologists from using OCT. Manual contrast injections should therefore be considered for OCT. The mean acceptable amount of extra time for ICI was 8 to 10 minutes. Most cardiologists preferred an automatic pullback method, as this results in more accurate interpretable data. Co-registration was rated as important, as it results in a more reliable image fusion and it could save time. Better outcome, higher quality procedures, assessment of vessel wall morphology, and reliable measurements were mentioned as major benefits of ICI. Extra time, patient risks, costs, and the unclear association with prognosis were mentioned as major drawbacks of ICI. Some benefits and drawbacks are in conflict. For example better outcomes and patient risks. Although OCT might improves clinical outcome, per definition there is extra patient risk. Namely, an extra catheter is inserted inside the patients, extra contrast injections are needed and fluor times increase. These extra contrast injections potentially increase the risk of CIN. Cardiologists should always find the balance between added value and patient risks. For example, cardiologists might be less eager to use OCT in patients with an impaired kidney function.

Most cathlab technicians are aware of the purposes of ICI. However, the benefits for the patients are not always clear for the cathlab technicians. Major drawbacks of ICI mentioned by the cathlab technicians were: difficult to interpret, extra time and the need for external data storage (DVD).

Optimization of PCI results and assessment of plaque morphology and composition were mentioned as main applications of OCT. Also assessment of the degree of calcification, assessment of dissections and the mechanisms of stent failure were mentioned as applications of OCT. All these applications were also mentioned for IVUS, but less frequently. Only the assessment of left main disease was exclusively mentioned for IVUS, which is in line with the literature review (Chapter 2).

Angiographically hazy lesions, assessment of plaque rupture and dissections in patients with ACS, stent optimization, and evaluation of stent thrombosis were the applications rated as more appropriate for OCT than IVUS. Guidance in left main stenosis, pre-PCI imaging for strategy guidance, evaluation of in-stent restenosis and guidance in bifurcation lesions were the applications rated as more appropriate for IVUS. However, all cases were rated as appropriate at least once for either IVUS or OCT.

Most respondents rarely experience issues using ICI (i.e. IVUS). Most frequently mentioned issues were technical issues with the catheter, software or system, or the inability to cross severe lesions. For both the cathlab technicians and interventional cardiologists, adequate training was the most important remark for the implementation of OCT.

3.4 General Discussion

The LUMC patient population was evaluated with data from all diagnostic CAG procedures and PCI between the first of January 2018 and the twentieth of December 2019. Site visits were undertaken to acquire insights in OCT implementations and clinical practice at other hospitals. The Erasmus MC, Maasstad Hospital and AMC were visited. In addition, OCT trainings provided by Abbott were attended. To evaluate the views on ICI within the department of interventional cardiology, a survey was conducted among all interventional cardiologists and cathlab technicians. With this survey, the views on both the implementation of OCT and clinical applications were acquired.

3.4.1 Intracoronary Imaging in Clinical Practice

IVUS was used in 8.7% of the diagnostic CAG procedures and in 11.9% of the PCI at the LUMC. This corresponds with respectively 1.4 and 2.5 times a week. On average, IVUS was used 4 times a week. There were no differences in most baseline characteristics. However, IVUS was used more frequently in patients who underwent previous PCI. IVUS was used more often during elective procedures than urgent procedures. Fluor times were longer during IVUS procedures and complications rarely occur.

The number of ICI differed per hospital, varying from 10 to 20% of the total number of procedures. The proportions of IVUS and OCT also differed per hospital based on operator preferences and differences in research programs. OCT is mainly used for strategy guidance (stent sizing and landing zone) and assessment of the final stent result. After assessment of the final result, OCT is used to optimize the result (expansion, apposition and edge dissections). At the Erasmus MC, OCT is used in most cases of stent failure. IVUS is indicated for ostial left-main stenoses as adequate contrast clearance is impossible. For the assessment of whether lesions should be treated or not, a functional test (i.e. FFR or iFR) is most appropriate. The question on how to treat the lesion can be answered with ICI.

3.4.2 Field of Application of Intracoronary Imaging

Table 3-5 summarizes the main areas of application for ICI. Most indication may be assessed by either OCT or IVUS. However, based on the site visits and the ICI survey, for some indications OCT or IVUS may be more appropriate. According to the site visits OCT was most appropriate for strategy guidance (including stent sizing and determining deployment site or landing zone). However, the cardiologists at the LUMC rated IVUS as most appropriate for strategy guidance. This difference might be explained by the fact that the cardiologists at the LUMC have extensive experience with IVUS, whereas they have none to limited experience with OCT. Especially optimization of stent implantation is the core application of OCT. This is in line with the findings in the literature review and European guidelines.[1, 17]

3.4.3 Implementation of OCT

At the Erasmus MC, an extensive data management process is built around ICI. It is important to consider a data management process before implementation of OCT, especially when OCT is considered for research purposes. User-friendliness, in-depth clinical training (interpretation, pitfalls and procedure), clear instruction, protocol and easy data storage are important to consider during the implementation process. Training of cathlab employees is part of the

service contract when OCT is acquired. These trainings should be considered for the training plan.

***Table 3-5**. The field of application of ICI according to the site visits and ICI survey. The first mentioned modality was more frequently rated as appropriate. "Both" indicates that it was not clear which modality is more appropriate.*

Application	Type of imaging
Strategy guidance	Both
Guidance in left-main stenosis	IVUS
Guidance in bifurcation lesions	Both
Assessment of plaque ruptures and dissections	OCT / IVUS
Identifying the culprit lesion in patients with ACS	OCT / IVUS
Plaque morphology and composition	OCT / IVUS
Optimization of the PCI result	OCT / IVUS
Mechanisms of stent failure	OCT / IVUS

Abbreviations: ACS, acute coronary syndrome; ICI, intracoronary imaging; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention.

3.5 Relevance of the Literature Review and Thesis Feasibility Study

Both the literature review and the thesis feasibility study provided extensive insights in current practices and controversies regarding ICI. Such insights are essential before implementation of new medical devices. These insights can be used to carefully execute the implementation, accounting for the interests of all stakeholders as much as possible, and to exploit the full potential of the new device. The ultimate goal is to provide an implementation where everyone is on board (acknowledging the added value of OCT) and enthusiast to use OCT in clinical practice. However, before implementation of new technologies, it can be valuable to assess cost-effectiveness. A cost-effectiveness analysis (CEA) may contribute to the awareness of the added-value of new technologies in terms of costs and effects. A CEA can be a decisive factor whether or not to invest in new technologies. Therefore, the knowledge gained from the literature review and feasibility study were not only used as input for the implementation, but also as input for the CEA (Chapter 4).

4. HEALTH ECONOMIC EVALUATION OF INTROCORONARY IMAGING IN PATIENTS WITH CORONARY ARTERY DISEASE

4.1 Abstract

4.1.1 Introduction

Coronary artery disease (CAD) alone accounts for 20% of the total mortality in Europe, which emphasizes the importance of adequate treatment. Coronary angiography (CAG) is the standard modality for the assessment of coronary stenosis and intraprocedural guidance of percutaneous interventions (PCI). However, CAG has well recognized limitations. Intracoronary imaging (ICI) along with CAG can potentially overcome these limitations. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the main ICI techniques utilized in clinical practice. However, it is still unclear whether OCT-guided PCI results into superior long-term clinical outcomes compared with IVUS-guided PCI. Therefore, the primary aim of this study was to assess cost-effectiveness of IVUS-guided PCI compared with OCT-guided PCI in terms of quality-adjusted life years (QALYs) and costs. The secondary aim was to assess cost-effectiveness of ICI-guidance in comparison with conventional CAG-guidance.

4.1.2 Methods

The patient population was considered to be all patients with single or multivessel disease in an academic medical setting in whom ICI is considered. The patient population was based on a cohort with a median age of 66 years (IQR 57-75) and predominantly male patients treated with elective PCI. The median number of stents implanted was 2 (IQR, 1-4). All stents were considered to be drug eluting stents (DES). A hypothetical cohort of 1,000 patients was considered for each treatment strategy. A deterministic Markov model was constructed to conduct a cost-effectiveness analysis (CEA) with a lifetime horizon. Recent ICI trials and expert input were used to define the model inputs.

4.1.3 Results

The primary analysis indicated that OCT is a dominant treatment option compared with IVUS, gaining 0.059 QALYs on average, saving €282 per patient. IVUS is only the dominant treatment option when optimal input variables for IVUS were compared with least beneficial model inputs for OCT. Probabilistic sensitivity analysis indicated a probability of OCT being the most cost-effective treatment strategy of 65%, regardless of the willingness-to-pay threshold. Similar results were obtained for the secondary outcome. Both IVUS and OCT were dominant treatment options compared with CAG alone, gaining respectively 0.784 and 0.844 QALYs, saving €650 and €933 per patient.

4.1.4 Conclusion

OCT along with CAG is a more cost-effective intracoronary treatment strategy than IVUS along with CAG for patients with CAD. However, the gain in QALYs and reduction in costs are limited. Both IVUS and OCT outperform CAG alone in terms of cost-effectiveness.

4.2 Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Europe. Coronary artery disease (CAD) alone accounts for 20% of the total mortality in Europe, which emphasizes the importance of adequate treatment.[6, 7] Treatment of patients with CAD exists of lifestyle changes on the one hand and optimal medical treatment (OMT) on the other hand. In addition, invasive treatment such as percutaneous interventions (PCI) and coronary artery bypass grafting (CABG) should be considered when OMT is insufficient.

Coronary angiography (CAG) is the standard modality for the invasive assessment of coronary anatomy and function and the intraprocedural guidance of PCI.[14] However, CAG has well recognized limitations. CAG results in a two-dimensional luminogram of a complex three-dimensional structure CAG only shows luminal dimensions and is limited in characterization of tissue or plaque and assessing features associated with suboptimal stent deployment.[14-16]

Intracoronary imaging (ICI) along with CAG can potentially overcome these limitations, providing detailed information about the three-dimensional vascular morphology. According to the most recent guidelines on myocardial revascularization from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), ICI should be considered for optimizing stent implantation and detecting stent-related mechanical problems leading to restenosis.[17]

Intracoronary ultrasound (IVUS) and optical coherence tomography (OCT) are the most common modalities for ICI and both modalities provide high resolution cross-sectional images of the vessel wall.[18, 19] The benefits of IVUS-guidance on clinical outcomes and stent optimization has been reported in multiple meta-analyses.[20-24] In addition, Alberti et al. (2016) assessed the cost-effectiveness of IVUS-guidance in comparison with solely CAG-guidance from an Italian healthcare payer perspective. IVUS-guidance was considered to dominate CAG-guidance in Italy in terms of cost-effectiveness.[93] OCT along with CAG has high potential in terms of health benefits compared with CAG alone and potentially IVUS, due to its higher resolution and easy image interpretation. However, it is still unclear whether OCT-guided PCI compared with IVUS-guided PCI results into superior long-term clinical outcomes.[94] Despite growing evidence, the adoption of ICI in clinical practice remains limited.[25]

Therefore, this study aimed at comparing the cost-effectiveness of:

(1) PCI guided by CAG along with OCT;
(2) PCI guided by CAG along with IVUS;
(3) PCI guided by CAG alone.

This study focused on all patients with CAD in an academic medical setting in whom ICI is considered. The primary aim of this study was to assess cost-effectiveness of IVUS-guided PCI compared with OCT-guided PCI in terms of quality-adjusted life years (QALYs) and costs. The secondary aim was to assess cost-effectiveness of ICI-guidance in comparison with conventional CAG-guidance. We hypothesize that CAG along with OCT is a more cost-effective intracoronary treatment strategy than CAG along with IVUS, as OCT provides a much higher resolution than IVUS. In addition, we think that CAG along with ICI in general is more cost-effective than CAG alone, as ICI provides detailed information about vascular and stent morphologies. These insights may result in a more optimal treatment, resulting in less adverse events and revascularization, ultimately reducing costs.

4.3 Methods

4.3.1 Patient Population

This study focused on all patients with single or multivessel disease in an academic medical setting in whom ICI is considered. The patient population was based on a cohort who underwent mainly elective PCI with IVUS at the Leiden University Medical Center (LUMC) between January 2018 and December 2019. These patients had a median age of 66 years (IQR, 57-75) and were predominantly male (75.6%). The median number of stents implanted was 2 (IQR, 1-4). All stents were considered to be drug eluting stents (DES), which is in correspondence with current practices and the model by Alberti et al. (2016).[93] Clinical outcomes after PCI, such as the number of revascularizations, myocardial infarctions (MI) and cardiac deaths, were derived from medical scientific literature.

4.3.2 Type of Evaluation

Randomized controlled trials (RCT) are the golden standard to demonstrate clinical effect of treatment. However, these trials often compare a limited number of endpoints and have short follow-up times. The advantage of modelling is the possibility to extrapolate the data in time. Modelling is therefore the preferred method for cost-effectiveness analyses (CEA) when lifetime effects are expected.[95-98] A deterministic Markov model was constructed to assess the cost-effectiveness of different intracoronary treatment strategies. The CEA was performed from a Dutch societal perspective with a lifetime horizon. This perspective was chosen in correspondence with Dutch guideline for economic evaluations in health care.[99]

4.3.3 Overview of the Model

In this paragraph, the characteristics and concepts of the Markov model used in this study are explained in an accessible manner. The model structure, transition probabilities, costs and utilities, discounting, base case analysis, sensitivity analyses, and scenario analyses are discussed. Each model characteristic is discussed in further detail in following paragraphs.

In medicine, Markov models are used to model the progression of chronic diseases and compare costs and effects of different interventions. The “disease”, in this case patients with CAD receiving PCI, is divided into a finite number of health states in which these patients can end up. Patients may transfer between health states based on predefined transition probabilities. Transition probabilities are defined as the probability that a patient in the cohort moves from one health state to another. For each health state, the transition probabilities to transfer to all other health states sum up to one. The transition probabilities were based on follow-up events reported in the literature (Table 4-1). Patients transfer between health states over discrete time intervals, which are called Markov cycles.

Figure 4-1 shows a diagrammatic representation of the Markov model designed for this study. For each treatment strategy a cohort of 1,000 patients was considered for PCI. After PCI, the patients in these cohorts were divided over the follow-up states based on the transition probabilities. During each cycle, patients moved between health states or stayed in the event free state. The model ended when all patients were in death state.

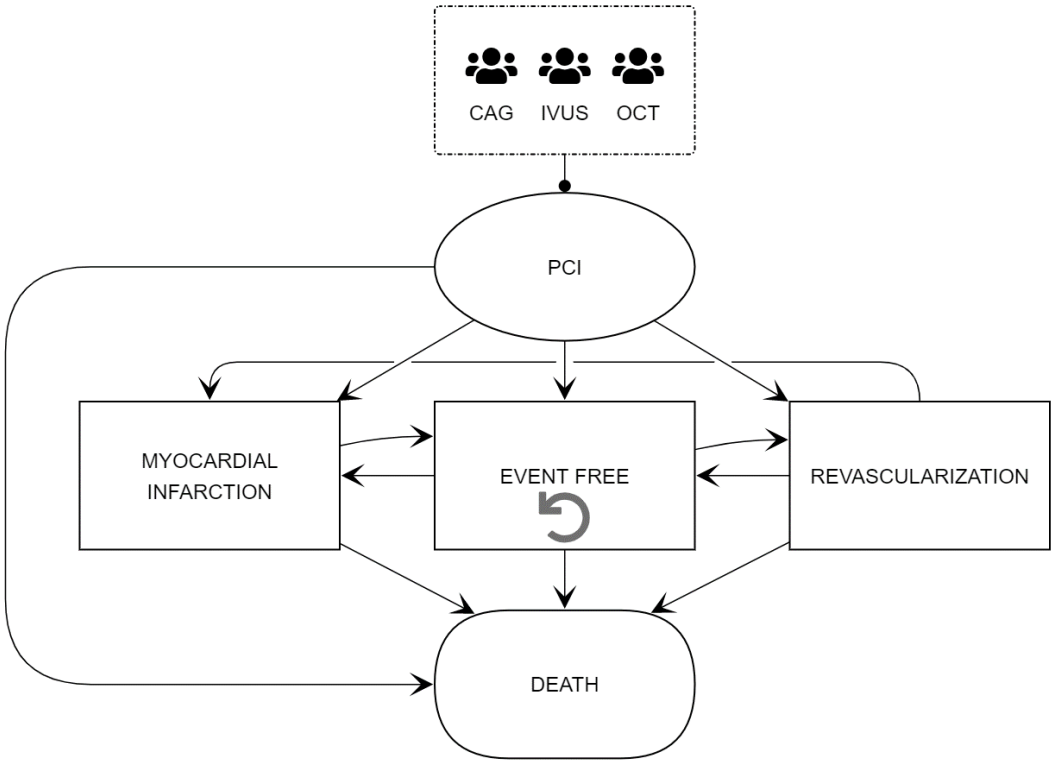


***Figure 4-1**. Diagrammatic representation of the Markov model. For each treatment strategy a cohort of 1,000 patients is treated with PCI. Oval represents start state; squares represent possible health and/or treatment states; rounded square represents terminal state; arrows represent possible transitions between states. Patients may stay in the event free state, indicated by the circular arrow. The model ends when all patients are in the death state. Abbreviations: CAG, coronary angiography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention.*

The outcomes of a Markov Model are typically the average costs and QALYs per patient. Therefore, weights for costs and quality of life were assigned to each health state in the model (Table 4-1). Costs for a specific health state are defined as the total costs for one patient in this health state during one cycle. Weights for quality of life are called utilities. Utilities are defined as the quality of life of a patient in a certain health state during one cycle. Utilities are defined between 0 and 1, where 0 represents death and 1 represents perfect health. The average costs and quality-adjusted cycle time per patient can be determined by running the model over multiple cycles (until all patients are in the death state) and summing the costs and utilities across these cycles. QALYs are then constructed by multiplying the quality-adjusted cycle time by the length of the cycles in years. In CEA, costs and utilities are reduced with a discount rate during each cycle (Table 4-1). Discounting is the process of determining the value of costs and utilities lying in the future based on the present value. Discounting is based on the assumption that the present value of a certain amount of money is higher than the value of the same amount of money in the future. Present quality of life in this context is assumed to more valuable than the quality of life in the future.

When all inputs (health states, transition probabilities, cost, utilities and discount rates) are defined, the model is ready to be evaluated. The primary analysis, comparing IVUS-guided PCI with OCT-guided PCI, is called the base case analysis. The model inputs for the base case were based on estimates derived from the literature. Thus, these inputs contained a certain level of uncertainty. Therefore, sensitivity analyses were performed. Two types of sensitivity analyses

***Table 4-1**. Model inputs as used in the Markov model. Lower and upper values were used for the DSA. PSA inputs were either SD or alpha and beta, depending on the defined distribution.*

Variable	Estimate	Lower	Upper	PSA	SD	Alfa	Beta	Source
Start age	66	57	75	Normal	11.9	-	-	*
Probabilities CAG (%)								
Revascularization	7.86	1.59	8.84	Beta	-	39.3	460.7	57, 59, 71, 80, 100
Myocardial infarction	2.84	0.10	8.70	Beta	-	2.8	97.2	57, 59, 71, 80, 100
Cardiac death	1.33	0.70	4.50	Beta	-	1.3	98.7	59, 71, 80, 100
Probabilities IVUS (%)								
Revascularization	6.15	2.50	7.16	Beta	-	30.8	469.2	66, 71, 100
Myocardial infarction	1.39	0.00	1.77	Beta	-	62.3	3713.8	66, 71, 100
Cardiac death	0.72	0.20	0.85	Beta	-	32.3	4443.7	66, 71, 100
Probabilities OCT (%)								
Revascularization	3.48	2.11	4.60	Beta	-	39.6	1099.4	57, 59, 66, 80
Myocardial infarction	2.69	0.50	5.40	Beta	-	13.5	486.5	57, 59, 66, 80
Cardiac death	0.53	0.00	1.20	Beta	-	5.4	1013.6	59, 66, 80
Probability of death after MI (%)	11.5	10.6	12.9	Beta	-	6857	52677	101-103
Utilities								
Initial PCI	0.71	0.47	0.95	Beta	-	1.8	0.74	104
Event free	0.85	0.77	0.94	Beta	-	119.6	21.1	93, 105
Revascularization	0.77	0.69	0.85	Beta	-	191.0	57.1	93, 105
Myocardial infarction	0.68	0.61	0.75	Beta	-	271.1	127.6	93, 106
Death	0	0	0	-	-	-	-	-
Costs (2020 €)								
Initial PCI, CAG	15,927	13,895	19,847	Gamma	1038.4	-	-	104, 107
Initial PCI, IVUS	16,698	14,666	20,618	Gamma	1038.4	-	-	104, 107
Initial PCI, OCT	17,450	15,418	21,370	Gamma	1038.4	-	-	104, 107
Event free	423	381	578	Gamma	57.2	-	-	104, 108, 109
Revascularization	7,693	6,096	9,290	Gamma	593.3	-	-	107
Myocardial infarction	6,875	5,696	11,761	Gamma	4886.0	-	-	110
Death	0	0	0	-	-	-	-	-
Discount rates (%)								
Costs	4.0	0	8.0	-	-	-	-	108
Utilities	1.5	0	3.0	-	-	-	-	108

Abbreviations: CAG, coronary angiography; IVUS, intravascular ultrasound; LUMC, Leiden University Medical Center; OCT, optical coherence tomography; PCI, percutaneous intervention; PSA, probabilistic sensitivity analysis; SD, standard deviation. * Based on a cohort who underwent PCI with IVUS at the Leiden University Medical Center (LUMC) between January 2018 and December 2019.

can be distinguished. Namely, the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). A univariate DSA was performed by varying one input parameter at the time and evaluating the influence of these variations on the model outcomes. This way the influence of the uncertainty introduced by a single parameter on the model outcomes could be assessed. Results of the univariate DSA were presented in tornado diagrams. These diagrams show the model outcomes of the DSA in relation to the outcomes of the base case analysis. A multivariate DSA was performed by changing all input variables to a worst and best case scenario. All input parameters were therefore changed to the most beneficial values for OCT and the least beneficial for IVUS and vice versa. This way the most extreme outcomes could be assessed. For the DSA, the input parameters were varied between the lower and upper values as reported in Table 4-1. These values were derived or calculated from the literature.

The PSA was used to assess the overall uncertainty of the Markov model. Each input parameter value was sampled from predefined probability distributions (Table 4-1). The model was then evaluated for these sampled input parameters. This process was repeated for 1,000 samplings, resulting in 1,000 model simulations. Model outcomes for these simulations were plotted in a cost-effectiveness plane. The cost-effectiveness plane is a graph which shows the outcomes in terms of costs and QALYs as a scatterplot. The intervention considered to be the current standard in clinical practice was considered to be the central strategy. This means that each point in the graph represents the incremental costs and QALYs of the new intervention relative to the standard intervention for one model simulation. A cost-effectiveness acceptability curve was then created by evaluating the outcomes of the 1,000 model simulations for different willingness to pay (WTP) thresholds. The WTP threshold is defined as the amount of money one is willing to pay for gaining one QALY. The WTP threshold ranges between €20,000-80,000/QALY, depending on disease burden.[111]

The Markov model was also evaluated for some specific situations, namely using only an RCT by Kubo et al. (2017) as input and evaluating the model with different discount rates. Such evaluations are called scenario analyses. The papers by Sonnenberg et al. (1993) and Briggs et al. (1998) provide good in-depth introductions on the concepts of Markov modelling.[97, 98]

4.3.4 Model Structure

The model structure designed for this study was based on clinical practice, the Markov model by Alberti et al. (2016), and expert input.[93] Figure 4-1 shows a diagrammatic representation of the model. The model solely focused on treatment by means of PCI, excluding CABG as a treatment option. Each cycle lasted one year, as most studies reported clinical outcomes after one year follow-up. Four possible health states were defined: *event free*, *revascularization*, *MI* and *death*. Revascularization was considered to be the composite of target lesion revascularization (TLR) and target vessel revascularization (TVR). MI was considered including treatment, as both MI and treatment occur at the same time. In addition, it was assumed that all MI patients were treated with revascularization.

For each treatment strategy a hypothetical cohort of 1,000 patients was considered at the start of the model. All patients underwent PCI during the first cycle. The patients then transfer to either *event free*, *revascularization*, *MI* or *death*, based on predefined transition probabilities (*See 4.3.5 Transition Probabilities and Table 4-1*). This process was repeated until all patients were in the death state (i.e. after 35 years). The R package *"heemod"*, developed by Filipovic-Pierucci et al. (2017), was used to perform model calculations (Appendix M).[112]

4.3.5 Transition Probabilities

A review was conducted to find recent studies that report on clinical outcomes after OCT-guided PCI in terms of revascularization, MI and/or cardiac death.[1] Due to the limited number of studies into clinical outcomes after OCT-guided PCI, available studies comparing OCT-guided PCI with PCI guided by CAG alone or IVUS were included.[57, 59, 66, 80] An RCT by Hong et al. (2015) comparing CAG-guidance with IVUS-guidance in DES implantation was included to model clinical outcomes after IVUS-guided PCI.[71] In addition, a recent large prospective multicenter nonrandomized trial, based on the ADAPT-DES study, assessing the benefits of IVUS compared with CAG after two years of follow-up was included.[100] Point estimates were calculated by

weighting the outcomes of each study with the number of included patients in those studies. The estimates for clinical outcomes after PCI guided by CAG alone were calculated based on previous mentioned studies comparing CAG with IVUS or OCT. Ranges around the point estimates were based on the lowest and highest values reported in the literature. It was assumed that the benefits of each treatment strategy would persist after one year. The mortality after MI was derived from Eindhoven et al. (2018). Eindhoven et al. reported on the one-year mortality after MI. The mean one-year MI mortality was 11.5%, which was in correspondence with the one-year MI mortality reported in ESC guidelines.[102, 103] As the cohort ages through each cycle, the all-cause mortality increases as a function of age and gender. To account for the all-cause mortality, mortality data was extracted from the World Health Organization (WHO) database using the "*rgho*" package in R.[113] These mortality rates were then averaged per age based on the gender distribution of the cohort. The total death probability was defined as the combined probability to die either from CAD (cardiac death or MI) or from other causes. It was assumed that these probabilities were independent. An overview of the transition probabilities and literature are shown in Table 4-1.

4.3.6 Costs and Quality of Life

Costs for the initial PCI state were calculated based on cost-effectiveness studies by Osnabrugge et al. (2015) and Van Hout et al. (2005).[104, 107] For IVUS and OCT-guided PCI, costs for the catheters and medical devices were added to the initial PCI costs according to the annuity method.[108] It was assumed that costs for the non-PCI states were the same for all models. Costs for MI and revascularization were based on Soekhlal et al. (2013) and Van Hout et al. (2005) respectively. The components included in the costs for the event free state (i.e. outpatient clinic costs, diagnostics, medication, patient expenses and productivity costs) were based on Osnabrugge et al. and expert input. Costs for the event free state were then calculated based on guidelines and current tariffs.[104, 109, 114, 115] Costs for the death state were set to zero for all models. All costs were adjusted to 2020 euros using consumer price indices.[116] Full calculations of costs are provided in Appendix J.

Utilities for the initial PCI state were derived from Osnabrugge et al.[104] The utilities as reported by Alberti et al. were used for the event free state, the MI state and the revascularization state.[93] Utilities for the death state were set to zero for all models.

4.3.5 Primary and Sensitivity Analysis

In the base case analysis, PCI guided by CAG along with IVUS was compared with PCI guided by CAG along with OCT. Results are presented as the average costs and QALYs, incremental costs and QALYs and incremental cost-effectiveness ratio (ICER). The ICER is defined as the amount of money one needs to pay to gain one QALY.

For all parameters a univariate DSA was performed using the highest and lowest values reported in the literature (Table 4-1). By varying one input parameter at the time to their lower and upper value, the influence of the uncertainty introduced by a single parameter on the model outcomes could be assessed. Results of the univariate DSA were presented in tornado diagrams. In addition, a multivariate DSA was performed to assess the best-case and worst case scenarios. All input parameters were therefore changed to the most beneficial values for OCT and the least beneficial for IVUS and vice versa. Initial costs for the PCI state

were not changed as it was assumed to be unrealistic that costs for IVUS and OCT differed more than the difference between the costs of their catheters.

Furthermore, a PSA was performed to assess the overall uncertainty of the Markov model. Input parameter values were sampled from predefined probability distributions (Table 4-1). The probability distributions around the point estimates were based on the ranges of parameter values as published in or calculated from the literature. The beta distribution is most commonly used for transition probabilities and utilities, as these parameters are defined between zero and one. The gamma distribution is most commonly used for cost distributions, as the gamma distribution is defined on the interval zero to positive infinity.[96] For each strategy, 1,000 simulations were performed. The results of the PSA were presented as incremental cost-effectiveness planes and cost-effectiveness acceptability curves.

For the secondary analysis, both the base case analysis and PSA were repeated comparing PCI solely guided by CAG with PCI guided by CAG along with IVUS and OCT.

4.3.6 Scenarios

To our knowledge, the study by Kubo et al. (2017) was the only RCT to date directly comparing clinical outcomes of IVUS-guidance with OCT-guidance with at least one year follow-up.[66] Therefore, a separate scenario analysis was conducted using the data from Kubo et al. for reconstructing state transition probabilities of both the IVUS and OCT cohort.

Furthermore, discount rates were considered to be 4% for costs and 1.5% for effects in the base case analysis. This is in correspondence with the Dutch guideline for economic evaluations in health care.[99] However, in European and international guidelines it is recommended that discount rates are the same for both costs and effects.[117, 118] Therefore, two scenario analyses were performed to assess the effects of discounting in the model. Discount rates for both costs and effects were set to zero for the first scenario and 3% for the second scenario.

4.4 Results

4.4.1 Primary Analysis

Table 4-2 shows the outcomes of the base case analysis comparing IVUS-guided PCI with OCT-guided PCI. The base case analysis indicated that OCT is a dominant (favorable) treatment option, regardless of the willingness-to-pay (WTP) per QALY. “Dominant” means that, on average, OCT-guided PCI resulted in more effect and less costs than IVUS-guided PCI. On average, 0.059 QALYs were gained with OCT, saving €282 per patient.

Table 4-2*. Base case analysis results. ‘Dominant’ indicates dominant (favorable) treatment options (less costs, more effect). ICER is defined as the amount of money one needs to pay to gain one QALY.*

Model outcome	IVUS	OCT
Average costs (€)	26,756	26,473
Average effect (QALYs)	11.755	11.814
Incremental costs (€)		-282
Incremental effect (QALYs)		0.059
ICER (€ per QALY gained)		Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QALYs, quality-adjusted life years.

4.4.2 Scenarios

The Scenario analyses show similar results as the base case analysis (Table 4-3). In the RCT scenario derived from Kubo et al. (2017), both costs and effect were higher for OCT guided PCI than for IVUS guided PCI.[66] The ICER of €4,233/QALY fell below the WTP threshold of €20,000/QALY. Discounting scenarios had no substantial effect on cost-effectiveness.

***Table 4-3**. Scenario analyses results. 'Dominant' indicates dominant (favorable) treatment options (less costs, more effect). The ICER is defined as the amount of money one needs to pay to gain one QALY.*

Scenario Model outcome	**IVUS**	**OCT**
RCT results [66]		
Average costs (€)	25,294	26,378
Average effect (QALYs)	12.436	12.692
Incremental costs (€)		1,084
Incremental effect (QALYs)		0.256
ICER (€ per QALY gained)		4,233
Discount rate 0%		
Average costs (€)	31,253	30,515
Average effect (QALYs)	13.488	13.560
Incremental costs (€)		-738
Incremental effect (QALYs)		0.072
ICER (€ per QALY gained)		Dominant
Discount rate 3%		
Average costs (€)	27,648	27,275
Average effect (QALYs)	10.366	10.415
Incremental costs (€)		-373
Incremental effect (QALYs)		0.050
ICER (€ per QALY gained)		Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QALYs, quality-adjusted life years.

4.4.3 Deterministic Sensitivity Analysis and Probabilistic Sensitivity Analysis

Figure 4-2 shows the results of the univariate DSA, including only the parameters which led to the largest variations from the mean incremental costs and effect as reported in the base case analysis. The tornado diagrams show how the incremental costs and effects change by varying one variable at the time. Model inputs which contributed the most to the uncertainty in costs, were the costs of the initial PCI, probability of revascularization and the probability of having MI. Model inputs which contributed the most to the uncertainty in effect, were the probability of dying from cardiac death and the probability of having MI. Full tornado diagrams are reported in Appendix K.

Table 4-4 shows the results of the multivariate DSA. For the multivariate DSA all input parameters were changed to the most beneficial values for OCT and the least beneficial for IVUS and vice versa. IVUS was the dominant treatment option when all input parameters were set to the most beneficial for IVUS. OCT was the dominant treatment option when all input parameters were set to the most beneficial for OCT.

Looking at the base case, scenarios and the multivariate DSA, IVUS is only the dominant treatment option when the optimal input variables for IVUS were compared with the worst case for OCT. Remarkably, the incremental effect of 2.076 QALYs, saving €7,594 on average, was the largest of all scenarios.

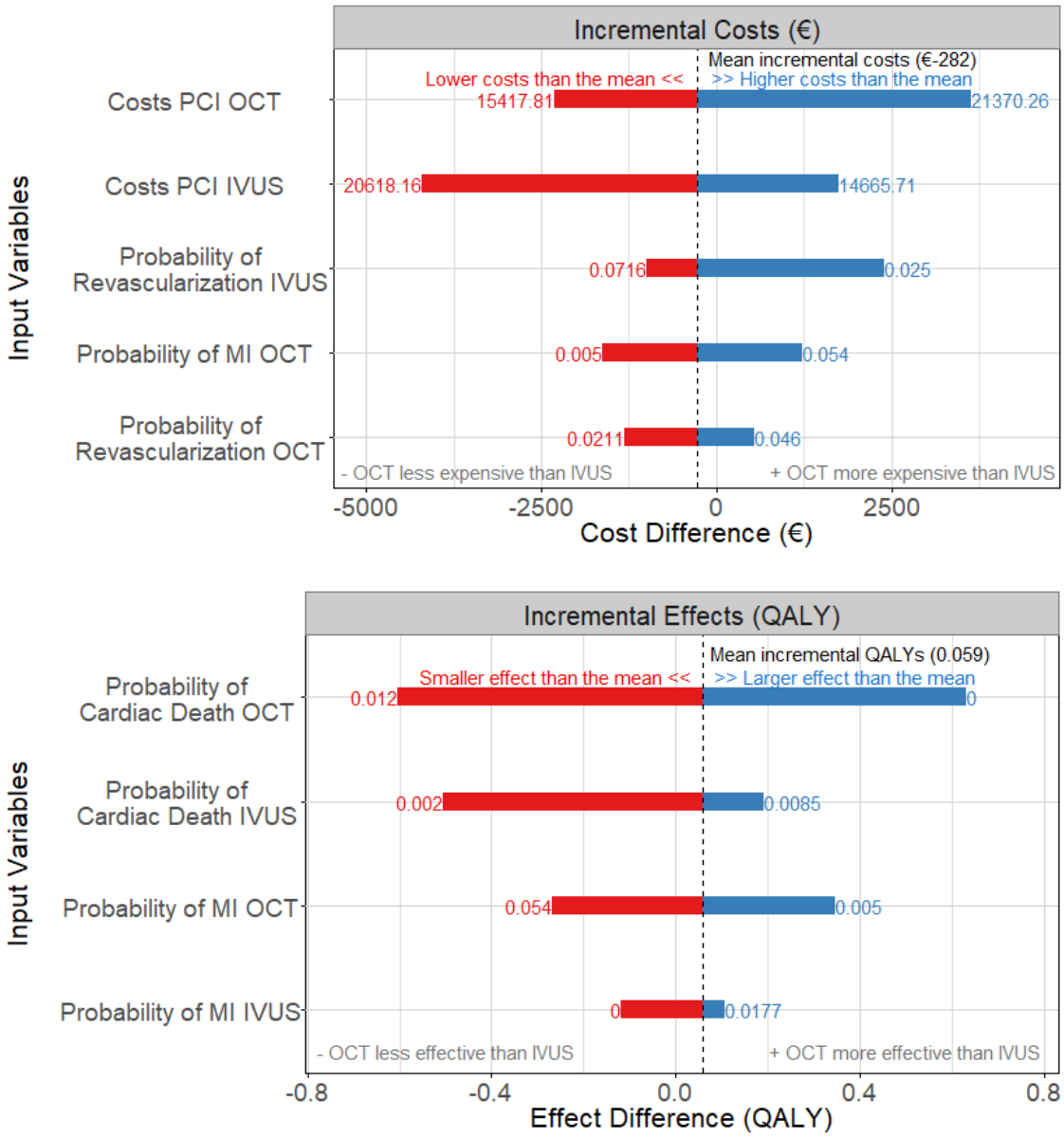


***Figure 4-2**. Tornado diagrams showing the results of the univariate DSA. Input variables were varied one at the time to their lower and upper values, indicated by red and blue numbers in the graphs (Table 4-1). Variations which resulted in a larger effect than the mean are shown in blue. Variations which resulted in a smaller effect than the mean are shown in red. A positive effect (or cost) difference corresponds with OCT being more effective (or expensive) than IVUS. A negative effect (or cost) difference corresponds with OCT being less effective (or expensive) than IVUS. Abbreviations: DSA, deterministic sensitivity analysis; IVUS, intravascular ultrasound; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous intervention; QALY, quality-adjusted life year.*

Figure 4-3 shows the result of the PSA as an incremental cost-effectiveness plane. This plot was created by sampling each input parameter from predefined probability distributions (Table 4-1). The model was then evaluated for these sampled input parameters. This process was repeated for 1,000 model simulations. The cost-effectiveness plane shows the incremental costs and effect of OCT relative to IVUS for all model simulations. Each dot represents one model simulation. IVUS is the central strategy or treatment, as IVUS is considered the current standard. The dark red diagonal indicates a WTP threshold of €20,000/QALY. It is noteworthy that most simulations fell below the WTP threshold, which is in line with the outcomes of the

base case analysis. In addition, the best and worst case scenarios as reported in Table 4-4 are presented in the cost-effectiveness plane as green and red diamonds, respectively.

***Table 4-4**. Results of the multivariate DSA, showing the best case scenarios for IVUS and OCT. 'Dominant' indicates dominant (favorable) treatment options (less costs, more effect). The ICER is defined as the amount of money one needs to pay to gain one QALY.*

Multivariate DSA	IVUS	OCT
Worst case scenario IVUS (Worst OCT)		
Average costs (€)	23,490	31,084
Average effect (QALYs)	13.753	11.676
Incremental costs (€)	-7,594	
Incremental effect (QALYs)	2.076	
ICER (€ per QALY gained)	Dominant	
Best case scenario OCT (Worst IVUS)		
Average costs (€)	29,231	24,590
Average effect (QALYs)	12.511	13.923
Incremental costs (€)		-4,641
Incremental effect (QALYs)		1.412
ICER (€ per QALY gained)		Dominant

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography; QALY, quality-adjusted life year.

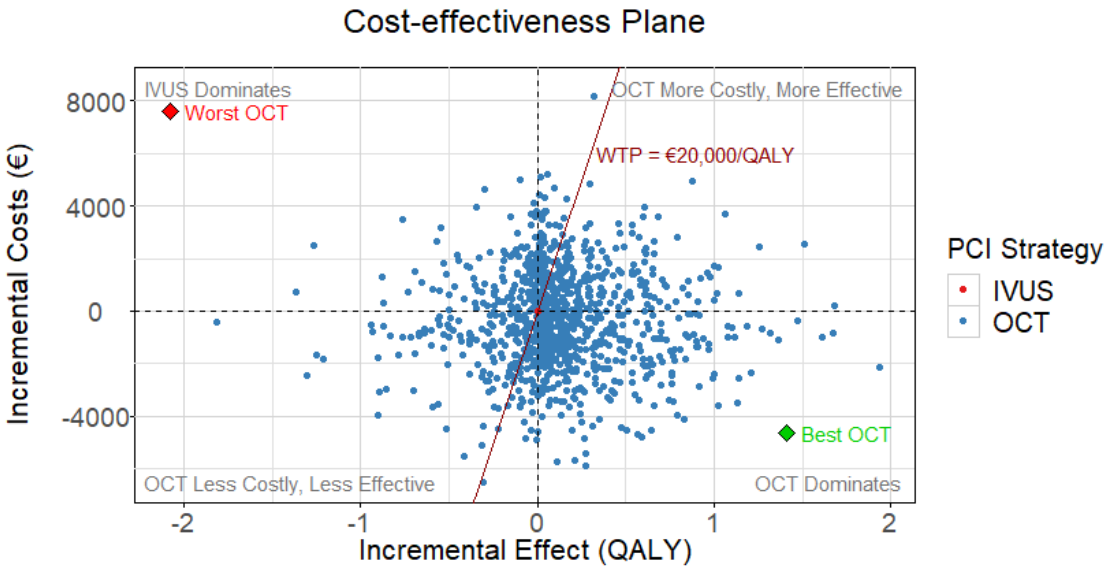


***Figure 4-3**. Incremental cost-effectiveness plane as result of the PSA. Each dot represents one model simulation. Diamonds indicate the worst and best scenarios according to the multivariate DSA (Table 4-4). Abbreviations: IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.*

Figure 4-4 shows the corresponding cost-effectiveness acceptability curve. This curve shows the probability of IVUS and OCT being the most cost-effective. The curve was created by evaluating the simulation results as shown in Figure 4-3 for different WTP thresholds. Each simulation which fell below the threshold resulted in OCT being more cost-effective, while the simulations which fell above the threshold resulted in IVUS being more cost-effective. As can be seen, the probability of OCT being the most cost-effective strategy is approximately 65%, regardless of the WTP threshold. The probability of IVUS being most cost-effective treatment strategy is approximately 35%.

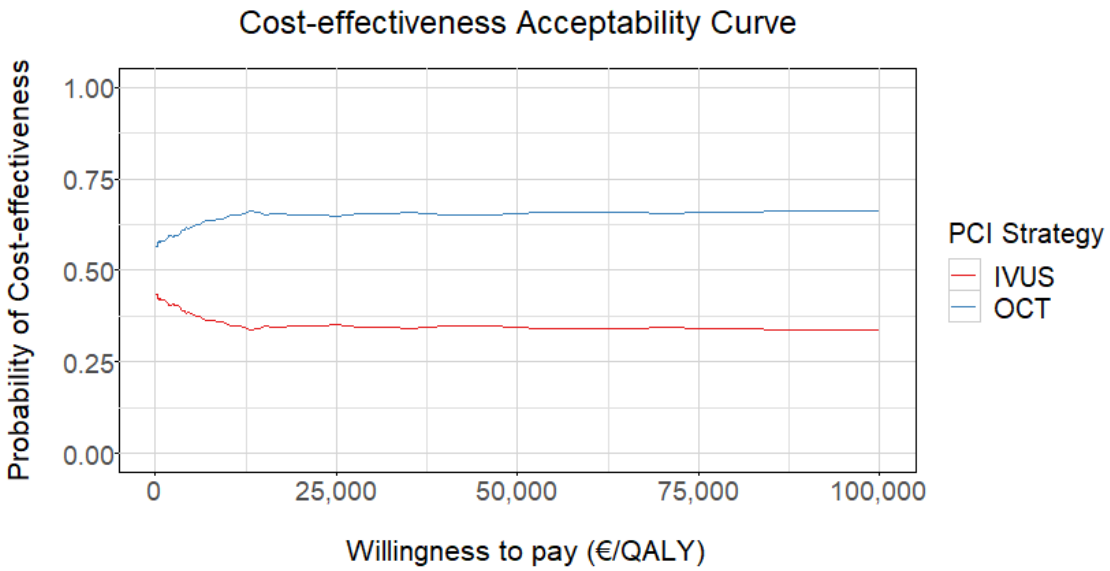


***Figure 4-4**. Cost-effectiveness acceptability curve as a result of the PSA. Abbreviations: IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.*

4.4.4 Intracoronary Imaging vs. Coronary Angiography

Table 4-5 shows the cost-effectiveness of IVUS and OCT-guided PCI in comparison with PCI guided by CAG alone. Both IVUS and OCT were dominant treatment options compared with CAG alone. This means that both IVUS and OCT-guided PCI resulted in more effect and less costs than PCI guided by CAG alone. On average, 0.784 QALYs were gained with IVUS, saving €650 per patient. With OCT, 0.844 QALYs were gained, saving €933 per patient.

***Table 4-5**. Secondary analysis including PCI guided solely by CAG. 'Dominant' indicates dominant treatment options (less costs, more effect) compared with CAG alone. The ICER is defined as the amount of money one needs to pay to gain one QALY.*

Outcomes base case	**CAG**	**IVUS**	**OCT**
Average costs (€)	27,406	26,756	26,473
Average effect (QALYs)	10.970	11.755	11.814
Incremental costs (€)		-650	-933
Incremental effect (QALYs)		0.784	0.844
ICER (€ per QALY gained)		Dominant	Dominant

Abbreviations: CAG, coronary angiography; ICER, incremental cost-effectiveness ratio; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

Figure 4-5 and Figure 4-6 show the cost-effectiveness plane and acceptability curve as a result of the PSA. As can be seen from Figure 4-5, most model simulations fell below the WTP threshold. This indicates that in terms of costs and effects, PCI guided by CAG along with ICI is preferred above PCI guided solely by CAG. Figure 4-6 emphasizes this finding. As can be seen, the probability of being the most cost-effective strategy was the highest for OCT (52%), regardless of the WTP threshold.

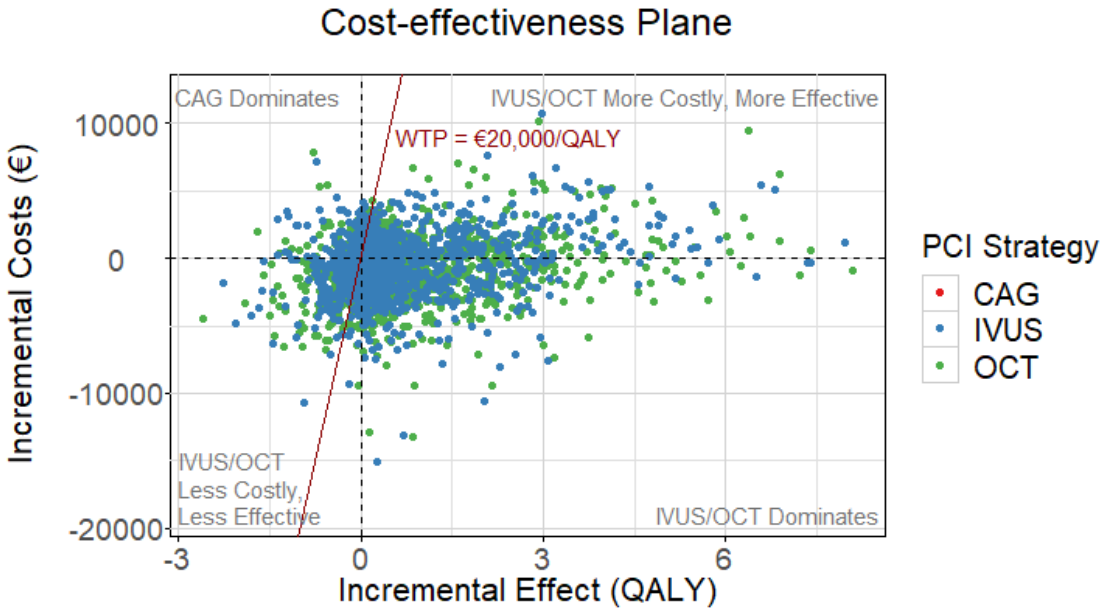


***Figure 4-5**. Incremental cost-effectiveness plane, including PCI solely guided by CAG as the central treatment strategy. Each dot represents one model simulation. Abbreviations: CAG, coronary angiography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.*

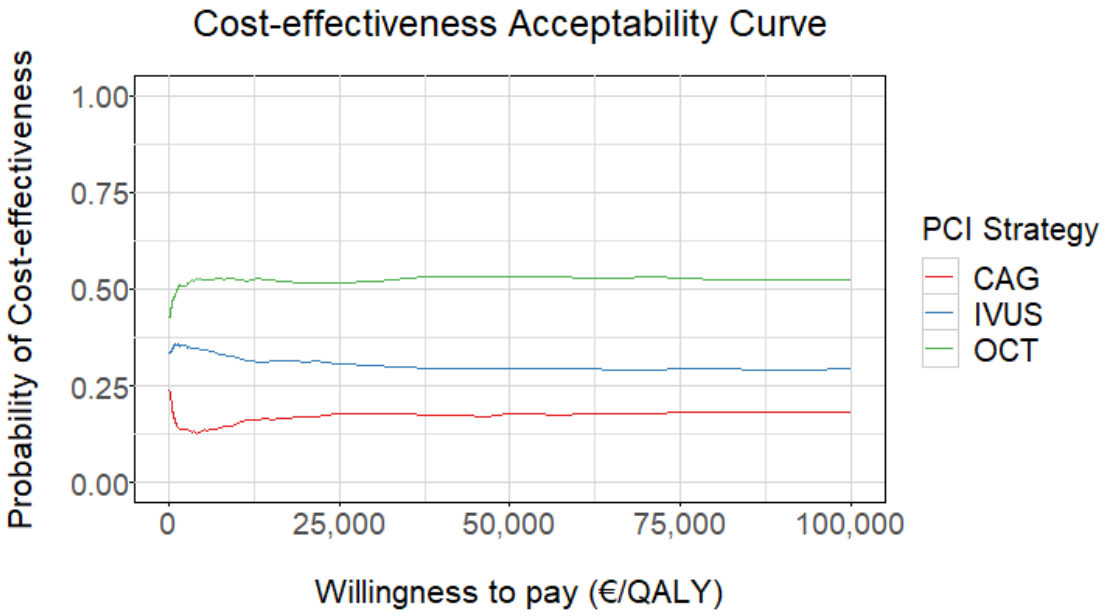


***Figure 4-6**. Cost-effectiveness acceptability curve as a result of the PSA. Abbreviations: CAG, coronary angiography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous intervention; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.*

4.5 Discussion

The primary aim of this study was to assess cost-effectiveness of PCI guided by IVUS along with CAG compared with PCI guided by OCT along with CAG. The secondary aim was to assess cost-effectiveness of PCI guided by ICI in comparison with conventional CAG-guidance. This study

used a deterministic Markov model to perform the CEA. Model parameters were derived from clinical evidence, expert input and guidelines. The results of this study indicated that OCT-guided PCI is a dominant treatment option compared with IVUS-guided PCI. On average, OCT-guided PCI resulted in a limited increase in QALYs (0.059) and reduction in costs per patient (€282). The probability of OCT being more cost-effective than IVUS was 65%, regardless of the WTP. In general, PCI guided by CAG along with ICI was a more cost-effective treatment strategy than PCI guided by CAG alone. On average, between 0.784 and 0.844 QALYs were gained, saving between €650 and €933 per patient. Sensitivity analysis, incorporating all three treatment strategies, showed that both IVUS and OCT outperform CAG alone in terms of cost-effectiveness.

Multiple scenarios were analyzed, incorporating only the clinical evidence from an RCT comparing IVUS directly with OCT and incorporating constant discount rates.[66] All scenarios, except one, indicated that OCT dominates IVUS in terms of costs and effect. IVUS was only the dominant treatment option when the optimal input variables for IVUS were compared with the least beneficial parameters for OCT. Remarkably, the incremental effect of 2.076 QALYs, saving €7,594 on average, was the largest of all outcomes. This can be explained by the fact that the estimates used in the model were weighted means, while for the best and worst cases the most extreme values as reported in the literature were used. In the best case scenario for IVUS, none of the patients ended up having MI. This had a large effect on both costs and effect.

The univariate DSA showed that in terms of costs, initial PCI costs and probabilities of having MI or revascularization had the largest influence on model uncertainty. This was not surprising, as changing the probability of having MI or revascularization in one group directly increases the costs for this group, as in the other group costs remain the same. Furthermore, a large range around the point estimate was chosen for initial PCI costs, resulting in large differences between treatment strategies in the univariate DSA. Probabilities of cardiac death and experiencing MI contributed the most to model uncertainty in terms of effect. The highest mortality in the model applies to patients experiencing MI, namely 11.5%. When patients are more likely to experience MI, patients are also more likely to die. Therefore, it is not surprising that the probability of having MI had effect on survival and thus the incremental QALYs.

This study provided insights in the current cost-effectiveness of different PCI treatment strategies in patients with CAD, reducing the uncertainty about the added value of ICI in clinical practice. This study can support departments considering the implementation of ICI. In addition, this study might persuade physicians to increasingly utilize ICI in clinical practice.

4.5.1 Model Limitations

This study had several limitations, which should be considered. First, the available evidence regarding clinical outcomes of OCT was limited. In addition, most clinical evidence was observational. Differences between study populations and methods possibly affected the differences in outcomes as reported in those studies. Point estimates were therefore weighted averages of all studies included. Lower and upper values were based on the smallest and highest rates reported in the literature to address full uncertainty. The differences between studies mainly influenced the best and worst case scenarios, as in those cases the most extreme values from the literature were used. Second, it was assumed that the benefits of each strategy would persist throughout the model. As a consequence, the probability of

cardiac death, revascularization and MI were constant over time for each treatment strategy. Due to the short follow-up in the available evidence, it is uncertain whether this assumption was appropriate. However, Jones et al. (2018) compared the all-cause mortality after PCI guided by CAG alone, with an IVUS and OCT-guided PCI group with a median follow-up of 4.8 years in a multicenter cohort study. Jones et al. reported an all-cause mortality of 15.7%, 12.2% and 7.7%, respectively.[79] These results support our assumption, as the all-cause mortality after 4.8 years was lower in ICI-guided groups than in the CAG-guided group. This is in correspondence with our model. Furthermore, it was assumed that ICI use during revascularization and MI was the same for all treatment strategies. Costs and effects related to ICI use during these follow-up states were therefore assumed to cancel out.

The current CEA was conducted from a Dutch perspective. This perspective was applied to the model inputs wherever possible. As a result, all costs included in the model were derived from Dutch literature, guidelines and tariffs. Although different absolute costs may be applicable in other European countries, the relative costs were assumed to be similar. Moreover, clinical outcomes used in the model were weighted means derived from international literature. The outcomes of the current CEA are therefore assumed to be applicable to most European countries, assuming similar outcomes across countries.

This study indicates that the implementation of OCT potentially improves the number of QALYs, while costs are reduced. However, the probability of OCT being the most cost-effective treatment strategy was 65%, while the probability of IVUS being the most cost-effective treatment strategy was 35%. It should be realized that the Markov model is a simplified representation of reality. It was solely focused on PCI, excluding CABG as a treatment option. Additional research might lead to different outcomes (*See Further Research*). In addition, as CEA are focused on value for patients, potential benefits regarding prestige, research revenues, innovation and competition with other hospitals were not taken into account. These additional benefits might be decisive factors for some hospitals to implement OCT, while other hospitals might be better off waiting for results of further research.

4.5.2 Further Research

The uncertainty in the Markov model might be diminished by further research. The results of the DSA suggests further research in clinical outcomes, such as the probability of having MI, revascularization and cardiac death. Future research should ideally differentiate between clinical outcomes after OCT-guided PCI and IVUS guidance, as current trials are mainly focused on demonstrating superiority of ICI techniques compared with conventional CAG guidance. A head-to-head comparison with longer follow-up times would contribute considerably to the discussion whether OCT or IVUS is superior in terms of long-term clinical outcomes.

At the moment, two large RCTs are initiated to demonstrate the superiority of OCT-guided stent implantation compared with CAG-guidance. The first results of these trials are expected mid-2021.[81, 82] Both trials aim to demonstrate that OCT-guided PCI improves clinical outcomes after two years of follow-up. A reduction in terms of major cardiac adverse events and target vessel failure is expected. These studies may contribute to more accurate model inputs and less uncertainty about clinical outcomes. Especially their longer follow-up times are of interest for modelling cost-effectiveness in the future.

4.6 Conclusion

OCT along with CAG is a more cost-effective intracoronary treatment strategy than IVUS along with CAG for patients with CAD. However, the gain in QALYs and reduction in costs are limited. Both IVUS and OCT outperform CAG alone in terms of cost-effectiveness.

5. THE IMPLEMENTATION OF OPTICAL COHERENCE TOMOGRAPHY

5.1 Introduction

This chapter provides an overview of the department's implementation processes and the considerations regarding the implementation of OCT.

The initial aim for this chapter was to assess the conditions which determine the success of implementations of medical devices at the department of interventional cardiology and providing a general implementation strategy or improvement plan based on these conditions. Unfortunately, due to the current corona crisis, this analysis was not performed. Instead, Paragraph 5.2 describes the department's implementation processes in relation to local guidelines. These processes were identified during the implementation of OCT and by expert input from the general clinical physicist, the quality advisor and the department of instrumental affairs.

In addition, Paragraph 5.3 provides an overview of how the *Convenant Veilige Toepassing van Medische Technologie in de medisch specialistische zorg* (Covenant) is implemented at the department.[119] The Covenant is an agreement between the government and Dutch healthcare organizations. The main purpose of the Covenant is to support risk management and safe application of medical devices in specialized medical care. For the purpose of this thesis, the focus was on chapters 3, 4 and 5 of the Covenant, which describe the introduction, use and disposal of medical technology respectively. This overview may be used in the future for further research into the implementation processes at the department.

Paragraph 5.4 describes the current status of the implementation of OCT. To conclude the implementation of OCT, Paragraph 5.5 discusses the considerations regarding the implementation of ICI in general.

5.2 The department's Implementation Processes

5.2.1 Purchasing Procedure of New Medical Devices

It all starts with the need for a medical device. This need is mostly identified by someone within the department (the initiator). The initiator explores different options and suggests these options to the head of department. Depending on the costs, the department needs permission from the division and the executive board (Box 5-1).

> The department can acquire the medical device directly from their exploitation budget when the costs do not exceed €10,000. When the investment does exceed €10,000, the department needs approval from the division. Each department is a subsection of a division (Figure 5-1). Each year the department needs to provide an overview of the investments they are planning to make the next year. Approval from a member of the board of directors (executive board) is needed when costs exceed €100,000.

***Box 5-1**. Investments within the LUMC organization.*

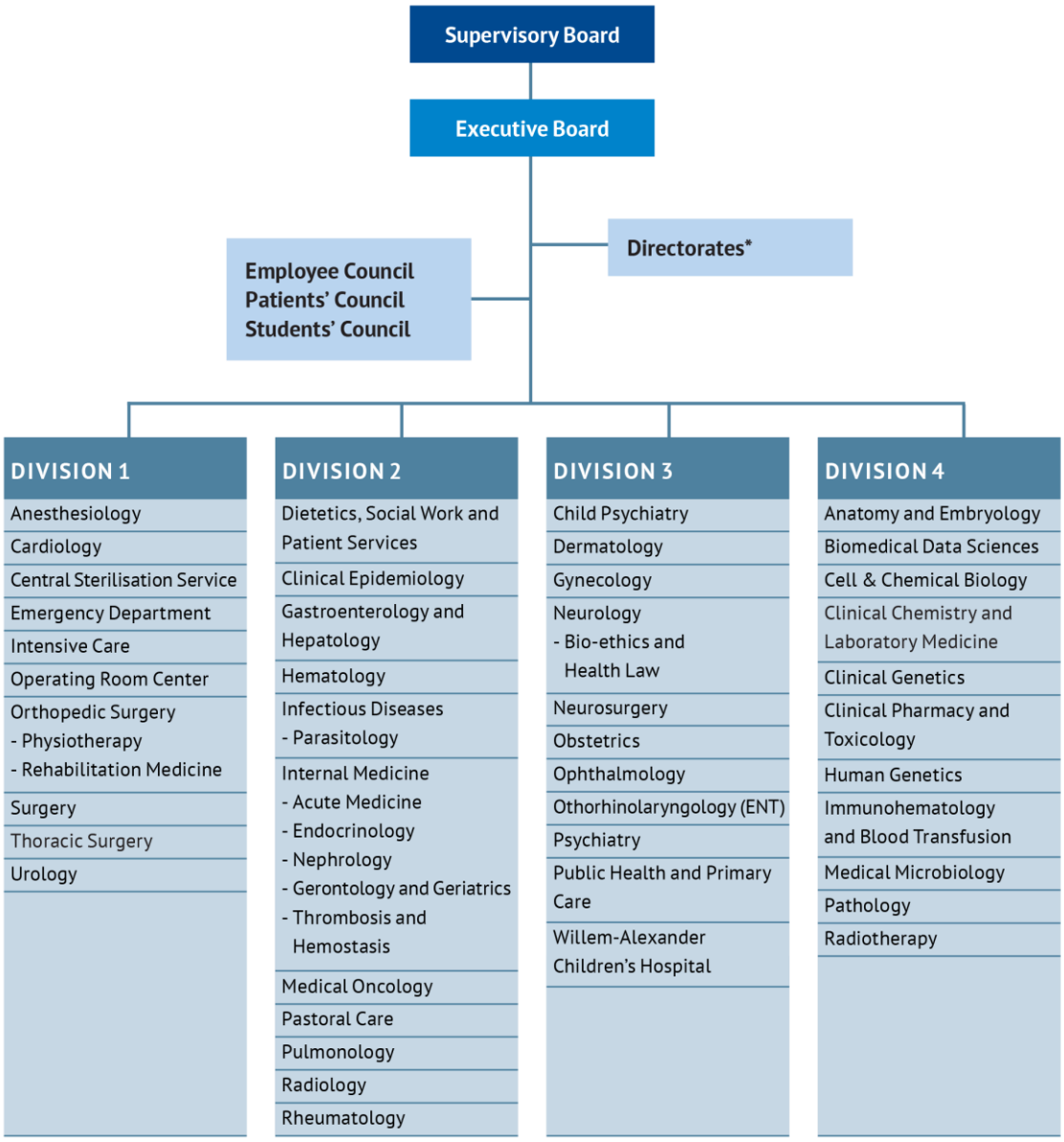


***Figure 5-1**. Organization chart of the LUMC.*

The initiator requests quotations from one or more companies. Depending on the costs of the medical device and the available budget, the device is purchased directly based on one or two quotations or an iterative negotiation process takes place (Box 5-2).

> For OCT, multiple negotiations took place. The initiator, the head of department, buyers from the purchase department and representatives from the manufacturer were present.

***Box 5-2**. OCT negotiations.*

When all parties agree on a definitive agreement, a contract and/or service agreement are signed. The medical device can now be ordered (Box 5-3).

Medical devices are ordered via FLITS, which is the purchasing software at the LUMC.

***Box 5-3**. The LUMC purchasing software.*

Parallel to the above described purchasing processes, a product file is composed by the initiator in cooperation with the general clinical physicist, who provides technical support during implementations (Box 5-4). In practice, this product file is primarily composed by the clinical physicist. In the ideal situation the clinical physicist is involved in the process somewhere between the identification of the need and requesting the quotations (Figure 5-2). However, in most cases (approximately 75%), the clinical physicist is not involved until the medical devices can be ordered (after agreement). This seems less efficient as most of the time not all technical aspects are accounted for, e.g. required installations, the need and possibility for sterilization, training, service options and the composition of the product file itself. The implementation is then delayed as most information still needs to be acquired. Installations, data management or other preparatory work is arranged and carried out when suitable. There is no specific time in the process when preparatory work takes place. Evidently, preparatory work does not take place before agreement between the department and the manufacturer.

The product file is an obligation originating from the Covenant. The product file contains at least the necessity for the implementation of the new medical device, a statement of requirements, a prospective risk analysis, a training plan and a periodic evaluation plan. In addition, the CE documentation and user manuals need to be obtained from the manufacturer and added to the product file. When the medical device is a class IIa or higher, an in-house developed risk scan is carried out. Dependent on the result of this scan, a concise or extensive risk analysis is performed in cooperation with the purchase department and all relevant stakeholders. Dependent on the novelty of the medical device, a simple training plan is established by the clinical physicist or a more profound training plan is established in cooperation with the quality advisor and the catheterization team leaders. A simple training plan comprises a couple of sentences which describe who provides the training and how often. A more profound training plan also describes the content of the training. Most of the times the evaluation plan contains a couple of words or sentences, which state that the use of the medical device is evaluated after one year. However, in practice medical devices are only evaluated when problems arise. The product file is archived in JOIN, which is a document management system. The product file for OCT was composed by the author of this thesis and is available at the department.

***Box 5-4**. The product file.*

Only when the order is placed in FLITS, all agreements are signed and the product file is completed, the purchase department and the department of instrumental affairs approve the order. The device is then actually ordered and registered in Ultimo (Box 5-5).

Ultimo is a software package, which supports the safety management system. An important tool in Ultimo is the monitoring of periodic maintenance.

***Box 5-5**. The safety management system.*

When the medical device arrives at the LUMC warehouse, the department of clinical technology (part of instrumental affairs) is notified (via FLITS). Clinical technology then checks whether the device meets its requirements and specifications according to the manuals. In addition, an electrical safety test is performed. When clinical technology gives the all-clear, the device is provided a yellow sticker with information about the next maintenance. The device is then transported to the department of interventional cardiology and ready to be used. Figure 5-2 provides a graphical representation of the department's purchase processes as described above.

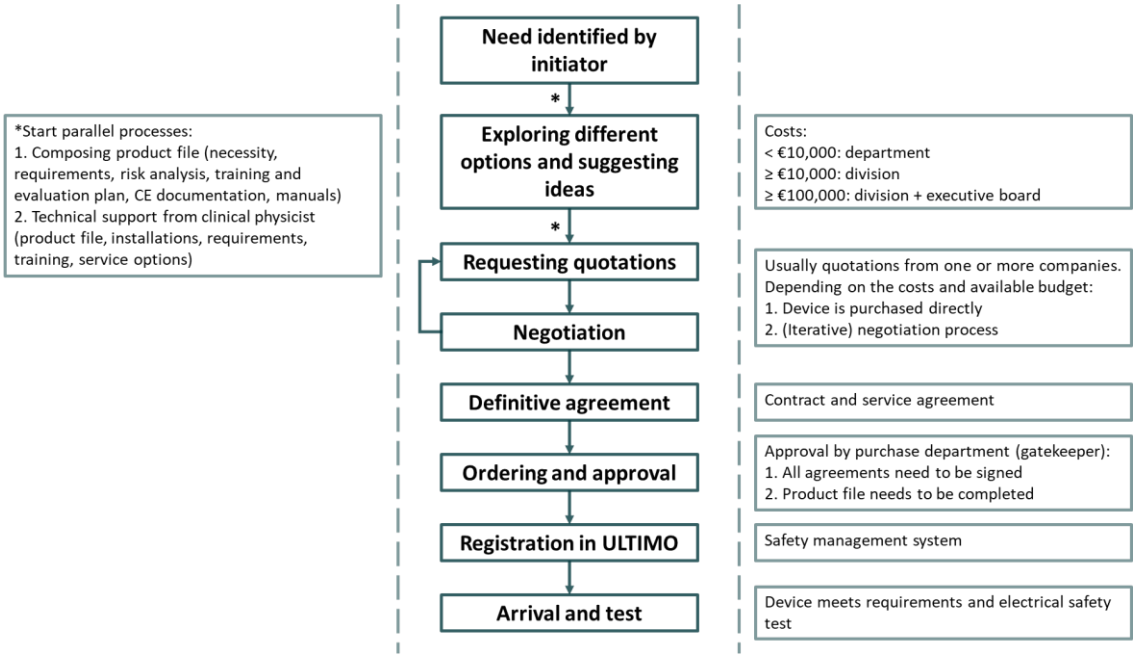


***Figure 5-2**. Schematic presentation of the purchase processes of new medical devices at the department of interventional cardiology (LUMC).*

5.2.2 Introduction and Use of New Medical Devices

Before medical devices can be used in clinical practice, training according to the training plan must have taken place. When employees are trained adequately, this is registered in their quality passport (Box 5-6). Re-training of employees is also registered in the quality passport. Employees are responsible for their own competences.

> The quality passport is a registration system where competences of employees are registered and monitored. Employees are responsible for determining and monitoring whether they are still competent or not.

***Box 5-6**. The quality passport.*

Furthermore, a cathlab protocol must be written and uploaded to iProva (Box 5-7). Each device at the cathlab is the responsibility of one cathlab technician. They write the cathlab protocol in cooperation with the physicians and team leaders and arrange training of other cathlab technicians. After training, this cathlab technician is responsible for the registration of the competences in the quality passport. This is all guided and monitored by the team leaders.

iProva is a quality management system, which can be used for document management, incident management and risk management. All cathlab protocols are available in iProva.

***Box 5-7**. The quality management system.*

When employees are adequately trained, the medical device can be used in clinical practice. It is important, however, to evaluate the medical device according to the evaluation plan. As stated before, this is not done very often. It is also not clear who is responsible for these evaluations. I would suggest making the initiator or one cathlab technician responsible for this evaluation. This evaluation could be a short questionnaire or small gathering to obtain information about the current status or issues regarding the device. In general, devices are only evaluated when problems or incidents arise. However, maintenance and malfunctions of medical devices from large contracts are evaluated every year.

Periodic maintenance is monitored in Ultimo. The yellow sticker, which is present on the device, states the next date for maintenance. After this date, it is not allowed to use the device. However, this is the responsibility of the user. Maintenance is performed by the department of clinical technology or by the manufacturer, when there is a service contract. Adequate training must be provided by the manufacturer for the employees who perform maintenance. Competences of technicians is monitored by the department of instrumental affairs.

5.2.3 Disposal of Medical Devices

Disposal of medical devices is arranged by the department of instrumental affairs. It is important that all patient data is deleted from the device. Also, when the device contains dangerous substances, these must be removed appropriately. In all cases, the department of instrumental affairs disposes the medical device or gives the department permission to dispose the device via normal waste.

5.3 The Covenant

The main purpose of the Covenant is to support risk management and safe application of medical technology in specialized medical care. The Covenant focuses at the whole life cycle of medical technology, from introduction to disposal. Chapter 1 of the Covenant describes the purpose of the Covenant and how it is constructed. Chapter 2 describes the position of medical devices in the safety management system, with emphasis on the responsibility of the board of directors. Chapter 3, 4 and 5 describe the introduction, use and disposal of medical devices respectively. For the purpose of this thesis, the focus was on chapters 3, 4 and 5 of the Covenant, which describe the introduction, use and disposal of medical technology respectively.

5.3.1 Implementation of the Covenant at the Department of Interventional Cardiology

The Dutch Health Inspectorate (IGJ) has the task to monitor the compliance with the Covenant in Dutch medical centers. The IGJ assessed the compliance with the Covenant at the LUMC in 2018. At the time, the IGJ concluded that the requirements of the Covenant were not yet sufficiently implemented. The main shortcomings identified by the IGJ were:

(1) The Covenant was not integrated in the existing systems in such a way that insights into the implementation status of the Covenant could be obtained throughout the entire LUMC;
(2) Not all purchasing procedures contained adequate prospective risk analyses;
(3) Maintenance was not always performed in time;
(4) Competences of employees were not always verifiable.

As a result, an intervention team was established to make sure the requirements of the Covenant were sufficiently implemented. Quality advisors of all divisions were actively involved in the implementation of measures associated with the above mentioned shortcomings. Some examples of implementations as a result of the audit are: a quality passport has been implemented to register and monitor the competences of employees; a risk scan with concise and extensive prospective risk analysis were developed; all purchases follow the same procedure and the purchase department act as a gatekeeper by checking if the procedure is adequately followed.

For this thesis the procedures mentioned in chapters 3, 4 and 5 of the Covenant were compared with current procedures at the LUMC, solely focusing on the interventional cardiology domain. Appendix L shows how each article of chapters 3, 4 and 5 of the Covenant are covered by the local guidelines. In general, all procedures referred to in the Covenant are currently implemented. However, for the scope of this thesis only the presence of the procedures was checked in the interventional cardiology domain. This does not mean that all procedures are always followed or implemented adequately. Especially the workflow could be improved, focusing on a more efficient workflow, where everybody involved knows where to find procedures, how to follow these procedures and which parties to involve at what time in the process. A future project could therefore be focused on how to improve the workflow, by analyzing how procedures are used in practice.

5.4 Current Status of the Implementation of OCT

At this point, the processes as described in Paragraphs 5.2.1 and 5.2.2 are completed. Employees followed theoretical training and are now authorized to use OCT. The next step is to become skilled with OCT in clinical practice. OCT will be used in clinical practice for the first time at the LUMC on June 24, 2020. The manufacturer of OCT (Abbott) will provide guidance during the first procedures.

Some important notices which should be considered in the near future:

(1) A DICOM work list can be imported into the software, providing an overview of all patients treated that day. Patients may then be selected prior to imaging. It is also possible to manually enter the patient data, such as name, date of birth and patient number. These data is necessary to export the data directly to PACS after the procedure. To import and export DICOM data to PACS, the device must be connected to an ethernet port. The department should consider which method best fits the workflow at the cathlab.

(2) OCT imaging results in two formats, namely DICOM and a raw format. The DICOM data can be exported to PACS by connecting the OCT device with an ethernet port. The OCT images can then be reviewed inside the EPD with the Curad viewer. However, for research purposes (advanced measurements) the raw data is essential. Unfortunately, it is

impossible to export this raw data automatically. Therefore, this data must be exported manually using an external hard drive, USB or DVD. A secured external hard drive has been purchased. In addition, a share (200 GB) is installed to store the data. The department should determine how they want to arrange the data management processes. Considering current practices at the cathlab, I would advise to make one or two persons responsible for exporting the data once a week. This could be a cathlab technician or interventional cardiologist, but preferably someone involved in research regarding ICI. This researcher can then store the data in a structure which works best for research purposes.

(3) The division of image processing (LKEB) is a research group within the department of radiology LUMC. They developed software (QCU-CMS) which can analyze IVUS and OCT images for research purposes. This software provides comparable features as the off-line review software provided by Abbott. The benefits of the QCU-CMS software over Abbot's off-line review station are that it is free to use, new features are easily and quickly implemented when necessary, and it can be installed on multiple computers. The LKEB is eager to set up a research branch regarding ICI in cooperation with the cardiology department.

5.5 Considerations for the Implementation of Intracoronary Imaging

With this thesis we have identified the current applications of OCT in relation to IVUS and CAG (Chapter 2), acquired insights into different views and clinical practices regarding ICI in the interventional cardiology domain (Chapter 3) and assessed the cost-effectiveness of OCT-guided PCI compared with IVUS-guided PCI and PCI solely guided by CAG (Chapter 4). In addition, the processes, procedures and considerations around the implementation of medical devices at the department of interventional cardiology were identified and described in this chapter. Hence, the central research questions are answered. This paragraph concludes the implementation by describing the main aspects and considerations arising from Chapters 2-4 that play a role during the implementation of ICI.

The main aspects that play a role while considering the implementation of new medical devices are the value for patients and costs. On the one hand, ICI-guidance in general improves patient outcome. Although this has been shown in the literature primarily for IVUS guidance. On the other hand ICI-guidance results in high initial costs. Initial costs in this context are defined as all costs associated with the purchase of the device and higher procedure costs while using the device. Especially when IVUS is already used at the department, the implementation of OCT requires an additional investment that was already made for IVUS in the past. This can result in resistance from physicians and cathlab technicians, as high costs and time are major drawbacks mentioned by clinicians. Therefore, a broad support and consensus within the department is indispensable for a successful implementation.

In addition, it is not always clear whether OCT results in better clinical outcomes than IVUS. Although the gain in QALYs and reduction in costs were limited, our CEA indicated that OCT is a more cost-effective intracoronary treatment strategy than IVUS. This means that in the long run OCT results in better patient outcomes and a reduction in costs. Therefore, when only health economic aspects are considered (i.e. costs and quality of life), OCT might be the first choice. However, due to the limited available clinical evidence and thus uncertainty in the Markov model, additional research might lead to different outcomes. Therefore, it is still not

entirely certain whether it is cost-effective to invest in OCT when IVUS is already present at the department.

Other aspects that play a role while considering the implementation of ICI are research, education and innovation. Especially for research oriented centers, such as academic hospitals, the ability to participate in (inter)national research programs or setting up their own research programs are of value. Short term benefits of such research programs are prestige and research revenues. Research also provides the opportunity to become experienced with ICI. Research eventually leads to a better understanding and a higher quality treatment of CAD. Due to its higher resolution, especially OCT has high potential to be used for the development of automated measurements, predicting prognosis and further optimization of treatment in the future. Also innovation or keeping up with developments in the field of interventional cardiology could be aspects that are considered. These additional considerations might be decisive factors to implement OCT.

The LUMC is amongst the top academic medical centers in Europe. The LUMC profile consists of three integrated pillars, namely: optimal and innovative patient care, high quality education, and international leading research. In essence, this means that the LUMC aims to provide innovative treatment and diagnostics by realizing breakthroughs in research. An innovative treatment like OCT fits with such a profile.

In conclusion, the considerations regarding the implementation of OCT go beyond the health economic perspective (Figure 5-3). Other aspects, such as research and innovation, are considered to be important. In addition, a broad support and consensus within the department are indispensable. Therefore, considering the LUMC profile and the findings in this report, OCT is complementary to IVUS, potentially resulting in better clinical outcomes, lower costs, and additional research and innovation opportunities.

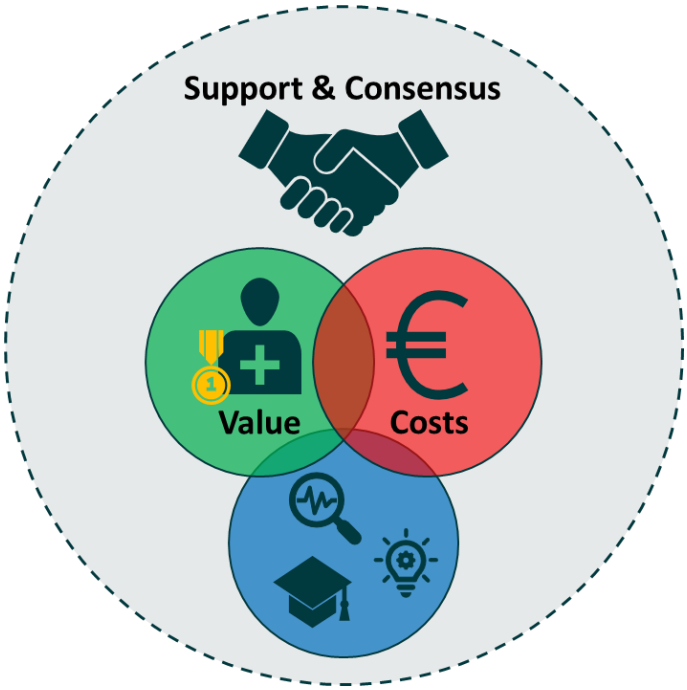


***Figure 5-3**. Considerations regarding the implementation of OCT.*

6. The Added Value of the Technical Physician

In 2006, the concept of Value Based Healthcare (VBHC) was first introduced to challenge the rising costs of the US healthcare system. Today, everybody is talking about VBHC. The idea of VBHC is not necessarily focused on the reduction of costs, but on increasing value, i.e. better health outcomes per monetary unit spent.[120] Multiple of such concepts exist, think of Lean Six Sigma, a process optimization method introduced in healthcare in the early 2000s. Lean Six Sigma aims to improve outcomes by removing all processes that do not add value. With other words, improve efficiency and reduce waste, eventually resulting in higher quality and more affordable healthcare.[121] According to the VBHC principle, value is defined as the health outcomes that matters to the patient divided by the total costs to deliver that value. In the Netherlands the first steps of the VBHC concept were implemented as the DBC system. This system encourages competition, which should ultimately result in increased value for patients at lower costs. With this system, healthcare providers receive compensation for specific care cycles, instead of the number of tests. This way, hospitals are encouraged to optimize their processes to reduce costs and increase value for patients.

Utilizing new technologies is one way how healthcare providers are trying to increase value for patients. Technology may contribute to better health outcomes by improving treatment or by contributing to better diagnosis of patients. Especially terms as eHealth, big data, personalized medicine, precision medicine and artificial intelligence are the popular terms of today. Essentially, all these concepts lead to the same goal: increasing value for patients. For example, by more accurate and faster diagnosis, predicting which patients benefit the most from a certain treatment or monitoring and predicting the prognosis. It is remarkable that technology on the one hand results in better health outcomes, while on the other hand is a key factor in increasing healthcare costs. This might be caused by insufficient use of technology, lack of knowledge about the added value of certain technologies or simply by buying fun gadgets which do not add value.

The technical physician is a new healthcare professional, particularly capable of determining added value of technology in clinical practice. The technical physician is able to quickly comprehend both medical and technical considerations, considering the limitations of technology and clinical evidence. Such a professional is therefore essential in the process of deciding to invest in new technologies. In particular by advising departments before implementation and guiding departments during and after implementations. In comparison with other MedTech professionals, such as clinal physicists and biomedical scientists, the technical physician is a more clinically oriented professional entitled to perform medical interventions independently. Hence, the technical physician is able to understand value of technology, assess this value in the context of clinical practice, and transfer this knowledge to both clinically and technically oriented healthcare professionals. Knowledge about cost-effectiveness analyses in this context is indispensable. In a world with continuous innovation at a high pace and where not healthcare providers, but value patients is the focus, the technical physician is a vital healthcare professional.

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APPENDIX A: Mathematical Explanation OCT

The electric field from the source is defined according to Equation A-1, where *k* is the wavenumber (Equation A-2) and *z* is the distance travelled.

$$E(z) = E_0 \cdot cos(k \cdot z) = E_0 \cdot e^{ikz} \quad \text{(A-1)}$$

$$k = \frac{2\pi}{\lambda} \quad \text{(A-2)}$$

The field contribution from the reference arm at the detector is defined according to Equation A-3 (Figure A-1). Similarly the field contribution from the sample arm at the detector is defined according to Equation A-4. The sum of these contributions gives the total field at the detector (Equation A-5).

$$E_{ref} = E_0 \cdot e^{ikx_0} \cdot \frac{1}{\sqrt{2}} \cdot e^{ik2z_0} \cdot \frac{1}{\sqrt{2}} \cdot e^{iky_0} = \frac{E_0}{2} \cdot e^{ik\,(x_0+2z_0+y_0)} \quad \text{(A-3)}$$

$$E_{sam} = \frac{E_0}{2} \cdot e^{ik\,(x_0+2(z_0+\Delta z)+y_0)} \quad \text{(A-4)}$$

$$E_{det} = E_{ref} + E_{sam} = \frac{E}{2} \cdot e^{ik\,(x_0+2z_0+y_0)} \cdot (1 + e^{ik2\Delta z}) \quad \text{(A-5)}$$

The detector measures the intensity, which is related to the complex field by multiplying E_{det} with its complex conjugate according to Equation A-6. The first part of Equation A-6 refers to the DC-term, which is constant, regardless of the pathlength difference Δz. Therefore, this constant is filtered out and only the interference term is kept (Equation A-7).

$$I_{det}(k) = \| E_{det} \|^2 = \frac{I_0}{2} + \frac{I_0}{2} \cdot cos(2k\Delta z) \quad \text{(A-6)}$$

$$I_{det}(k) = \frac{I_0}{2} \cdot cos(2k\Delta z) \quad \text{(A-7)}$$

In OCT, the Fourier transform (FT) of $I_{det}(k)$ gives the position of the reflector (i.e. sample) Δz. This results in a peak whose shape is defined by the FT of $I_0(k)$ shifted to the position of $2\Delta z$ (Figure A-1). This is also true when there are multiple reflectors in the sample, which results in multiple peaks. Rotating the image lens and repeating this process many times in adjacent points in space allows for the reconstruction of cross-sectional images or B-scans.

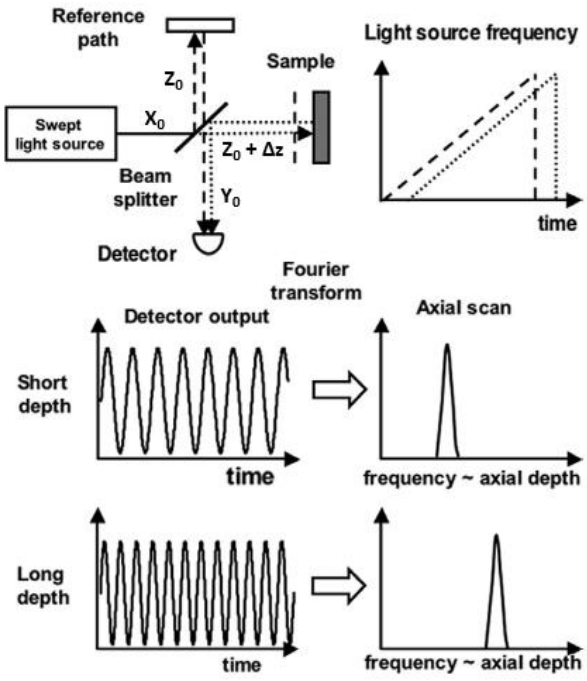

***Figure A-1**. Schematic of OCT. Derived from Lowe et al. (2011).*[30]

APPENDIX B: Stent Optimization Criteria

Study	Year	Stent under-expansion	Stent malapposition	Edge dissection	Other
Imola et al. [58]	2010	1. MLA < 90% of the average reference lumen area with asymmetric stent expansion (defined by min. LD/max. LD < 0.7).	1. Distance between strut and vessel wall > 200 µm, over a length of at least 600 µm).	1. Luminal disruption in the 5 mm proximal or distal part of the stent.	1. > 100 µm protrusion of tissue towards the lumen.
Habara et al. [63]	2012	1. MSA < 90% of the distal reference vessel lumen area.	1. Incomplete stent apposition to the vessel wall.	-	1. Residual plaque burden at MSA site > 50%.
Prati et al. (CLI-OPCI) [59]	2012	1. MSA < 90% of the average reference vessel lumen area or < 100% of lumen area of the reference segment with the smallest lumen area.	1. Stent lumen distance > 200 µm.	1. Linear rim of tissue ≥ 200 µm and clear separation from the vessel wall or plaque within 5 mm of the stent edge.	1. Reference lumen area < 4.0 mm^2; 2. Intraluminal mass ≥ 200 µm with no direct continuity with the surface of the vessel or highly backscattered luminal protrusion with continuity with the vessel wall and resulting in signal free shadowing.
Prati et al. (CLI-OPCI II) [68]	2015	1. In-stent MLA < 4.5 mm^2; 2. In-stent MLA < 70% of the average reference lumen area.	1. Stent-adjacent vessel lumen distance > 200 µm.	1. Linear rim of tissue with a width ≥ 200 µm and clear separation from the vessel wall or underlying plaque within 5 mm of the stent edge.	1. Reference lumen area < 4.5 mm^2 in the presence of significant residual plaque adjacent to stent endings; 2. Tissue prolapsing between stent struts inside a circular arc connecting adjacent struts or intraluminal mass ≥ 500 µm with no direct continuity with the surface of the vessel wall or highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing.

Study	Year	Stent under-expansion	Stent malapposition	Edge dissection	Other
Antonsen et al. (OCTACS) [64]	2015	1. MSA < 90% of the average reference vessel lumen area.	1. ≥ 3 struts per cross-sectional area detached > 140 µm from the underlying vessel wall.	1. Causing an MLA < 4 mm^2.	1. Residual stenosis causing an MLA < 4 mm^2.
Wijns et al. (ILUMIEN I) [55]	2015	1. ≥ 30% on OCT compared with reference distal lumen area and > 20% in-stent residual diameter stenosis on QCA.	1. > 200 µm in axial diameter and present in at least five consecutive frames.	1. > 180° in more than five frames.	1. Thrombus or tissue protrusion causing flow reduction (i.e. TIMI < 3 and/or obstruction visible by CAG).
Ali et al. (ILUMIEN III) [16]	2016	1. Proximal MSA < 90% of the proximal reference lumen area and distal MSA < 90% of the distal reference lumen area.	1. Struts clearly separated from the vessel wall by ≥ 200 µm.	1. ≥ 60° or ≥ 3 mm in length.	-
Meneveau et al. (DOCTORS) [57]	2016	1. MSA ≤ 80% of the average reference vessel lumen area.	1. Management of malapposition at the operator's discretion.	1. Management of edge dissection at the operator's discretion.	1. Incomplete lesion coverage.
Kubo et al. (OPINION) [65, 66]	2017	1. MLA < 90% of the average reference lumen area. 2. Asymmetric stent expansion (min. LD/max. LD < 0.7).	1. Any incomplete apposition of the stent against the vessel wall.	1. Edge dissections with potential to provoke flow disturbances.	1. No plaque protrusion or thrombus with potential to provoke flow disturbances.
Leistner et al. (OPTICO) [56]	2018	1. MLA < 90% of the average reference lumen area.	1. Stent lumen distance ≥ 200 µm).	1. Therapy of edge-dissection was only recommended if they were angiographically visible or if there was OCT evidence for deeper vessel injury.	1. Complete lesion coverage.

Abbreviations: LD, lumen diameter; MLA, minimum lumen area; MSA, minimum stent area; OCT, optical coherence tomography; QCA, quantitative coronary analysis.

APPENDIX C: Post-PCI Results Reported by OCT Studies

Study	Year	Study design	Post-PCI result	
Habara et al. [63]	2012	RCT (OCT vs. IVUS)	MSA: Mean SA: Focal stent expansion: Diffuse stent expansion:	6.1 ± 2.2 vs. 7.1 ± 2.1 (p=0.04) 7.5 ± 2.5 vs. 8.7 ± 2.4 (p=0.04) 64.7 ± 13.7% vs. 80.3 ± 13.4% (p=0.002) 84.2 ± 15.8% vs. 98.8 ± 16.5% (p=0.003)
Antonsen et al. (OCTACS) [64]	2015	RCT (OCT vs. CAG)	Uncovered struts: Complete covered struts: No significant differences in stent malapposition or MSA after 6 months.	Median 4.3% (IQR 1.2-9.8) vs. 9.0% (IQR 5.5-14.5) (p<0.01) 17.5% vs. 2.2% (p=0.02)
Maehara et al. (ILUMIEN II) [35]	2015	Post-hoc (OCT vs. IVUS)	Relative Stent expansion*: Any malapposition: Any tissue protrusion: Any stent edge dissection:	Median 72.8% (IQR 63.3-81.3) vs. 70.6% (IQR 62.3-78.8) (p=0.29) 26.6% vs. 13.6% (p=0.0002) 63.6% vs. 27.3% (p<0.0001) 23.1% vs. 5.2% (p<0.0001)
Ali et al. (ILUMIEN III) [16]	2016	RCT (OCT vs. IVUS vs. CAG)	MSA after OCT: MSA after IVUS: MSA after CAG: OCT-guidance was non-inferior to IVUS-guidance (p=0.001), but not superior (p=0.42). OCT-guidance resulted in a significant higher minimum and mean stent expansion (%) compared to CAG (p=0.02 and 0.001 respectively).	5.79 mm^2 (IQR 4.54-7.34) 5.89 mm^2 (IQR 4.67-7.80) 5.49 mm^2 (IQR 4.39-6.59)
Meneveau et al. (DOCTORS) [57]	2016	RCT (OCT vs. CAG)	FFR: FFR > 90%:	0.94±0.04 vs. 0.92±0.05 (p=0.005) 82.5% vs. 64.2% (p=0.0001)
Gatto et al. (CLIO-OPCI II sub-study) [78]	2018	Retrospective (OCT vs. CAG)	Suboptimal stent positioning was identified by OCT in 54% of the lesions in patients who experienced MACE, where CAG showed optimal stenting results. MLA < 4.5 mm^2, distal and proximal reference narrowing, and distal edge dissections were found in 30, 25, 15 and 7% of the lesions respectively.	
Lee et al. [77]	2018	RCT (OCT vs. CAG)	The median percentage of uncovered struts at three months was lower in the OCT-guided group (7.5%) than the CAG-guided group (9.9%), p=0.009, with a mean difference of 2.8% (95% CI: 0.8-4.8, p=0.009).	

Abbreviations: CAG, coronary angiography; IVUS, intravascular ultrasound; MLA, minimum lumen area; MSA, minimum stent area; OCT, optical coherence tomography; SA, stent area.

APPENDIX D: Post-OCT Procedural Complications

Study	Year	Study design	Reported procedural complications
Imola et al. [58]	2010	Prospective (OCT)	1/114 transient vessel spasm; 3/114 ventricular ectopic beats during contrast infusions; 1/114 OCT probe was unable to cross the distal stent. No death, MI, major arrhythmias, dissections or CIN were reported.
Prati et al. (CLI-OPCI) [59]	2012	Retrospective (OCT vs. CAG)	In 335 patients, no cases of significant spasm, dissection or life-threatening arrhythmia occurred. No significant differences in post-PCI renal function comparing CAG guidance with CAG plus OCT guidance. In-hospital cardiac death (2 (0.6%) vs. 3 (0.9%), p=1.0) and non-fatal MI (13 (3.9%) vs. 22 (6.5%), p=0.118) were comparable for OCT and CAG respectively.
Wijns et al. (ILUMIEN I) [55]	2015	Prospective (OCT)	In 418 patients, no case of CIN or other serious adverse events related to OCT imaging were observed.
Ali et al. (ILUMIEN III) [16]	2016	RCT (OCT vs. IVUS vs. CAG)	Intraprocedural complications (dissection, slow flow or no reflow, abrupt closure or perforation) were similar for OCT (N=13/158), IVUS (N=16/146) and CAG (N=12/146). Post-PCI 1 dissection was observed in the OCT-group, 1 dissection and 1 slow flow was observed in the IVUS-group and 1 dissection, 1 slow flow and 1 abrupt closure was observed in the CAG group.
Meneveau et al. (DOCTORS) [57]	2016	RCT (OCT vs. CAG)	No differences in procedural complications, 7/120 (5.8%) events in both the OCT-group and CAG-group. The proportion of type 4a MI (48/120 (40%) vs. 40/120 (33%)) and AKI (2/120 (1.6%) each group) did not differ between groups. No differences in CIN (2/120 (1.6%) for both groups).
Kubo et al. (OPINION) [66]	2017	RCT (OCT vs. IVUS)	Procedure related complications (acute coronary occlusion, air embolization, slow flow, distal embolization, side branch occlusion, dissection, thrombus formation, vasospasm and ventricular arrhythmia) for both OCT and IVUS were very low and comparable: 3/412 (0.7%) vs. 1/405 (0.3%), p=0.62.
Jones et al. (Pan-London PCI registry) [79]	2018	Cohort (OCT vs. IVUS vs. CAG)	Procedural complications were generally low and similar across the three groups (OCT, IVUS and CAG), p=0.135. In the propensity-matched cohort (1134 patient pairs), OCT-guided PCI was associated with lower in-hospital MACE compared with CAG-guidance alone (0.80% vs. 2.00%, p=0.01). No differences in in-hospital MACE between the OCT-guided and IVUS-guided group (0.80% vs. 1.00%, p=0.84) was observed.

Abbreviations: AKI, acute kidney injury; CAG, coronary angiography; CIN, contrast induced nephropathy; IVUS, intravascular ultrasound; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; RCT, randomized controlled trial.

APPENDIX E: Post-OCT Clinical Outcomes

Study	Year	Study design	Clinical endpoint	Results
Imola et al. [58]	2010	Prospective (OCT)	Clinical follow-up after a minimal of 1 month after OCT-guided PCI	In 88 patients with mean follow-up of 4.6±3.2 months, no deaths, MI or stent thrombosis occurred. Angina recurrence was observed in 3 patients with restenosis.
Prati et al. (CLI-OPCI) [59]	2012	Retrospective (OCT vs. CAG)	12-month rate of cardiac death or non-fatal MI	In 335 matched patient pairs, the 12-month risk of cardiac death was 4 (1.2%) vs. 15 (4.5%), p=0.010. 12-month risk of non-fatal MI was 18 (5.4%) vs. 29 (8.7%), p=0.096. The 12-month risk for either events was 22 (6.6%) vs. 43 (13.0%), p=0.006.
Antonsen et al. (OCTACS) [64]	2015	RCT (OCT vs. CAG)	Cardiac events during 6-months follow-up	85 patients were included (40 vs. 45). During a 6-month follow-up, 2 patients (4%) from the CAG-group had MACE (1 subacute stent thrombosis and 1 cardiac death). No cardiac events were reported in the OCT-group.
Wijns et al. (ILUMIEN I) [55]	2015	Prospective (OCT)	Adverse events after 30 days follow-up	In 418 patients, low rates of MACE were observed for all subgroups. Rates of periprocedural MI were significantly lower when procedural changes were made based on pre-PCI and post-PCI OCT (p=0.029).
Meneveau et al. (DOCTERS) [57]	2016	RCT (OCT vs. CAG)	6-months clinical follow-up	In 240 patients, MACE was similar for the OCT-group and CAG-group. There was 1 death in the OCT-guided group and 1 recurrent MI in each group. No stent thrombosis was observed and no significant difference in the rate of target vessel revascularization.
Iannaccone et al. (FORMIDABLE) [80]	2017	Retrospective (OCT vs. CAG)	Incidence of MACE	540 patients were included after propensity score matching (270 vs. 270) comparing OCT-guided PCI with CAG-guided PCI. After a follow-up of 700 days (450-890) no differences in MI (6% vs. 6%, p=0.86) were observed.
Kubo et al. (OPINION) [66]	2017	RCT (OCT vs. IVUS)	12-months follow-up of target vessel failure	791 patients (401 OCT vs. 390 IVUS) were analyzed in a per-protocol analysis. Within 12 months, target vessel failure was observed in 21 patients (5.2%) in the OCT-guided group vs. 19 patients (4.9%) in the IVUS-guided group, p=0.042 for non-inferiority testing. There were no differences in secondary outcomes. No cases of CIN were observed in both groups.
Jones et al. (Pan-London PCI registry) [79]	2018	Cohort (OCT vs. IVUS vs. CAG)	All-cause mortality during follow-up	87,166 patients who received PCI between 2005 and 2015 were included. OCT was used in 1,149 patients, IVUS in 10971 patients and CAG alone in 75,046 patients. A significant difference in mortality was found at a median follow-up of 4.8 years (IQR 2.2-6.4): 7.7% vs. 12.2% vs. 15.7%, p<0.0001. This difference persisted for OCT vs. CAG after multivariate Cox analysis (HR=0.48, 95% CI (0.26-0.81), p=0.001) and propensity score matching (HR=0.39, 95% CI (0.21-0.77), p=0.0008). No differences in matched OCT and IVUS cohorts (HR=0.88, 95% CI (0.61-1.38), p=0.43).

Abbreviations: CAG, coronary angiography; CIN, contrast induced nephropathy; IVUS, intravascular ultrasound; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; RCT, randomized controlled trial

APPENDIX F: Characteristics of the LUMC Population

Table F-1. *Characteristics of non-IVUS PCI/CAG vs. IVUS PCI/CAG. Bold p-values indicate significant differences between groups.*

Characteristics	non-IVUS (N=3385)	IVUS (N=396)	p-value
Age [years], median (IQR)	67 (58-74)	65 (56-73)	**0.023**
Sex, N (%)			**0.009**
Male	2295 (67.8)	294 (74.2)	
Female	1090 (32.2)	102 (25.8)	
BMI [kg/m²], median (IQR)	26.6 (24.2-29.7)	26.6 (24.4-29.0)	0.296
Medical history, N (%)			
Heart failure	247 (7.3)	6 (1.5)	**<0.001**
Coronary artery bypass grafting	299 (8.8)	23 (5.8)	**0.033**
Previous PCI	854 (25.2)	149 (37.6)	**<0.001**
Myocardial infarction	675 (19.9)	117 (29.5)	**<0.001**
Chronic kidney failure	235 (6.9)	21 (5.3)	0.182
Dialysis	31 (0.9)	4 (1.0)	0.782
Smoking, N (%)			0.685
Current smoker	488 (14.4)	51 (12.9)	
Used to smoke	1019 (30.1)	124 (31.3)	
Never smoked	791 (23.4)	92 (23.2)	
Smoking unknown	1087 (32.1)	129 (32.6)	
Risk factors, N (%)			
Hypertension	1290 (38.1)	129 (32.6)	0.052
Diabetes	618 (18.3)	66 (16.7)	0.521
Hypercholesterolemia	980 (29.0)	95 (24.0)	0.381
PCI/CAG status, N (%)			**0.046**
Urgent	1026 (30.3)	106 (26.8)	
Elective	1488 (44.0)	198 (50.0)	
Unknown	871 (25.7)	92 (23.2)	
PCI/CAG indication, N (%)			0.267
Elective	1030 (30.4)	144 (36.4)	
STEMI	643 (19.0)	64 (16.2)	
NSTEMI	290 (8.6)	34 (8.6)	
Post ACS	258 (7.6)	28 (7.1)	
Unstable AP	157 (4.6)	16 (4.0)	
Unknown/Other	1007 (29.7)	110 (27.8)	
Complications, N (%)			**<0.001**
Yes	82 (2.4)	26 (6.6)	
No	2982 (88.1)	337 (85.1)	
Unknown	321 (9.5)	33 (8.3)	
Total fluor time [min], median (IQR)	8 (4-14)	13 (7-22)	**<0.001**

Abbreviations: *ACS, acute coronary syndrome; AP, angina pectoris; CAG, coronary angiography; IQR, interquartile range; IVUS, intravascular ultrasound; (N)STEMI, (non)-ST-elevation myocardial infarction; PCI, percutaneous intervention.*

Table F-2. *Characteristics of CAG with and without IVUS. Bold p-values indicate significant differences between groups.*

Characteristics	CAG without IVUS (N=1568)	CAG with IVUS (N=150)	p-value
Age [years], median (IQR)	65 (57-72)	63 (54-71)	**0.024**
Gender, N (%)			0.053
Male	1005 (64.1)	108 (72.0)	
Female	563 (35.9)	42 (28.0)	
BMI [kg/m²], median (IQR)	26.6 (24.0-30.0)	26.3 (24.2-28.1)	0.174
Medical history, N (%)			
Heart failure	157 (10.0)	2 (1.3)	**0.001**
Coronary artery bypass grafting	162 (10.3)	6 (4.0)	**0.008**
Previous PCI	372 (23.7)	69 (46.0)	**<0.001**
Myocardial infarction	239 (15.2)	55 (36.7)	**<0.001**
Chronic kidney failure	135 (8.6)	5 (3.3)	**0.021**
Dialysis	14 (0.9)	0 (0.0)	0.628
Smoking, N (%)			0.189
Current smoker	200 (12.8)	24 (16.0)	
Used to smoke	532 (33.9)	58 (38.7)	
Never smoked	454 (29.0)	35 (23.3)	
Smoking unknown	382 (24.4)	33 (22.0)	
Risk factors, N (%)			
Hypertension	656 (41.8)	59 (39.3)	0.333
Diabetes	281 (17.9)	24 (16.0)	0.346
Hypercholesterolemia	483 (30.8)	38 (25.3)	0.374
CAG status, N (%)			**0.043**
Urgent	189 (12.1)	26 (17.3)	
Elective	585 (37.3)	48 (32.0)	
Unknown	794 (50.6)	76 (50.7)	
CAG indication, N (%)			**0.015**
Elective	396 (25.3)	24 (16.0)	
STEMI	58 (3.7)	11 (7.3)	
NSTEMI	46 (2.9)	9 (6.0)	
Post ACS	73 (4.7)	6 (4.0)	
Unstable AP	77 (4.9)	6 (4.0)	
Unknown	918 (58.5)	93 (62.6)	
Complications, N (%)			0.660
Yes	15 (1.0)	2 (1.3)	
No	1387 (88.5)	136 (90.7)	
Unknown/Other	166 (10.6)	12 (8.0)	
Total fluor time [min], median (IQR)	5 (3-9)	7 (4-11)	**<0.001**

Abbreviations: *ACS, acute coronary syndrome; AP, angina pectoris; CAG, coronary angiography; IQR, interquartile range; (N)STEMI, (non)-ST-elevation myocardial infarction; PCI, percutaneous intervention.*

APPENDIX G: Example ICI Form as used at Erasmus MC

Patient number:
DOB:
Age:
Length:
Weight:
Sex:

Procedure type:
Procedure indication:
Study:
Cardiologist(s):
Nurse(s):
Starting time:

Pullback 1:

Modality:	☐IVUS	☐OCT	☐iFR	☐FFR	☐etc.
Vessel:	☐LAD	☐RCA	☐RCx	☐etc.	
Wire:	☐BMW	☐Pilot	☐BHW	☐etc.	
Machine:	☐Vulcano	☐OPTIS	☐etc.		
Speed:	…. mm/sec	Contrast:	…. mL/sec	Total	… mL
Remarks:					

Pullback 2:

Modality:	☐IVUS	☐OCT	☐iFR	☐FFR	☐etc.
Vessel:	☐LAD	☐RCA	☐RCx	☐etc.	
Wire:	☐BMW	☐Pilot	☐BHW	☐etc.	
Machine:	☐Vulcano	☐OPTIS	☐etc.		
Speed:	…. mm/sec	Contrast:	…. mL/sec	Total	… mL
Remarks:					

Pullback 3:

Modality:	☐IVUS	☐OCT	☐iFR	☐FFR	☐etc.
Vessel:	☐LAD	☐RCA	☐RCx	☐etc.	
Wire:	☐BMW	☐Pilot	☐BHW	☐etc.	
Machine:	☐Vulcano	☐OPTIS	☐etc.		
Speed:	…. mm/sec	Contrast:	…. mL/sec	Total	… mL
Remarks:					

Pullback 3:

Modality:	☐IVUS	☐OCT	☐iFR	☐FFR	☐etc.
Vessel:	☐LAD	☐RCA	☐RCx	☐etc.	
Wire:	☐BMW	☐Pilot	☐BHW	☐etc.	
Machine:	☐Vulcano	☐OPTIS	☐etc.		
Speed:	…. mm/sec	Contrast:	…. mL/sec	Total	… mL
Remarks:					

Etcetera.

Figure G-1. Example form representing the ICI form used by the imaging technicians at the cathlab of the Erasmus MC.

APPENDIX H: ICI Survey Interventional Cardiologists

INTRACORONARY IMAGING SURVEY LUMC

1. Introduction
This survey is part of an OCT feasibility study prior to implementation of OCT at the LUMC. This survey is intended for interventional cardiologists and imaging technicians involved with percutaneous interventions at a cathlab. By attending this survey, you will contribute to a structured implementation of OCT at the LUMC. The main goals are: (1) Accessing whether the implementation of OCT is supported among clinicians (2) Identifying the field of application of intracoronary imaging (3) Accessing how intracoronary imaging is implemented in daily clinical practice This survey contains 37 questions. First you will be asked about your personal experience with percutaneous interventions and intracoronary imaging. Second, questions will be asked to access your personal opinion on intracoronary imaging. Third, questions related to the field of application of intracoronary imaging will be asked. Last, you will be asked about issues with intracoronary imaging in daily clinical practice. This survey should take no longer than twenty minutes. After filling in this survey, please send it to t.t.m.oosterveer@lumc.nl. If you have any questions related to this survey, please send an email. Your data will be processed anonymously. Thank you for attending this survey, we really appreciate your input!

2. Personal information *For each criterium below, check the boxes applicable for your situation or specify when asked.*		
Profession	☐Interventional cardiologist ☐Imaging technician	☐Heart function lab technician ☐Other, namely Click here to enter text.
Since (year)	Click here to enter text.	
Workplace	☐LUMC	☐Other, namely Click here to enter text.

3. Personal experience with percutaneous interventions and intracoronary imaging *Answer the questions below by checking the boxes applicable for your situation. Please specify when asked.*	
How many percutaneous interventions (including diagnostics only) did you perform or assist over the last year (i.e. over the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None → Go to 4
How many OCT acquisitions did you perform or assist over the last year (i.e. the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None

How many IVUS acquisitions did you perform or assist over the last year (i.e. over the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None

4a. Personal opinion on intracoronary imaging *To what extend do you agree with the following statements? Motivate your answers.*					
	Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
Intracoronary imaging in general is an essential tool for interventional cardiology	☐	☐	☐	☐	☐
Only IVUS is an essential tool for interventional cardiology	☐	☐	☐	☐	☐
Only OCT is an essential tool for interventional cardiology	☐	☐	☐	☐	☐
I would like OCT as a novel imaging technique at the Cath lab of the LUMC	☐	☐	☐	☐	☐
OCT and IVUS are complementary	☐	☐	☐	☐	☐
OCT and IVUS are interchangeable	☐	☐	☐	☐	☐
I prefer only one technique, either IVUS or OCT, rather than choosing between them	☐	☐	☐	☐	☐
The need for an automatic contrast injector for OCT image acquisition would resist me from using OCT	☐	☐	☐	☐	☐
Motivation Click here to enter text.					

4b. Personal opinion on intracoronary imaging *Answer the questions below. Motivate your answers.*	
In your opinion, how much time is acceptable for intracoronary imaging?	Click here to enter text.
Which pullback method would you prefer and why?	☐manual pullback ☐automatic pullback Click here to enter text.
In your opinion, is co-registration between the angiogram and the intracoronary images important? Motivate your answer.	☐not important ☐important Click here to enter text.
In your opinion, what are major benefits of intracoronary imaging?	Click here to enter text.
In your opinion, what are major drawbacks of intracoronary imaging?	Click here to enter text.

5a. Field of application of intracoronary imaging *Name at least five situations where you would rate the use of intracoronary imaging appropriate. For each situation, specify which modality or which modalities are appropriate. Motivate your answers.*		
1. Click here to enter text.	☐IVUS	☐OCT

2. Click here to enter text.	☐IVUS	☐OCT
3. Click here to enter text.	☐IVUS	☐OCT
4. Click here to enter text.	☐IVUS	☐OCT
5. Click here to enter text.	☐IVUS	☐OCT
6. Click here to enter text.	☐IVUS	☐OCT
7. Click here to enter text.	☐IVUS	☐OCT
8. Click here to enter text.	☐IVUS	☐OCT
9. Click here to enter text.	☐IVUS	☐OCT
10. Click here to enter text.	☐IVUS	☐OCT
Motivation Click here to enter text.		

5b. Field of application of intracoronary imaging

For each situation below, select the technique(s) you would rate appropriate. Motivate or specify your answers.

	Angiography	**Functional (iFR/FFR)**	**IVUS**	**OCT**
Pre-PCI imaging for strategy guidance (stent sizing, deployment site)	☐	☐	☐	☐
Guidance in left-main stenoses	☐	☐	☐	☐
Post-procedural stent optimization (expansion, apposition, edge dissections)	☐	☐	☐	☐
Guidance in bifurcation lesions	☐	☐	☐	☐
Guidance in chronic total occlusions	☐	☐	☐	☐
Identifying the culprit lesion in patients with acute coronary syndrome	☐	☐	☐	☐
Identifying the mechanisms behind acute coronary syndrome (plaque rupture or dissection)	☐	☐	☐	☐
Evaluating in-stent restenosis	☐	☐	☐	☐
Evaluating stent thrombosis	☐	☐	☐	☐
Symptomatic patients with normal angiograms	NA	☐	☐	☐
Assessment of proximal intermediate lesions with uncertain severity	☐	☐	☐	☐
Assessment of non-proximal intermediate lesions with uncertain severity	☐	☐	☐	☐
Assessment of angiographically hazy lesions	☐	☐	☐	☐

Motivation/Specification

Click here to enter text.

Are there any other cases which may be appropriate for either IVUS or OCT which have not been mentioned yet? If yes, please specify the case(s) and for which technique the case(s) is (are) applicable.

☐Yes, namely Click or tap here to enter text.

☐No

6a. Implementation of intracoronary imaging *Answer the questions below about your department. Motivate your answers.*	
Is there a protocol on <u>when</u> to use intracoronary imaging?	☐Yes ☐No ☐I do not know
Imagine there is a protocol on <u>when</u> to use intracoronary imaging. Would you follow this protocol? If not, why not?	☐Yes ☐No, Click here to enter text. ☐I do not know
Is there a protocol on <u>how</u> to use intracoronary imaging?	☐Yes ☐No ☐I do not know
How often do you experience problems while using intracoronary imaging? Please enter a ratio (e.g. 1 out of 8). Specify for each modality.	IVUS: Click here to enter text. OCT: Click here to enter text. ☐I never experience any problems → Go to 6b ☐I never use intracoronary imaging → Go to 6b
Give some examples of the most frequently occurring problems with IVUS	Click here to enter text. ☐I never use IVUS
Give some examples of the most frequently occurring problems with OCT	Click here to enter text. ☐I never use OCT
Can you remember the implementation of IVUS at the LUMC?	☐Yes ☐No → Go to 6b
Were there any problems during the implementation process? If yes, please specify	☐Yes, Click or tap here to enter text. ☐No
Wat went well during the implementation process?	Click or tap here to enter text.

6b. Implementation of intracoronary imaging *Are there any remarks you want to share, related to the implementation of intracoronary imaging, which we should keep in mind during the implementation process?*
Click here to enter text.

7. Please write down any other remarks you want to share.
Click here to enter text.

Thank you for attending this survey, we really appreciate your input! You can send this survey to t.t.m.oosterveer@lumc.nl.

APPENDIX I: ICI Survey Cathlab Technicians

INTRACORONARY IMAGING SURVEY LUMC

1. Introduction
This survey is part of an OCT feasibility study prior to implementation of OCT at the LUMC. This survey is intended for heart function laboratory technicians involved with percutaneous interventions at a cathlab. By attending this survey, you will contribute to a structured implementation of OCT at the LUMC. The main goals are: (1) Accessing whether the implementation of OCT is supported among clinicians (2) Identifying the field of application of intracoronary imaging (3) Accessing how intracoronary imaging is implemented in daily clinical practice This survey contains 21 questions. First you will be asked about your personal experience with percutaneous interventions and intracoronary imaging. Second, questions will be asked to access your personal opinion on intracoronary imaging. Third, questions related to the field of application of intracoronary imaging will be asked. Last, you will be asked about issues with intracoronary imaging in daily clinical practice. This survey should take no longer than fifteen minutes. After filling in this survey, please send it to t.t.m.oosterveer@lumc.nl. If you have any questions related to this survey, please send an email. Your data will be processed anonymously. Thank you for attending this survey, we really appreciate your input!

2. Personal information *For each criterium below, check the boxes applicable for your situation or specify when asked.*		
Profession	☐Interventional cardiologist ☐Imaging technician	☐Heart function lab technician ☐Other, namely Click here to enter text.
Since (year)	Click here to enter text.	
Workplace	☐LUMC	☐Other, namely Click here to enter text.

3. Personal experience with percutaneous interventions and intracoronary imaging *Answer the questions below by checking the boxes applicable for your situation. Please specify when asked.*	
How many percutaneous interventions (including diagnostics only) did you perform or assist over the last year (i.e. over the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None → Go to 4
How many OCT acquisitions did you perform or assist over the last year (i.e. the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None

How many IVUS acquisitions did you perform or assist over the last year (i.e. over the last 365 days or in 2018)?	☐< 50 ☐> 50 & < 100 ☐> 100 ☐None

4. Personal opinion on intracoronary imaging *Answer the questions below. Motivate your answers.*		
Do you feel comfortable using intracoronary imaging?	☐Yes	☐No
Are you aware of the purposes of intracoronary imaging?	☐Yes	☐No
Are you aware of the benefits of intracoronary imaging for the patients?	☐Yes	☐No
In your opinion, what is a major drawback of intracoronary imaging?	Click here to enter text.	

5a. Implementation of intracoronary imaging *Answer the questions below about your department. Motivate your answers.*	
Is there a protocol on <u>when</u> to use intracoronary imaging?	☐Yes ☐No ☐I do not know
Imagine there is a protocol on <u>when</u> to use intracoronary imaging. Would you follow this protocol? If not, why not?	☐Yes ☐No, Click here to enter text. ☐I do not know
Is there a protocol on <u>how</u> to use intracoronary imaging?	☐Yes ☐No ☐I do not know
How often do you experience problems while using intracoronary imaging? Please enter a ratio (e.g. 1 out of 8). Specify for each modality.	IVUS: Click here to enter text. OCT: Click here to enter text. ☐I never experience any problems → Go to 6b ☐I never use intracoronary imaging → Go to 6b
Give some examples of the most frequently occurring problems with IVUS	Click here to enter text. ☐I never use IVUS
Give some examples of the most frequently occurring problems with OCT	Click here to enter text. ☐I never use OCT
Can you remember the implementation of IVUS at the LUMC?	☐Yes ☐No → Go to 6b
Were there any problems during the implementation process? If yes, please specify	☐Yes, Click or tap here to enter text. ☐No
Wat went well during the implementation process?	Click or tap here to enter text.

5b. Implementation of intracoronary imaging *Are there any remarks you want to share, related to the implementation of intracoronary imaging, which we should keep in mind during the implementation process?*
Click here to enter text.

6. Please write down any other remarks you want to share.
Click here to enter text.

Thank you for attending this survey, we really appreciate your input! You can send this survey to t.t.m.oosterveer@lumc.nl.

APPENDIX J: Full Cost Calculations per Markov State

PCI state

Osnabrugge et al. (2015) assessed the cost-effectiveness of PCI vs. CABG, whereas Van Hout et al. (2005) assessed the cost-effectiveness of DES vs. bare metal stents (BMS).[104, 107] All patients included in the analysis by Osnabrugge et al. had either three-vessel or left main CAD. The patients included in the DES group in the analysis by Van Hout et al. had stable or unstable angina receiving 1.03 DES per procedure. Both studies reported full costs after one year, including hospital stay, follow-up, medication and rehabilitation. Costs were recalculated to 2020 euros based on the consumer price index (CPI) reported by CBS StatLine using equations J-1 and J-2.[116] As the CPI for 2020 is yet unknown, it was assumed that the CPI difference between 2020 and 2019 was the same as the difference between 2019 and 2018.

$$costs\ 2020 = f \cdot reported\_costs\_year \quad \text{(J-1)}$$

$$f = \left(\frac{\mathrm{CPI}_{2020}}{\mathrm{CPI}_{reported\ year}}\right) \quad \text{(J-2)}$$

It was assumed that the costs by Van Hout et al. were applicable on patients receiving one or two stents. Costs by Osnabrugge et al. were considered for patients receiving three or more stents. Therefore the initial costs for the first year were €15,927.10. Table J-1 shows the calculation of these costs based on the LUMC population between the first of January 2018 and the twentieth of December 2019. Lower and upper values were calculated based on weights of 1.00 and 0.00.

Table J-1. *Initial PCI cost calculations (including one year of follow-up).*

	Costs	Year	Factor	2020 €	Weight	Total (€)
Osnabrugge et al. (2015)	17,495	2012	1.1344	19,847.01	0.34	6,777.03
Van Hout et al. (2005)	9,969	2001	1.3938	13,894.56	0.66	9,150.08
Total						**15,927.10**

Costs for the catheters were added to the costs in the IVUS and OCT model to account for the difference in catheter costs, as OCT catheters are more expensive than IVUS catheters (Table J-2). In addition, in the OCT and IVUS model, costs for medical devices were added to the total costs. Costs for medical devices were calculated using Equations J-3 and J-4. All values were based on costs for OCT. It was assumed that medical device costs for OCT and IVUS are comparable. Furthermore, as CAG is used in all models, no additional medical device costs for CAG were taken into account. Table J-3 shows the input values and calculations for medical device costs.

Table J-2. *Catheter costs IVUS and OCT based on LUMC tariffs.*

Catheter	Costs (excl. BTW)	Year	BTW	Costs (incl. BTW)
IVUS	560.00	2020	9%	610.40
OCT	1250.00	2020	9%	1,362.50

$$medical\ device\ costs\ per\ annum = \frac{Rep - \frac{Rest}{(1+i)^n}}{a_{n,i}} \quad \text{(J-3)}$$

$$a_{n,i} = \frac{1}{i} \cdot \left(1 - \frac{1}{(1+i)^n}\right) \quad \text{(J-4)}$$

Where,

Rep = replacement value (€)
Rest = rest value after n years (€)
i = interest (%)
n = depreciation period (years)
a = annuity factor

Table J-3. *Input variables equations J-3 and J-4 and outcomes for the calculation of medical device costs per procedure. * Calculated based on quotations by Abbott Medical Nederland B.V.*

Variables	Value	
Rep, replacement value* (€)	139,029.00	
Rest, rest value after *n* years (€)	0	
i, interest (%)	4.2	
n, depreciation period (years)	10	
a, annuity factor	8.03	(Eq. B-4)
Total medical device costs per annum	**24,112.10**	
Medical device costs per annum (€)	17,312.10	(Eq. B-3)
Maintenance per annum (€)	6,800.00	
Procedures per annum (N)	**150**	
Costs per procedure (€)	**160.75**	

Event free state

Costs during the event free state were based on expert input, the Dutch Healthcare Authority database, Dutch medicine costs, and Dutch laboratory tariffs.[99, 108, 109, 114, 115] Costs for the event free state were considered from one year after the initial PCI. Table J-4 shows the full calculation of the point estimate. Lower and upper values were based on follow-up costs published by Osnabrugge et al. (2015) (Table J-5).[104] The upper value was calculated as mean follow-up costs for year 1 to 5, excluding rehospitalization. The lower value was calculated as mean follow-up costs, excluding both rehospitalization as rehabilitation. Costs for year 1 were set to zero. The latter was considered to be justifiable as follow-up costs for year 1 were already incorporated in the PCI state and patients in the study by Osnabrugge et al. were all patients with severe disease. Lower and upper values were recalculated to 2020 euros using the factor as presented in Table J-1.

Table J-4. *Calculation of the point estimate of the event free state one year after PCI. Total costs are in 2020 euros. *P2Y12 inhibitors were considered only during the first year.*

	2015	Factor	2020	Number	Total
Outpatient clinic	163.00	1.0895	177.59	1	**177.59**
Patient expenses	18.33	1.0895	19.97	1	**19.97**
Travel expenses	1.33	1.0895	1.45	1	1.45
Parking costs	3.00	1.0895	3.27	1	3.27
Informal care	14.00	1.0895	15.25	1	15.25
Diagnostics			23.81	1	**23.81**
Order costs			12.13	1	12.31
Creatinine			1.71	1	1.71
HDL-cholesterol			2.39	1	2.39
Triglycerides			2.51	1	2.51
Total cholesterol			1.79	1	1.79
Glucose			1.71	1	1.71
Albumin			1.57	1	1.57
Productivity costs	48.75	1.0895	53.11	1	**53.11**
Employed	34.75	1.0895	37.86	1	37.86
Unemployed	14.00	1.0895	15.25	1	15.25
Medication			-	1	**148.35**
Ascal			0.06	365.25	21.92
Statin			0.04	365.25	15.34
Pantoprazole			0.03	365.25	9.13
Ace inhibitor			0.21	365.25	77.62
Beta-blocker			0.07	365.25	24.35
P2Y12-inhibitors*			0	0	0
Total					**422.84**

Table J-5. *Follow-up costs as presented by Osnabrugge et al. (2015). Costs are in 2012 euros.*

	Year 1	Year 2	Year 3	Year 4	Year 5	Mean
Rehospitalization	2,647	1,285	1,033	1,092	1,066	-
Outpatient services	240	141	73	91	81	-
Rehabilitation	114	13	13	15	16	-
Medication	176	197	202	213	223	-
MD fees	280	135	106	118	99	-
Lower	0	473	381	422	403	335.80
Upper	810	486	394	437	419	509.20
Lower (2020 €)						**380.94**
Upper (2020 €)						**577.94**

Revascularization state

Van Hout et al. (2005) mentioned costs for patients receiving a first revascularization or an additional revascularization. For the point estimate, it was assumed that the proportion of patients receiving either a first or a second revascularization was 50%. The lower and upper values were considered to be the costs for a first and additional revascularization respectively. Full calculations of the point estimate, lower and upper values are shown in Table J-6.

Table J-6. *Calculation of the point estimate of the revascularization from state one year after PCI. Total costs are in 2020 euros.*

	Costs	Year	Factor	2020 €	Weight	Total (€)
First revascularization	4,374.00	2001	1.3938	6,096.38	0.50	3,048.19
Additional revascularization	6,665.00	2001	1.3938	9,289.52	0.50	4,644.76
Total						**7,692.95**

Myocardial infarction state

Costs for the myocardial infarction state were calculated based on Soekhlal et al. (2013).[110] Soekhlal et al. aimed to calculate the treatment costs for acute myocardial infarction in the Netherlands. The study by Soekhlal et al. included 25,657 patients in 2012. Mean treatment costs reported by Soekhlal et al. was € 5,021 (2012 euros). These costs included all sorts of treatment. The highest cost were €6,060 for non-STEMI patients receiving PCI. Based on expert input, it was assumed that patients experiencing MI after PCI receive a revascularization. Therefore the point estimate was set the highest costs reported by Soekhlal et al. The lower value was set to the mean costs, regardless treatment. The upper value was set to the point estimate plus the standard deviation as reported by Soekhlal et al. Table J-7 shows the full calculations.

Table J-7. *Calculation of the point estimate of the MI state from one year after PCI. Total costs are in 2020 euros.*

	Costs	Year	Factor	2020 €
Mean costs, regardless treatment (lower)	5,021.00	2012	1.1344	5,696.02
Non-STEMI receiving PCI	6,060.00	2012	1.1344	6,874.70
Non-STEMI receiving PCI plus SD (upper)	10,367.00	2012	1.1344	11,760.73

APPENDIX K: Full Results of the Univariate Deterministic Sensitivity Analysis

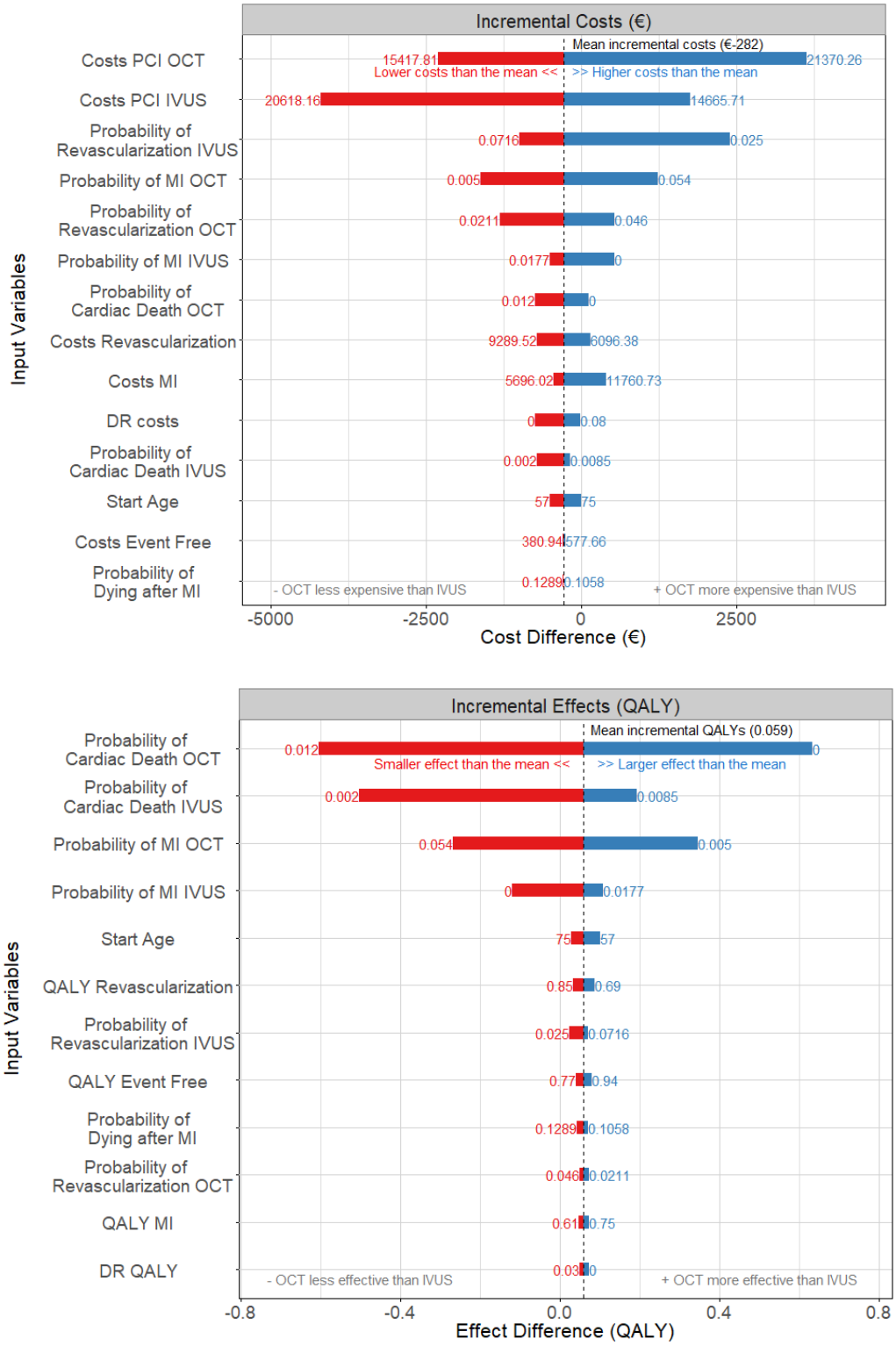

Figure K-1. *Tornado diagrams showing the full results of the univariate deterministic sensitivity analysis. Abbreviations: DR = discount rate; IVUS = intravascular ultrasound; MI = myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous intervention; QALY = quality-adjusted life year.*

APPENDIX L: The Covenant in Relation to the Procedures at the LUMC

Table L-1. *Procedures for the introduction of medical devices according to the Covenant (chapter 3) in relation to the procedures at the department of interventional cardiology at the LUMC.*

Article	Short description	Department procedure
3.1	Procedure for composing and archiving product files	Product files are composed by the general clinical physicist (in cooperation with the initiator). Product files are archived in JOIN.
3.2	Purchase procedure	Procedure is described schematically (available on Albinusnet) incorporating the tasks of all relevant disciplines.
3.3	Replacement procedure based on risk management	Covered in the risk analysis. No specific replacement procedure.
3.4	Ordering procedure	FLITS (PeopleSoft) software is used to manage the order process. Orders are only approved when the product file is complete.
3.5	Identification and registration at delivery	Registration in FLITS / Match with purchase order at delivery.
3.6	Procedure for the management of registration data of medical devices	Managed by the department of instrumental affairs / Registration in Ultimo.
3.7	Involved employees can access and are aware of the instruction manual	Instruction manuals are published on iProva, a quality management system, and are hard-copy provided with medical devices.
3.8	Procedure for providing competences to employees	Training is provided and registered in the quality passport (competence registration system) before initial use.
3.9	Procedure for inspection and verification device specifications and statement of requirements	Clinical technology (dep. of instrumental affairs) performs check after delivery / Registration in Ultimo.
3.10	Procedure for compatibility check IT and infrastructure	Described in purchase procedure and covered in the risk analysis.
3.11	Procedure for trial or at-sight installations	Described in the purchase procedure.
3.12	Implementation procedure	Same as purchase procedure. No separate implementation procedure.

Table L-2. *Procedures for the use of medical devices according to the Covenant (chapter 4) in relation to the procedures at the department of interventional cardiology at the LUMC.*

Article	Short description	Procedure
4.1	User has access to quality of the device in terms of maintenance, configuration, expiration date, sterility and compatibility infrastructure prior to use	Checked by clinical technology. A yellow sticker is attached to the device with the next maintenance date. All information is stored in Ultimo.

Article	Short description	Procedure
4.2	Procedure for cleaning, disinfecting and sterilization	Protocols are available on iProva. Employees are notified before use. The need is covered in the risk analysis.
4.3	Storage procedure	Covered in risk analysis. No separate storage procedure.
4.4	Loan procedure	Procedure is described schematically (available on Albinusnet) incorporating the tasks of all relevant disciplines.
4.5	Procedure for research with medical devices	Procedure is available on Albinusnet.
4.6	Procedure for reporting incidents with medical devices	General incident reporting form. It is possible to indicate the involvement of a medical device.
4.7	Procedure for registration and management of competences of employees	Training and retraining is provided and registered in the quality passport.
4.8	Procedure for concessions when defects of the medical device are observed	Defects need to be reported to the department of instrumental affairs. No concession procedure available. The user is responsible.
4.9	Procedure for undiscovered defects in used medical devices.	General incident reporting form. It is possible to indicate the involvement of a medical device.
4.10	Procedure to verify competences of internal technicians	Technicians are responsible for a specific device group. These device groups are allocated in line with education and courses undergone by the technicians. Education and training is monitored by de department of instrumental affairs.
4.11	Procedure to verify competences of external technicians	Competences of external technicians is assured in the service agreements with manufacturers.
4.12	Procedure to check quality of training of employees	Education and training is monitored by de department of instrumental affairs, including content and dates. Education and training of clinicians is monitored in the quality passport.
4.13	Procedure for planning and execution of preventive maintenance	Registration in Ultimo.
4.14	Procedure for quality assurance	Carried out by clinical technology on arrival and after maintenance / Registration in Ultimo.

Article	Short description	Procedure
4.15	Procedure for extended use beyond the expiration date	In general, devices beyond the expiration date are not used in clinical practice. However, this is the responsibility of the user.
4.16	Procedure for reporting maintenance data periodically to management	Registration in Ultimo.
4.17	Procedure for evaluating maintenance plan, quality assurance plan and validations	With large companies, maintenance and malfunctions are discussed on a yearly basis. With smaller companies, evaluation is only performed when there is a specific reason.
4.18	Procedure to resolve defects	Defects need to be reported to the department of instrumental affairs. Specific procedures can vary based on the service contracts with manufacturers.
4.19	Procedure for the storage of maintenance data	Registration in Ultimo.
4.20	Procedure to analyze and evaluate defects to improve maintenance procedures	Malfunctions are registered in Ultimo. Technicians analyze these registration for trends. When necessary, malfunctions are discussed in a group of technicians or with the manufacturer. This is a standard agenda item during monthly meetings.
4.21	Procedure for receiving and dealing with urgent notifications considering the reliability of medical devices	There is a contact point, where manufacturers can report issues with their devices. In addition, notifications from world organizations are monitored (e.g. ECRI.org). Experiences and data between academic centers in the Netherlands is exchanged (WIBAZ). Clinicians can report issues via the incident management system.

Table L-3. *Procedures for the disposal of medical devices according to the Covenant (chapter 5) in relation to the procedures at the department of interventional cardiology at the LUMC.*

Article	Short description	Procedure
5.1	Procedure for physical removal of medical devices from the department	Procedure available on Albinusnet. Contact department of instrumental affairs. Mark device clearly as out of order.
5.2	Medical devices present at the department only for training purposes are clearly identified as such	Medical devices for training purposes are clearly marked with a label.
5.3	Procedure for administering disposal of medical devices	Registration in Ultimo.

APPENDIX M: Source Code Markov Model in R

```
"This script runs a Markov model comparing the costs and effects of ICI techniques.
The following comparisons were performed:
- Base case: IVUS vs. OCT
- Scenarios: RCT results (Kubo et al. (2017)), Best/Worst cases, Discounting scenarios
- Secondary base case: IVUS vs. OCT vs. CAG
-----------------------------------------------------------------------------------------------------------------------------------------------
Based on the heemod package, Source: https://cran.r-project.org/web/packages/heemod/index.html
Filipović-Pierucci A, Zarca K, Durand-Zaleski I. Markov Models for Health Economic Evaluations: The R Package heemod. arXiv
preprint arXiv:170203252.2017
-----------------------------------------------------------------------------------------------------------------------------------------------
Author: Timo Oosterveer
Date: April-June 2020"
-----------------------------------------------------------------------------------------------------------------------------------------------
# Load required R packages
library(heemod)
library(diagram)
library(survival)
library(flexsurv)
library(ggplot2)
require(scales)

"Base case / Secondary Base case - Model inputs"

# Defining transition matrix OCT model (state names and transition probabilities)
mat_oct <- define_transition(
  state_names = c("pci", "ef", "reva", "mi", "death"),

  0, C, p_reva_oct, p_mi_oct, p_death_oct,
  0, C, p_reva_oct, p_mi_oct, p_death_oct,
  0, C, 0, p_mi_oct, p_death_oct,
  0, C, 0, 0, p_death_mi,
  0, 0, 0, 0, 1)

# Defining transition matrix IVUS model (state names and transition probabilities)
mat_ivus <- define_transition(
  state_names = c("pci", "ef", "reva", "mi", "death"),

  0, C, p_reva_ivus, p_mi_ivus, p_death_ivus,
  0, C, p_reva_ivus, p_mi_ivus, p_death_ivus,
  0, C, 0, p_mi_ivus, p_death_ivus,
  0, C, 0, 0, p_death_mi,
  0, 0, 0, 0, 1)

# Defining transition matrix CAG model (state names and transition probabilities)
mat_angio <- define_transition(
  state_names = c("pci", "ef", "reva", "mi", "death"),

  0, C, p_reva_angio, p_mi_angio, p_death_angio,
  0, C, p_reva_angio, p_mi_angio, p_death_angio,
  0, C, 0, p_mi_angio, p_death_angio,
  0, C, 0, 0, p_death_mi,
  0, 0, 0, 0, 1)

# Defining utilities and costs for health states as named above (all models)
# PCI state
state_pci <- define_state(
  cost_treat = dispatch_strategy(                  # Different costs for CAG, OCT & IVUS
    angio = cost_angio,
    oct = cost_oct,
    ivus = cost_ivus),
  cost_total = discount(cost_treat, r = cost_dr),  # Cost_total is discounted with rate 'r'
  qaly = qaly_pci,                                 # Utility for PCI state (all models)
  qaly_total = discount(qaly, r = qaly_dr))        # Discounting utilities
```

```
# EF state
state_ef <- define_state(
  cost_treat = cost_ef,
  cost_total = discount(cost_treat, r = cost_dr),
  qaly = qaly_ef,
  qaly_total = discount(qaly, r = qaly_dr))

# REVA state
state_reva <- define_state(
  cost_treat = cost_reva,
  cost_total = discount(cost_treat, r = cost_dr),
  qaly = qaly_reva,
  qaly_total = discount(qaly, r = qaly_dr))

# MI state
state_mi <- define_state(
  cost_treat = cost_mi,
  cost_total = discount(cost_treat, r = cost_dr),
  qaly = qaly_mi,
  qaly_total = discount(qaly, r = qaly_dr))

# Death state
state_death <- define_state(
  cost_treat = cost_death,
  cost_total = discount(cost_treat, r = cost_dr),
  qaly = qaly_death,
  qaly_total = discount(qaly, r = qaly_dr))

# Defining different strategies (CAG, OCT and IVUS)
strat_angio <- define_strategy(
  transition = mat_angio,                    # Assigning previous defined transition matrix
  pci = state_pci,                           # Assigning utilities and costs to CAG strategy
  ef = state_ef,
  reva = state_reva,
  mi = state_mi,
  death = state_death)

strat_oct <- define_strategy(
  transition = mat_oct,                      # Assigning previous defined transition matrix
  pci = state_pci,                           # Assigning utilities and costs to OCT strategy
  ef = state_ef,
  reva = state_reva,
  mi = state_mi,
  death = state_death)

strat_ivus <- define_strategy(
  transition = mat_ivus,                     # Assigning previous defined transition matrix
  pci = state_pci,                           # Assigning utilities and costs to IVUS strategy
  ef = state_ef,
  reva = state_reva,
  mi = state_mi,
  death = state_death)

# Defining global model parameters (all models)
par_mod <- define_parameters(
  age_start = 66,                            # Start age cohort: i.e. mean age cohort LUMC
  age_cycle = model_time + age_start)        # counter to model cohort age

# Defining death probabilities (all models)
par_mod <- modify(                           # Modify par_mod (contains all input parameters)
  par_mod,

  sex_mle = "MLE",                           # Define male gender
  p_death_mle = get_who_mr(                  # Retrieve death probability WHO database (lifetable)
    age = age_cycle,                         # Death probability is age and gender dependent
    sex = sex_mle,
```

```
  country = "NLD",                          # Retrieve death probability for the Dutch population
  local = TRUE),                            # Data is stored locally for 1 hour (increases performance)

 sex_fmle = "FMLE",
 p_death_fmle = get_who_mr(
  age = age_cycle,
  sex = sex_fmle,
  country = "NLD",
  local = TRUE),

 p_death_lifetable = (0.756*p_death_mle) +  # Calculate mean death probability per age/gender
                     (0.244*p_death_fmle),

 p_death_angio_cardiac = 0.0133,            # Probability of cardiac death CAG model
 p_death_angio = combine_probs(             # Combine lifetable with cardiac death CAG
  p_death_angio_cardiac,
  p_death_lifetable),

 p_death_oct_cardiac = 0.00533,             # Probability of cardiac death OCT model
 p_death_oct = combine_probs(               # Combine lifetable with cardiac death OCT
  p_death_oct_cardiac,
  p_death_lifetable),

 p_death_ivus_cardiac = 0.00722,            # Probability of cardiac death IVUS model
 p_death_ivus = combine_probs(              # Combine lifetable with cardiac death IVUS
  p_death_ivus_cardiac,
  p_death_lifetable),

 p_death_mi_no_lt = 0.1152,                 # Probability of death after MI (all models)
 p_death_mi = combine_probs(                # Combine lifetable with death after MI
  p_death_mi_no_lt,
  p_death_lifetable))

# Defining transitions probabilities for revascularization and MI states
par_mod <- modify(
 par_mod,

 p_reva_angio = 0.0786,                     # Probability of revascularization CAG
 p_reva_oct = 0.0348,                       # Probability of revascularization OCT
 p_reva_ivus = 0.0615,                      # Probability of revascularization IVUS
 p_mi_angio = 0.0284,                       # Probability of MI CAG
 p_mi_oct = 0.0269,                         # Probability of MI OCT
 p_mi_ivus = 0.0139)                        # Probability of MI IVUS

# Defining costs, qaly's and discount rates
par_mod <- modify(
 par_mod,

 cost_angio = 15927.10,                     # Costs
 cost_oct = 17450.35,
 cost_ivus = 16698.25,
 cost_ef = 422.84,
 cost_reva = 7692.95,
 cost_mi = 6874.70,
 cost_death = 0,
 qaly_pci = 0.71,                           # QALYs
 qaly_ef = 0.85,
 qaly_mi = 0.68,
 qaly_reva = 0.77,
 qaly_death = 0,
 cost_dr = 0.04,                            # Discount rates
 qaly_dr = 0.015)

"Base case / Secondary Base case – Running Models"

# Running the Base case: IVUS vs. OCT
```

```
res_mod <- run_model(                          # Run model and store results in 'res_mod'
  parameters = par_mod,                        # Use 'par_mod' as input parameters
  oct = strat_oct,                             # Strategies
  ivus = strat_ivus,
  cycles = 35,                                 # Number of cycles
  cost = cost_total,                           # Outcome costs
  effect = qaly_total,                         # Outcome effects
  central_strategy = "ivus",                   # Reference strategy (i.e. old treatment)
  method = "end")                              # State_time is assumed to be an integer (1, 2, 3, etc.)

summary(res_mod, threshold = c(1000, 5000, 15000)) # Print results 'res_mod' to screen
plot(res_mod, type="ce")                       # Plot cost-effectiveness plane
plot(res_mod, type = "counts")                 # Plot number of patients per state per cycle
plot(res_mod, type = "values")                 # Plot cost/effect contribution per cycle

# Running the Secondary Base case: IVUS vs. OCT vs. CAG
res_mod2 <- run_model(                         # Run model and store results in 'res_mod2'
  parameters = par_mod,                        # Use 'par_mod' as input parameters
  angio = strat_angio,                         # Strategies
  oct = strat_oct,
  ivus = strat_ivus,
  cycles = 35,                                 # Number of cycles
  cost = cost_total,                           # Outcome costs
  effect = qaly_total,                         # Outcome effects
  central_strategy = "angio",                  # Reference strategy (i.e. old treatment)
  method = "end")                              # State_time is assumed to be an integer (1, 2, 3, etc.)

summary(res_mod2, threshold = c(1000, 5000, 15000)) # Print results 'res_mod2' to screen
plot(res_mod2, type="ce")                      # Plot cost-effectiveness plane
plot(res_mod2, type = "counts")                # Plot number of patients per state per cycle
plot(res_mod2, type = "values")                # Plot cost/effect contribution per cycle

"Base case - Deterministic Sensitivity Analysis (DSA)"

# Define DSA parameters (i.e. upper and lower values as reported in the literature)
def_dsa <- define_dsa(
  age_start, 57, 75,                           # Start age
  p_reva_oct, 0.0211, 0.0460,                  # Transition probabilities
  p_reva_ivus, 0.0250, 0.0716,
  p_mi_oct, 0.005, 0.054,
  p_mi_ivus, 0.00, 0.0177,
  p_death_oct_cardiac, 0.00, 0.012,
  p_death_ivus_cardiac, 0.002, 0.0085,
  p_death_mi_no_lt, 0.1058, 0.1289,
  cost_oct, 15417.81, 21370.26,                # Costs
  cost_ivus, 14665.71, 20618.16,
  cost_ef, 380.94, 577.66,
  cost_reva, 6096.38, 9289.52,
  cost_mi, 5696.02, 11760.73,
  qaly_pci, 0.47, 0.95,                        # Utilities
  qaly_ef, 0.77, 0.94,
  qaly_mi, 0.61, 0.75,
  qaly_reva, 0.69, 0.85,
  cost_dr, 0, 0.08,                            # Discount rates
  qaly_dr, 0, 0.03)

# Running dsa and plotting DSA results
res_dsa <- run_dsa(res_mod, dsa = def_dsa)     # Run DSA and store results in 'res_dsa'

title_dsa_plot_costs <- c(difference = "Incremental Costs (€)") # Define title plot costs

plot(res_dsa, type = "difference", widest_on_top = TRUE,  # Plot DSA (costs)
       limits_by_bars = TRUE, result = "cost", remove_ns = TRUE, bw = TRUE) +
  scale_color_brewer(name = "PCI Strategy", labels=c("IVUS", "OCT"), palette = "Set1") + # Assign colors
  scale_y_discrete(labels = c("p_reva_oct" = "Probability of Revascularization OCT", # Rename variables
                              "p_mi_oct" = "Probability of MI OCT", "p_reva_ivus" =
```

```
                    "Probability of Revascularization IVUS", "cost_ivus" =
                    "Costs PCI IVUS", "cost_oct" = "Costs PCI OCT",
                    "p_mi_ivus" = "Probability of MI IVUS", "p_death_oct_cardiac" =
                    "Probability of Cardiac Death OCT", "cost_reva" =
                    "Costs Revascularization", "cost_mi" = "Costs MI", "cost_dr" =
                    "DR costs", "p_death_ivus_cardiac" = "Probability of Cardiac Death IVUS",
                    "age_start" = "Start Age", "cost_ef" = "Costs Event Free",
                    "p_death_mi_no_lt" = "Probability of Dying after MI")) +
 labs(x = "Cost Difference (€)", y = "Input Variables") +              # Rename x- and y-labels
 ggplot2::facet_wrap(stats::as.formula("~ .strategy_names"),
                     labeller=labeller(.strategy_names = title_dsa_plot_costs)) + # Rename title
 geom_vline(xintercept = -282, linetype = "dashed") +                  # Insert Dashed line for the mean outcome
 annotate("text", x=1400, y=14.4, color = "black",
          label = "Mean incremental costs (€-282)") +                  # Insert annotations in the plot
 annotate("text", x=2800, y=0.8, color = "grey45", label = "+ OCT more expensive than IVUS") +
 annotate("text", x=-3400, y=0.8, color = "grey45", label = "- OCT less expensive than IVUS") +
 annotate("text", x=1350, y=13.7, color = "dodgerblue3", label = ">> Higher costs than the mean") +
 annotate("text", x=-1850, y=13.7, color = "red2", label = "Lower costs than the mean <<")

title_dsa_plot_effects <- c(difference = "Incremental Effects (QALY)") # Define title plot effects

plot(res_dsa, type = "difference",  widest_on_top = TRUE,             # Plot DSA (effects)
     limits_by_bars = TRUE, result = "effect", remove_ns = TRUE, bw = TRUE) +
 scale_color_brewer(name = "PCI Strategy", labels=c("IVUS", "OCT"), palette = "Set1") + # Assign colors
 scale_y_discrete(labels = c("p_death_oct_cardiac" = "Probability of Cardiac Death OCT", # Rename variables
                    "p_mi_oct" = "Probability of MI OCT", "p_death_ivus_cardiac" =
                    "Probability of Cardiac Death IVUS", "p_mi_ivus" = "Probability of MI IVUS",
                    "age_start" = "Start Age", "p_reva_ivus" = "Probability of Revascularization IVUS",
                    "p_death_mi_no_lt" = "Probability of Dying after MI", "p_reva_oct" = "Probability of
                    Revascularization OCT", "qaly_mi" = "QALY MI", "qaly_dr" = "DR QALY", "qaly_pci" =
                    "QALY PCI", "qaly_ef" = "QALY Event Free", "qaly_reva" = "QALY Revascularization")) +
 labs(x = "Effect Difference (QALY)", y = "Input Variables") +         # Rename x- and y-labels
 ggplot2::facet_wrap(stats::as.formula("~ .strategy_names"),
                     labeller=labeller(.strategy_names = title_dsa_plot_effects)) + # Rename title
 geom_vline(xintercept = 0.059, linetype = "dashed") +                  # Insert Dashed line for the mean outcome
 annotate("text", x=0.33, y=12.4, color = "black",
          label = "Mean incremental QALYs (0.059)") +                  # Insert annotations in the plot
 annotate("text", x=0.5, y=0.8, color = "grey45", label = "+ OCT more effective than IVUS") +
 annotate("text", x=-0.5, y=0.8, color = "grey45", label = "- OCT less effective than IVUS") +
 annotate("text", x=0.33, y=11.7, color = "dodgerblue3", label = ">> Larger effect than the mean") +
 annotate("text", x=-0.22, y=11.7, color = "red2", label = "Smaller effect than the mean <<")
```

"(Secondary) Base case - Probabilistic Sensitivity Analysis (PSA)"

```
# Define PSA parameters (i.e. distributions)
def_psa <- define_psa(
 age_start ~ normal(mean = 66, sd = 11.9),                            # Start age

 p_reva_angio ~ beta(shape1 = 39.31, shape2 = 460.69),                # Transition probabilities
 p_reva_oct ~ beta(shape1 = 39.60, shape2 = 1099.40),
 p_reva_ivus ~ beta(shape1 = 30.8, shape2 = 469.2),
 p_mi_angio ~ beta(shape1 = 2.84, shape2 = 97.16),
 p_mi_oct ~ beta(shape1 = 13.5, shape2 = 486.5),
 p_mi_ivus ~ beta(shape1 = 62.3, shape2 = 3713.8),
 p_death_angio_cardiac ~ beta(shape1 = 1.33, shape2 = 98.67),
 p_death_oct_cardiac ~ beta(shape1 = 5.43, shape2 = 1013.57),
 p_death_ivus_cardiac ~ beta(shape1 = 32.32, shape2 = 4443.68),
 p_death_mi_no_lt ~ beta(shape1 = 6857, shape2 = 52677),
 cost_angio ~ gamma(mean = 15927.10, sd = 1038.43),                   # Costs
 cost_oct ~ gamma(mean = 17450.35, sd = 1038.43),
 cost_ivus ~ gamma(mean = 16698.25, sd = 1038.43),
 cost_ef ~ gamma(mean = 422.84, sd = 57.16),
 cost_reva ~ gamma(mean = 7692.95, sd = 593.32),
 cost_mi ~ gamma(mean = 6874.70, sd = 4886.03),
 qaly_pci ~ beta(shape1 = 1.7913, shape2 = 0.739),                    # Utilities
 qaly_ef ~ beta(shape1 = 119.57, shape2 = 21.1),
```

```
  qaly_mi ~ beta(shape1 = 271.10, shape2 = 127.56),
  qaly_reva ~ beta(shape1 = 191.00, shape2 = 57.05))

# Running and ploting PSA results
res_psa <- run_psa(res_mod, psa = def_psa, N = 1000)          # Run PSA (Base case) and store results in 'res_psa'
res_psa2 <- run_psa(res_mod2, psa = def_psa, N = 1000)        # Run PSA (Secondary Base case), store in 'res_psa2'

plot(res_psa, type = "ce", bw = TRUE) +                       # Plot res_psa (Cost-effectiveness plane)
  scale_color_brewer(name = "PCI Strategy", labels=c("IVUS", "OCT"), palette = "Set1") + # Assign colors
  xlab("Incremental Effect (QALY)") + ylab("Incremental Costs (€)") +          # Rename x- and y-labels
  geom_hline(yintercept = 0, linetype = "dashed") +                           # Insert dashed helplines
  geom_vline(xintercept = 0, linetype = "dashed") +
  geom_abline(intercept = 0, slope = 20000, linetype = "solid", color = "darkred") +  # Willingness-to-pay line
  labs(title = "Cost-effectiveness Plane", subtitle = "") +                   # Graph Title
  geom_point(aes(x=1.412, y=-4641), color="black", size=3, pch=23, fill="green3") +  # Insert Best OCT point
  annotate("text", x=1.75, y=-4641, color = "green3", label = "Best OCT") +
  geom_point(aes(x=-2.076, y=7594), color="black", size=3, pch=23, fill="red") +     # Insert Worst OCT point
  annotate("text", x=-1.70, y=7594, color = "red", label = "Worst OCT") +
  annotate("text", x=1.65, y=-6500, color = "grey45", label = "OCT Dominates") +     # Annotations
  annotate("text", x=1.25, y=8500, color = "grey45", label = "OCT More Costly, More Effective") +
  annotate("text", x=-1.8, y=8500, color = "grey45", label = "IVUS Dominates") +
  annotate("text", x=-1.4, y=-6500, color = "grey45", label = "OCT Less Costly, Less Effective") +
  annotate("text", x=0.9, y=6000, color = "darkred", label = "WTP = €20,000/QALY")

plot(res_psa, type = "ac", scientific=FALSE, bw=TRUE) +                       # Plot res_psa (AC curve)
  scale_color_brewer(name = "PCI Strategy", labels=c("IVUS", "OCT"), palette = "Set1") +          # Assign colors
  scale_x_continuous(labels = comma) +                                        # continuous axis scale
  labs(title = "Cost-effectiveness Acceptability Curve", subtitle = "") +     # Graph title
  xlab("Willingness to pay (€/QALY)") + ylab("Probability of Cost-effectiveness")  # Rename x- and y-labels

plot(res_psa2, type = "ce", bw = TRUE) +                                      # Plot res_psa2 (Cost-effectiveness plane)
  scale_color_brewer(name = "PCI Strategy", labels=c("CAG", "IVUS", "OCT"), palette = "Set1") + # Assign colors
  xlab("Incremental Effect (QALY)") + ylab("Incremental Costs (€)") +         # Rename x- and y-labels
  geom_hline(yintercept = 0, linetype = "dashed") +                           # Insert dashed helplines
  geom_vline(xintercept = 0, linetype = "dashed") +
  geom_abline(intercept = 0, slope = 20000, linetype = "solid", color = "darkred") +  # Willingness-to-pay line
  labs(title = "Cost-effectiveness Plane", subtitle = "") +                   # Graph Title
  annotate("text", x=6.7, y=-19000, color = "grey45", label = "IVUS/OCT Dominates") +  # Annotations
  annotate("text", x=5.35, y=12000, color = "grey45", label = "IVUS/OCT More Costly, More Effective") +
  annotate("text", x=-1.7, y=12000, color = "grey45", label = "CAG Dominates") +
  annotate("text", x=-2.1, y=-15000, color = "grey45", label = "IVUS/OCT") +
  annotate("text", x=-1.95, y=-17000, color = "grey45", label = "Less Costly,") +
  annotate("text", x=-1.84, y=-19000, color = "grey45", label = "Less Effective") +
  annotate("text", x=2.45, y=9000, color = "darkred", label = "WTP = €20,000/QALY")

plot(res_psa2, type = "ac", scientific=FALSE, bw=TRUE) +                      # Plot res_psa2 (AC curve)
  scale_color_brewer(name = "PCI Strategy", labels=c("CAG", "IVUS", "OCT"), palette = "Set1") +    # Assign colors
  scale_x_continuous(labels = comma) +                                        # Continuous axis scale
  labs(title = "Cost-effectiveness Acceptability Curve", subtitle = "") +     # Graph Title
  xlab("Willingness to pay (€/QALY)") + ylab("Probability of Cost-effectiveness")  # Rename x- and y-labels
```

"Scenario RCT results: Kubo et al. (2017)"

```
# Modify Model inputs
par_kubo <- par_mod                                           # Store model inputs in new variable 'par_kubo'

par_kubo <- modify(                                           # Modify model inputs to Kubo et al. (2017)
  par_kubo,

  p_death_oct_cardiac = 0,
  p_death_oct = combine_probs(
    p_death_oct_cardiac,
    p_death_lifetable),

  p_death_ivus_cardiac = 0.002,
  p_death_ivus = combine_probs(
```

```
  p_death_ivus_cardiac,
  p_death_lifetable),

 p_reva_oct = 0.046,
 p_reva_ivus = 0.042,
 p_mi_oct = 0.005,
 p_mi_ivus = 0.007)

# Running the RCT scenario and store in 'res_kubo'
res_kubo <- run_model(
 parameters = par_kubo,
 oct = strat_oct,
 ivus = strat_ivus,
 cycles = 35,
 cost = cost_total,
 effect = qaly_total,
 central_strategy = "ivus",
 method = "end")

summary(res_kubo, threshold = c(1000, 5000, 15000)) # Print results to screen
```

"Best Case Scenario OCT"

```
# Modify Model inputs
par_best <- par_mod                          # Store model inputs in new variable 'par_best'

par_best <- modify(                          # Modify model inputs to optimal values for OCT
 par_best,

p_death_oct_cardiac = 0.00,
p_death_oct = combine_probs(
 p_death_oct_cardiac,
 p_death_lifetable),

p_death_ivus_cardiac = 0.0085,
p_death_ivus = combine_probs(
 p_death_ivus_cardiac,
 p_death_lifetable),

p_death_mi_no_lt = 0.1288,
p_death_mi = combine_probs(
 p_death_mi_no_lt,
 p_death_lifetable),

p_reva_oct = 0.0211,
p_reva_ivus = 0.0716,
p_mi_oct = 0.005,
p_mi_ivus = 0.0177,
cost_ef = 381,
cost_reva = 9290,
cost_mi = 11761,
qaly_ef = 0.94,
qaly_mi = 0.61,
qaly_reva = 0.69)

# Running the best case scenario and store in 'res_best'
res_best <- run_model(
 parameters = par_best,
 oct = strat_oct,
 ivus = strat_ivus,
 cycles = 35,
 cost = cost_total,
 effect = qaly_total,
 central_strategy = "ivus",
 method = "end")
```

```
summary(res_best, threshold = c(1000, 5000, 15000))  # print results to screen

"Worst Case Scenario OCT"

# Modify Model inputs
par_worst <- par_mod                                  # Store model inputs in new variable 'par_worst'

par_worst <- modify(                                  # Modify model inputs to optimal values for IVUS
 par_worst,

 p_death_oct_cardiac = 0.012,
 p_death_oct = combine_probs(
  p_death_oct_cardiac,
  p_death_lifetable),

 p_death_ivus_cardiac = 0.002,
 p_death_ivus = combine_probs(
  p_death_ivus_cardiac,
  p_death_lifetable),

 p_death_mi_no_lt = 0.1288,
 p_death_mi = combine_probs(
  p_death_mi_no_lt,
  p_death_lifetable),

 p_reva_oct = 0.046,
 p_reva_ivus = 0.025,
 p_mi_oct = 0.054,
 p_mi_ivus = 0.00,
 cost_ef = 381,
 cost_reva = 9290,
 cost_mi = 11761,
 qaly_ef = 0.94,
 qaly_mi = 0.61,
 qaly_reva = 0.69)

# Running the worst case scenario and store in 'res_worst'
res_worst <- run_model(
 parameters = par_worst,
 oct = strat_oct,
 ivus = strat_ivus,
cycles = 35,
 cost = cost_total,
 effect = qaly_total,
 central_strategy = "ivus",
 method = "end")

summary(res_worst, threshold = c(1000, 5000, 15000))  # print results to screen

"Discounting scenarios"

# Modify discount to 0% for both costs and qalys
par_discount <- par_mod                               # Store model inputs in new variable 'par_discount'

par_discount <- modify(
 par_discount,

 cost_dr = 0,
 qaly_dr = 0)

# Running the scenario and store in 'res_discount0'
res_discount0 <- run_model(
 parameters = par_discount,
 oct = strat_oct,
 ivus = strat_ivus,
 cycles = 35,
```

```
  cost = cost_total,
  effect = qaly_total,
  central_strategy = "ivus",
  method = "end")

summary(res_discount0, threshold = c(1000, 5000, 15000)) # print results to screen

# Modify discount to 3% for both costs and qalys
par_discount <- modify(
  par_discount,

  cost_dr = 0.03,
  qaly_dr = 0.03)

# Running the scenario and store in 'res_discount3'
res_discount3 <- run_model(
  parameters = par_discount,
  oct = strat_oct,
  ivus = strat_ivus,
  cycles = 35,
  cost = cost_total,
  effect = qaly_total,
  central_strategy = "ivus",
  method = "end")

summary(res_discount3, threshold = c(1000, 5000, 15000)) # print results to screen
```