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Application of Intravascular Ultrasound in the Treatment of Diffuse Coronary Artery Disease

DOCTORAL DISSERTATION

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VILNIAUS UNIVERSITETAS

Povilas Budrys

Difuzinės širdies vainikinių arterijų ligos perkateterinis gydymas pasitelkiant intrakraujagyslinį ultragarsinį tyrimą

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1 ABBREVIATIONS

BMS bare metal stent

CABG coronary artery bypass graft surgery

CAD coronary artery disease

DES drug-eluting stent

EEM external elastic membrane

FFR fractional flow reserve

IVUS intravascular ultrasound

LAD left anterior descending artery

LCx left circumflex artery

LDL low-density lipoprotein

MACE major adverse cardiac events

MI myocardial infarction

MLA minimal lumen area

MSA minimal stent area

NSTE-ACS acute coronary syndrome without ST segment elevation

OCT optical coherence tomography

OMT optimal medical therapy

PCI percutaneous coronary intervention

RCA right coronary artery

SIHD stable ischemic heart disease

TV-death target vessel related death

TVF target vessel failure

TV-MI target vessel related myocardial infarction

TV-R target vessel related revascularization

CONTENT

2 INTRODUCTION

2.1 Background

Coronary artery disease (CAD) is a cardiovascular disorder characterized by the buildup of atherosclerotic plaques in the coronary arteries, which supply oxygen and nutrients to the heart muscle. These plaques are made up of cholesterol, fat, calcium, and other substances that can accumulate over time, causing the arterial walls to thicken and narrow, which can reduce blood flow to the heart. This process is known as atherosclerosis and can lead to various complications such as angina, heart attack, heart failure, and arrhythmias.

CAD is a multifactorial disease that results from complex interactions between genetic, environmental, and lifestyle factors. Some of the major risk factors for CAD include high blood pressure, dyslipidemia, smoking, diabetes, obesity, lack of physical activity, and family history of heart disease[1].

As per the World Health Organization, it is the top cause of mortality globally, responsible for millions of deaths annually[2]. The prevalence of CAD differs based on demographics and the country but generally rises with age and is more frequently found in men compared to women. With increasing life expectancy, there is a higher likelihood that individuals will develop CAD. This suggests that the prevalence of CAD may also increase over time. As a result of the natural aging process and an increased incidence of additional risk factors, the complexity of CAD also tends to escalate.

The objectives of CAD treatment are to enhance the patient's quality of life and prognosis. Medical therapy and revascularization (coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)) are the two primary components of CAD treatment. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial serves as a recent reminder of the long-standing fact that medical therapy is the fundamental aspect of CAD treatment. This is the most recent large-scale, randomized clinical trial designed to determine whether an invasive strategy (CABG or PCI) in addition to optimal medical therapy (OMT) reduces the risk of major adverse cardiovascular events (MACE) compared to a conservative strategy of OMT alone in patients with stable ischemic heart disease (SIHD) and moderate to severe ischemia on stress testing. During a median follow-up of 3.2 years, the adoption of an invasive strategy did not result in a reduction in major adverse cardiovascular events (MACE) compared to a conservative approach. However, the invasive strategy did result in greater symptom relief and improved quality of life[3]. Although the critical role of medical therapy in the management of CAD is widely

acknowledged, revascularization strategies have been shown to confer benefits to patients who experience angina symptoms despite receiving optimal medical therapy, as well as those who have had a myocardial infarction[4,5,6]. Although there have been ongoing advancements in surgical and percutaneous treatments for coronary artery disease, there remain several ongoing discussions regarding the management of complex CAD, particularly regarding the treatment of long, diffuse disease.

Long diffuse coronary artery lesions can be considered complex lesions due to their challenging nature for diagnosis and treatment. The definition of long lesion varies depending on the diagnostic criteria used but it is generally considered to be a lesion that measures at least 20 millimeters in length[7]. However, in more recent trials, a higher – 28 mm threshold has been used more often to define long coronary lesions[8,9,10]. Performing percutaneous coronary intervention (PCI) on long coronary lesions often necessitates the use of long or overlapping stents, which could be associated with the increased risk of periprocedural myocardial infarction (due to side branch closure under the stent) and may also lead to suboptimal functional outcomes and a higher risk of target vessel failure (TVF; defined as repeat revascularization of the target vessel (TV) and TV related myocardial infarction or death)[11,12,13]. Consequently, bypass surgery is commonly chosen as the preferred revascularization method for extended segments of atheromatous disease, however, there is insufficient proof to support this approach. Furthermore, it is worth noting that CABG is a considerably more invasive procedure than PCI, which may render it unsuitable for certain patients who are too frail or have underlying health conditions that would make the surgery too risky. Additionally, in some cases, patients may decline CABG as a treatment option altogether. Therefore, the ultimate verdict on the revascularization strategy is typically personalized and considers a multitude of factors, including the patient's age, comorbidities, recommendations from the interventional cardiologist and heart surgeon, as well as the patient's preferences. This decision-making process aims to optimize patient outcomes by tailoring the approach to each individual's unique clinical situation.

Over the years following the initial performance of the first PCI by Dr. Andreas Gruentzig in 1977[14], there has been a remarkable evolution in the devices, tools, and techniques used in the field of PCI. These advancements have significantly improved the safety and efficacy of the procedure, and have enabled more patients to benefit from it. First, the emergence of drug-eluting stents has significantly decreased the incidence of repeat revascularization when compared to the use of bare metal stents[15,16,17]. This has resulted in a noteworthy improvement in the long-term efficacy of the procedure and a consequent decrease in the need for subsequent interventions. Moreover, the

applicability of advanced tools, such as fractional flow reserve (FFR) and intravascular imaging techniques (intravascular ultrasound (IVUS) and optical coherence tomography (OCT)), has not only facilitated the diagnosis of pathology and the determination of the need for invasive treatment but has also enabled the optimization of PCI, thereby further reducing the occurrence of negative outcomes.

Fractional flow reserve (FFR) is a physiological metric employed for evaluating the functional importance of lesions in coronary arteries. It is determined as the ratio of the pressure at the distal part of the coronary artery to the pressure at the aorta during maximum hyperemia. FFR values range from 0 to 1, where an FFR value of 1 indicates normal blood flow, and an FFR value equal to or less than 0.80 demonstrates myocardial ischemia. FFR has been extensively validated in multiple clinical trials and has been shown to be superior to angiography alone in guiding revascularization decisions[18,19,20]. Its use has been associated with improved clinical outcomes[21,22] and reduced healthcare costs[23]. FFR has become an essential tool in contemporary cardiology practice and is recommended by major guidelines for the evaluation of intermediate coronary artery stenosis[24,25]. However, while FFR is the established method for assessing the functional significance of a lesion before PCI, it is not often measured after PCI to assess the functional result. This is despite evidence showing a strong correlation between FFR values ≤ 0.80 after PCI and adverse outcomes[26,27,28,29]. Additionally, angiographically successful PCI, determined by visual inspection, is often inadequate when residual ischemia persists after PCI with rates as high as 30% of cases[13,30,31,32]. These disappointing outcomes have been observed in short to medium length lesions and are likely to be even more prevalent in long, diffuse coronary lesions. The growing body of evidence suggests that post-PCI FFR measurement can be a useful tool for optimizing the functional result of the procedure. The TARGET-FFR (Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention) trial employed a physiology-guided incremental optimization strategy which involved the use of a pressure wire pull-back to identify significant pressure drops in stented or non-stented segments, followed by either post-dilatation (in stented segments) or additional stent implantation to improve the functional outcome of the procedure. The trial demonstrated a significant reduction in the proportion of patients with suboptimal outcomes (FFR values of ≤ 0.8) compared to angiography-only approach, indicating that physiology-guided optimization may be a valuable tool for improving the functional outcomes of PCI[30].

The evidence from previous trials strongly supports the role of intravascular imaging in optimizing PCI results. Both intravascular ultrasound

(IVUS) and optical coherence tomography (OCT) have been shown to provide more accurate and detailed information regarding the coronary artery anatomy and plaque morphology compared to angiography-only guidance[33,34]. Furthermore, these imaging techniques can be used to evaluate stent expansion and apposition, as well as the plaque volume near the stent and any dissections near stent edges that may be present. Multiple randomized controlled trials and meta-analyses have demonstrated that the use of IVUS or OCT during PCI leads to improved procedural outcomes, including better stent apposition and expansion, and a lower incidence of adverse cardiovascular events such as target vessel revascularization[9,10,35,36,37,38,39,40].

In general, PCI optimization through the use of intravascular imaging or physiological assessments, such as fractional flow reserve, has demonstrated superior outcomes in terms of reducing target lesion failure compared to angiography-guided PCI. However, it should be noted that achieving optimal stent placement as determined by intravascular imaging does not necessarily ensure an optimal functional outcome as determined by FFR, and vice versa. Moreover, the optimal strategy for optimizing PCI results and predicting adverse events remains uncertain, as most clinical studies have evaluated the impact of FFR or IVUS in isolation on clinical outcomes, and these studies have mainly focused on short to medium length lesions. Furthermore, despite evidence suggesting that PCI for long diffuse coronary lesions frequently results in suboptimal functional and anatomical outcomes, there is insufficient data available on the best PCI optimization strategy while treating these complex lesions.

2.2 The hypothesis of the study

Long coronary lesions PCI optimized with IVUS will lead to superior functional outcomes, specifically a lower incidence of poor functional PCI result (defined as FFR $\leq$ 0.8) immediately post-PCI and at follow-up, and lower rates of target vessel failure and functional target lesion restenosis compared to the FFR optimization strategy.

2.3 The aim of the study

The aim of the study is to assess functional result of intravascular ultrasound optimized percutaneous treatment of long diffuse coronary artery lesions and to compare it to the long lesions percutaneous coronary interventions optimized with fractional flow reserve.

2.4 The objectives of the study

The objectives of the study are:

1. To evaluate the frequency of achieving optimal (FFR > 0.9) and poor (FFR ≤ 0.8) functional PCI result after using IVUS to optimize long lesions PCI.
2. To assess the long-term functional PCI outcome of IVUS-optimized long lesions PCI by measuring FFR nine to twelve months post PCI.
3. To compare the functional PCI results of IVUS-optimized long lesions PCI with those of a historical group of FFR-optimized long lesions PCI.
4. To compare the rates of target vessel failure and functional target lesion restenosis between the two PCI optimization strategies during a one-year follow-up period.

2.5 Defense statements of the doctoral thesis

Employing IVUS optimization during percutaneous treatment of long diffuse coronary artery lesions is associated with the lower occurrence of ischemic functional PCI outcomes (FFR ≤ 0.8) both immediately after the procedure and during follow-up, in comparison to the FFR optimization strategy.

The IVUS-optimized approach for long coronary lesions is associated with reduced rates of target vessel failure and functional target lesion restenosis during a one-year follow-up when compared to the group undergoing FFR-optimized treatment for long lesions.

2.6 The scientific novelty of the study

Treating long diffuse coronary artery disease using angiography alone can be challenging and often leads to poor outcomes and increased risk of target vessel failure. Therefore, the use of PCI optimization tools such as IVUS or FFR is necessary to improve the outcome. There is a lack of data on the functional outcomes after IVUS-optimized long lesions PCI. Moreover, to our knowledge, no trials have ever compared the effectiveness of two different PCI optimization strategies (IVUS versus FFR) on the functional PCI outcomes, especially in these complex lesions. The purpose of the present study is to evaluate the functional outcome of each approach and to determine which strategy is more effective for treating long diffuse coronary artery lesions. The findings of the study may provide important insights for healthcare professionals and improve patient outcomes in the future.

3 LITERATURE REVIEW

3.1 Myocardial ischemia and fractional flow reserve

Myocardial ischemia is associated with various symptoms and the severity and extent of ischemia are significant risk factors for patients with CAD[41]. Reducing myocardial ischemia is an important therapeutic goal for these patients and revascularization of affected lesions has been shown to improve their outcomes[18,42,43]. However, it is important to avoid revascularization of stenotic lesions that do not result in myocardial ischemia as this can be harmful to the patient[44]. Hence, the determination of whether to perform revascularization should rely on the existence of myocardial ischemia and the severity of patients' symptoms.

Although coronary angiography is valuable for detecting coronary artery stenosis, it has constraints when it comes to assessing the physiological significance of such stenotic lesions. This limitation becomes especially apparent in cases of intermediate stenosis, where angiographic findings may not reliably align with the functional significance of the lesion[45]. This uncertainty can lead to unnecessary invasive treatment of hemodynamically non-significant stenoses or failure to revascularize significant ones.

The extent of coronary artery lesion is typically characterized by multiple parameters, such as geometric dimensions, pressure gradient-flow relations, resistance to flow, coronary flow reserve, and maximum flow capacity after maximum arteriolar vasodilation[46]. However, a direct relation between coronary pressure and flow can only be inferred if the resistances within the coronary circulation remain constant and minimal, which is theoretically achieved during maximum arteriolar vasodilation. In such circumstances, pressure measurements can be used to predict maximum flow and evaluate the functional severity of stenosis. This concept was named fractional flow reserve (FFR) and introduced by N. Pijls and B. De Bruyne. It was validated in humans through the use of a positron emission tomography scan in 1994[47].

FFR is defined as the ratio between the maximum achievable blood flow in the presence of a stenosis and the maximum flow that would occur if there were no obstructive epicardial coronary disease[20]. Consequently, FFR represents a lesion-specific index that characterizes the influence of epicardial coronary stenosis on myocardial perfusion. FFR value is the ratio of the distal coronary pressure (Pd) to the aortic pressure (Pa) during maximum hyperemia (FFR = Pd / Pa) and is not significantly affected by variations in hemodynamic parameters, including blood pressure, heart rate, or myocardial contractility, and therefore remains an independent index[48]. As intravenous adenosine

induces stable hyperemia, which is essential for accurate FFR measurement, it is widely utilized as the preferred pharmacological agent.

Initially, a cut-off value of 0.75 was established for FFR to determine functionally significant coronary lesions. This decision was based on the findings from the DEFER (FFR to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenoses) trial. This study enrolled 325 patients who were scheduled to undergo PCI for an intermediate stenosis. All patients with an FFR < 0.75 underwent PCI (n=144, Reference group). Patients with an FFR ≥ 0.75 were randomly assigned to either medical treatment (n=91, Defer group) or PCI (n=90, Perform group). The study followed up the patients for 5 years and found that there was no significant difference in the event-free survival rate between the Defer and PCI groups, which stood at 80% and 73%, respectively. Similarly, the proportion of patients who experienced chest pain relief during the follow-up period was comparable between the two groups. In addition, the combined incidence of death and acute myocardial infarction was only 3.3% in the Defer group over the course of 5 years. The study concluded that deferring PCI based on FFR resulted in excellent patient outcomes and that the risk of death or acute MI was less than 1% per year, which could not be further reduced by stenting[49]. The DEFER trial maintained a similar trend over a long-term follow-up period. After 15 years, the death rate was not significantly different between the Defer, Perform, and Reference groups. The Defer group had a death rate of 33.0%, the Perform group had 31.1%, and the Reference group had 36.1%. The Defer group had a significantly lower incidence of myocardial infarction (2.2%) compared to the Perform group (10.0%). Deferring PCI for a functionally non-significant stenosis was found to be associated with a favorable long-term outcome without any late "catch-up" phenomenon[44]. However, in the validation phase, it was observed that FFR values ranging from 0.76 to 0.80 fell within a "grey zone," where a non-invasive test could still produce a positive result, but the sensitivity and specificity were not optimal. Thus, it was recommended to exercise clinical judgement when dealing with values in this range.

In order to predict outcomes, the FAME (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) studies shifted the FFR cut-off point to a value of 0.80[18]. The primary objective of this randomized clinical trial was to assess the comparative efficacy of treatment strategies that incorporate FFR measurements in addition to angiography versus that time standard of care that employed angiography alone, in patients diagnosed with multivessel coronary artery disease for whom PCI was deemed an appropriate therapeutic option. In this multicenter trial 1005 patients

diagnosed with multivessel CAD were randomly assigned to undergo PCI with drug-eluting stents guided either by angiography alone or by FFR measurements combined with angiography. Lesions requiring PCI were identified based on their angiographic appearance before randomization. In the angiography-guided group, stenting was performed for all indicated lesions, whereas in the FFR-guided group, stenting was performed only for indicated lesions with FFR of 0.80 or less. The primary endpoint of the study was the occurrence of death, nonfatal myocardial infarction, or repeat revascularization within 1 year. At the end of 1 year, the incidence of the primary endpoint was significantly lower in the FFR group (13.2%, 67 patients) compared to the angiography group (18.3%, 91 patients) with a P-value of 0.02. The percentage of patients without angina at 1 year was similar between the groups (78% in the angiography group vs. 81% in the FFR group, P=0.20). These findings indicated that the routine use of FFR measurement during PCI with drug-eluting stents in patients with multivessel CAD could significantly reduce the incidence of adverse events at 1 year.

The FAME 2 (Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease) study results were published in 2012, three years after the FAME trial results were made public. This new study aimed to determine if using FFR-guided PCI with drug-eluting stents alongside the optimal medical therapy (OMT) was superior to just the medical therapy alone in reducing death, myocardial infarction, or urgent revascularization in patients with stable coronary artery disease. The study involved 888 patients from 28 centers, and it was stopped early due to interim analysis showing clear benefits of the PCI + OMT arm over the OMT arm. The study's primary endpoint, MACE (death, MI and urgent revascularization), was found to be significantly lower in the PCI + OMT arm (4.3%) than in the OMT arm (12.7%). The primary factor contributing to this outcome was the reduction in the need for urgent revascularization (1.6% vs. 11.1%, $p < 0.001$). Additionally, the FFR arm had lower rates of nonurgent revascularizations (1.6% vs. 8.6%, $p < 0.001$)[50]. The primary endpoint results remained consistent after 5 years of follow-up for the PCI + OMT group compared to the OMT group (13.9% vs. 27.0%, $p < 0.001$). While there were no significant differences in death rates (5.1% vs. 5.2%, HR 0.98, 95% CI 0.55-1.75) and MI rates (8.1% vs. 12.0%, HR 0.66, 95% CI 0.43-1.0) between the two groups, urgent revascularization rates were considerably lower in the PCI group (6.3% vs. 21.1%, HR 0.27, 95% CI 0.18-0.41)[51].

After the introduction of FFR, the effectiveness of employing an FFR-guided approach to revascularization has been studied and validated in challenging clinical contexts, including cases of multivessel disease, in-stent

restenosis, post-PCI, left main disease, bifurcation lesions, and patients who have experienced MI[52,53,54,55,56,57]. The utilization of this index is expanding, and the current revascularization guidelines have precisely defined the clinical scenarios where it should be employed[24,25]. European Society of Cardiology (ESC) guidelines on myocardial revascularization recommends to assess the hemodynamic relevance of intermediate-grade stenosis (typically around 40-90% stenosis) in cases where evidence of ischemia is not available. This recommendation is classified as a class I, level A recommendation. For patients with multivessel disease undergoing PCI, the guidelines suggest using FFR to guide the procedure, which is rated as a class IIa, level B recommendation[24].

Similarly, the guidelines established by the American College of Cardiology (ACC) and the American Heart Association (AHA) for coronary artery revascularization recommend using FFR to determine whether PCI is appropriate in patients with angina or an anginal equivalent, angiographically intermediate stenoses, and undocumented ischemia. This recommendation is rated as 1A. Additionally, for stable patients with angiographically intermediate stenoses and an FFR value of greater than 0.8, the guidelines suggest that PCI should not be performed[25].

3.1.1 The role of post-PCI FFR measurement

Although the utilization of FFR for establishing baseline myocardial ischemia and deciding whether to perform or defer PCI is increasing, there is a lack of regular practice in conducting post-PCI FFR measurements, despite compelling evidence that connects post-PCI FFR value with clinical outcomes. Several clinical trials and meta-analyses have highlighted the significance of post-PCI FFR as a valuable tool in risk stratification, as lower post-PCI FFR values have been consistently linked to a worse prognosis[27,28,29,58]. The abnormal post-PCI FFR detects residual hyperemic pressure gradient and abnormal resistance present in both the stented segment and the surrounding vessel segments. Therefore, inadequate stent expansion or apposition, dissections near stent edges, or residual functionally significant disease proximal or distal to the stent are plausible contributors to the suboptimal post-PCI FFR values, which might all contribute to the treated vessel failure in the long-term.

The first evidence of an association between post-PCI FFR and patient outcomes was identified in the era of bare metal stents. Pijls et al. conducted a prospective study involving 750 patients who underwent angiographically successful PCI, with subsequent measurement of post-PCI FFR. The patients

were then monitored for a period of six months for major adverse events, including repeat target vessel revascularization. The study demonstrated that FFR normalized (> 0.95) in 36% of patients, with an associated event rate of 4.9%. Among 32% of patients, post-stent FFR ranged between 0.90 and 0.95, and the event rate was 6.2%. Conversely, in 32% of patients, post-stent FFR was < 0.90, and the event rate was 20.3%. Additionally, for 6% of the patients, FFR was < 0.80, and the event rate was 29.5% ($P < 0.001$)[59]. These findings suggest that FFR measurements taken after angiographically successful PCI procedures may be useful in predicting major adverse events. Specifically, the study shows that patients with FFR values below 0.90 after PCI are at a significantly higher risk of experiencing adverse events compared to those with FFR values above this threshold.

Following the adoption of drug-eluting stents, several trials were carried out to examine the impact of post-PCI FFR on patient outcomes. The FAME 1 and 2 trials were particularly noteworthy as they included patients who had undergone post-PCI FFR measurements. The primary endpoint of these trials was a vessel-oriented composite endpoint at 2 years, which included vessel-related cardiovascular death, vessel-related spontaneous myocardial infarction, and ischemia-driven target vessel revascularization. The analysis was conducted on 838 vessels in 639 patients. The findings of the study showed that post-PCI FFR was significantly lower in vessels with a vessel-oriented composite endpoint compared to those without (0.88 ± 0.06 versus 0.90 ± 0.06, respectively; $P=0.019$). When the lower and upper tertiles of post-PCI FFR were compared, a significant difference was found in favor of the upper tertile in terms of overall vessel-oriented composite endpoint (9.2% versus 3.8%, respectively; hazard ratio, 1.46; 95% confidence interval, 1.02–2.08; $P=0.037$) and target vessel revascularization (7.0% versus 2.4%, respectively; hazard ratio, 1.59; 95% confidence interval, 1.03–2.46; $P=0.037$)[60]. The study also found that a post-PCI FFR of 0.92 had the highest diagnostic accuracy. In conclusion, the trial demonstrated that a higher post-PCI FFR value, obtained immediately after DES implantation, was associated with a lower rate of clinical events related to the stented vessel over a period of 2 years.

The largest meta-analysis to evaluate the clinical significance of post-PCI FFR values was conducted by Rimac et. al. Authors aimed to examine the correlations between immediate post-PCI FFR values and the incidence of repeat intervention and major adverse cardiac events (MACE), as well as to assess the prognostic value of post-PCI FFR. The meta-analysis included a total of 105 studies, with a sample size of 7470 patients. Out of these, 46 studies reported post-PCI FFR values, while 59 studies evaluated the

relationship between post-PCI FFR and clinical outcomes up to 30 months after PCI. The results of the meta-analysis revealed that higher post-PCI FFR values were significantly associated with a lower incidence of repeat intervention and MACE. Additionally, the analysis demonstrated that a post-PCI FFR value of ≥0.90 was significantly associated with a reduced risk of repeat PCI (odds ratio 0.43, 95% CI 0.34-0.56, P<0.0001) and MACE (odds ratio 0.71, 95% CI 0.59-0.85, P=0.0003)[27]. These findings suggest that post-PCI FFR value is an important prognostic indicator in assessing clinical outcomes in patients undergoing PCI. Once again, the results of this meta-analysis reinforced the prognostic importance of post-PCI FFR.

3.1.2 In search for post-PCI FFR cut-off to define optimal result and factors affecting post-PCI FFR value

Currently, there remains a lack of agreement among the scientific community regarding the most appropriate post-PCI FFR cut-off value for defining an optimal functional PCI result. Available studies report varying values, with ranges spanning from >0.86 to >0.96[13,58,61,62,63]. However, a majority of these studies have utilized a post-PCI FFR cut-off value of 0.90 or greater to indicate optimal functional result[27,30,64,65]. Despite these differences in cut-off values, there is a consensus across studies that higher post-PCI FFR values are associated with better prognoses for patients.

Theoretically, the use of stent to treat a focal lesion and achieving an optimal stenting result should lead to the restoration of FFR to near-normal levels, approximately 1.0. However, in clinical practice, such desirable levels are infrequently observed. Several trials have reported that only 38-62% of patients achieve FFR values of 0.90 or higher after stenting, and residual ischemia (FFR ≤ 0.8) persists in as many as 30% of cases post-PCI[13,30,31,32,62,66]. The suboptimal post-PCI FFR values are usually attributed to multiple factors such as:

1. *Treated vessel.* The FFR is influenced by the perfusion territory of the myocardium that is supplied by a given vessel. Arteries supplying larger myocardial beds will produce more severe ischemia, as determined by FFR, than those supplying smaller beds, even for the same degree of stenosis. Therefore, the left anterior descending coronary artery (LAD), which supplies blood to the largest myocardial territory, is more often associated with suboptimal functional PCI result compared to the right coronary artery (RCA) or left circumflex artery (LCx). Multiple trials evaluating post-PCI FFR

have established that the LAD artery is an independent predictor of suboptimal functional outcome following PCI[31,32].

2. *Lesion length*. To effectively cover long lesions, longer stents are necessary. Stent implantation itself creates a gradient, as demonstrated by longitudinal observations[67]. As a result, it can be speculated that an optimally implanted long stent will produce a higher trans-stent gradient compared to a short stent. Furthermore, longer stented segments carry an increased risk of mechanical stent problems, such as underexpansion or malapposition, which could increase the gradient through the stent even more.
3. *Suboptimal stent implantation*. Stent underexpansion or malapposition, tissue protrusion, and dissections near stent edges are all mechanical issues that can cause an increase in the trans-stent gradient and lead to reduction in post-PCI FFR values.
4. *Residual focal disease proximal or distal to the stent.* In some cases, tandem lesions that are not properly identified or appreciated may experience a significant increase in their gradients after PCI for the primary stenosis. As a result, the post-PCI FFR of the index lesion could exhibit a slight improvement, no change, or even a decline[68].
5. *Residual diffuse disease.* The pathogenesis of atherosclerosis involves a widespread and diffuse process that is often not apparent on angiography. In cases where there is diffuse coronary atherosclerosis without any focal stenosis detected on angiography, it leads to a progressive and continuous reduction in pressure along the length of the coronary artery[69].

As the myocardial mass supplied by the target vessel is one of the major factors contributing to the final post-PCI FFR result Hwang et al. conducted a study to investigate the influence of the target vessel on the prognostic relevance of FFR after PCI. The study aimed to determine whether different cut-off values of post-PCI FFR should be applied based on the target vessel. The study included 835 patients who underwent DES implantation and had available FFR. The primary outcome was target-vessel failure (TVF), which included cardiac death, target vessel-related myocardial infarction, and clinically driven target vessel revascularization. The study found that the optimal cut-off values for predicting TVF were different for the LAD and non-LAD vessels, with values of 0.82 and 0.88, respectively. Patients with post-PCI FFR values below the cut-off had a significantly higher cumulative incidence of TVF than those with values above the cut-off.[70] These results imply that the target vessel significantly influences post-PCI FFR values, and

distinct post-PCI FFR thresholds should be considered depending on the target vessel.

3.1.3 Fractional flow reserve and coronary artery bypass graft surgery

Given that optimal functional result with PCI is not commonly achieved, particularly in cases involving long LAD lesions, and that a significant number of lesions still cause ischemia even after angiographically successful PCI, CABG surgery should always be considered as an alternative approach. As such, there was an ongoing interest in investigating the FFR values following the grafting of the affected artery.

Before 2007, the amount of data available on FFR in bypasses was limited. In order to address this gap, Glineur et al. conducted a study to evaluate the functional capacity of bypass grafts six months after surgery. The study revealed that in a mammarian (ITA) bypass graft, the resistance to blood flow is relatively small under maximum hyperemic conditions, although it is not entirely negligible as evidenced by the FFR values of 0.90 ± 0.04 for the left ITA and 0.95 ± 0.03 for the right ITA. Furthermore, the study demonstrated that a normal venous bypass graft has negligible resistance (FFR = 0.96 ± 0.03)[71].

The study conducted by Glineur et al. offers confidence that post-grafting perfusion pressure is adequate for the distal segments of coronary arteries, as evidenced by the high FFR values. Nevertheless, it is crucial to also take into account the patency of the grafts. An important study was conducted by Shiono et al. with 89 patients who underwent pressure guidewire pullback in the LAD prior to CABG using the IMA. They classified LAD lesions into functional focal disease (abrupt pressure step-up; n=58) or functional diffuse disease (gradual pressure increase; n=31) based on pressure guidewire pullback data. Before CABG, FFR in LAD did not differ between the functional focal and diffuse disease groups (0.68 ± 0.07 vs. 0.69 ± 0.07, $p = 0.244$) and was significantly below the ischemic threshold. The CABG procedure characteristics were comparable between the two groups. Follow-up computed tomography angiography was conducted within 1 year after CABG to assess the bypass graft patency. It demonstrated a high incidence of graft occlusions, which were found to occur more frequently in the functional diffuse disease group compared to the functional focal disease group (26% vs. 7%, $p = 0.021$)[72]. The study indicates that functional diffuse disease in the recipient coronary artery during CABG is associated with a higher risk of graft failure compared to functional focal disease.

3.1.4 Fractional flow reserve as a tool to optimize PCI

It is known that higher post-PCI FFR values are linked with a lower incidence of target vessel failure. Therefore, the primary aim of PCI should be to achieve the highest possible post-PCI FFR. Several trials have shown that FFR is not only useful in determining the baseline myocardial ischemia and the final functional result of PCI, but it can also be employed as an important tool to optimize the procedure's result.

Agarwal et al. conducted a study that involved 574 patients (664 lesions) to examine the influence of FFR after PCI on subsequent in-lab interventional management of vessels that had previously undergone pre-PCI FFR measurements. Despite angiographically satisfactory appearance, 21% of lesions had post-PCI FFR in the ischemic range. In cases where the post-PCI FFR was persistently ischemic or deemed unsatisfactory by the operator, an additional intervention was performed, which could have involved further stenting, post-dilation, intravascular ultrasound (IVUS), optical coherence tomography (OCT), or a combination thereof, at the operator's discretion. Following the subsequent intervention, a final FFR measurement was taken, revealing an increase in FFR from 0.78 ± 0.08 to 0.87 ± 0.06 ($p < 0.0001$) in this subgroup and the proportion of patients with residual myocardial ischemia was reduced from 21% to <9%. The investigators also observed that patients with a final FFR > 0.86 had significantly lower rates of major adverse cardiac events (MACE) compared to those with a final FFR ≤ 0.86 (17% vs. 23%; log-rank $p = 0.02$)[62]. This study highlights the importance of post-PCI FFR measurements by demonstrating that there is a significant proportion of patients with ischemic lesions despite angiographically satisfactory PCI results and this proportion could be significantly reduced by performing additional interventions.

A different clinical trial, known as TARGET-FFR (Trial of Angiography versus pressure-Ratio Guided Enhancement Techniques - Fractional Flow Reserve), was conducted with a more rigorously defined functional optimization protocol. The trial aimed to assess a physiology-guided incremental optimization strategy in comparison to standard care among patients who had undergone angiographically successful PCI. Following PCI, patients underwent FFR measurement in the target vessel and were randomized to either a physiology-guided incremental optimization strategy (PIOS; n = 131) or a blinded control group (n = 129). The study concluded for all patients in the control group and for those in the PIOS intervention group with FFR ≥ 0.90. For patients in the PIOS group with post-PCI FFR < 0.90, operators followed the PIOS steps, which included stent post-dilation with a

larger non-compliant (NC) balloon to 18 atm if the trans-stent gradient was ≥ 0.05 and additional stent deployment if there was a focal FFR increase ≥ 0.05 in an unstented segment shorter than 20mm. If FFR remained below 0.9 after the first two steps, the option of further post-dilation or one more additional stent was available (option to repeat the first two steps accordingly). The final pull-back and completion of the procedure occurred if the residual pressure gradient reflected diffuse atherosclerosis with no focal step-changes in pressure gradient, and the result was accepted with no further optimization attempted. The study findings indicated that persistently abnormal post-PCI FFR values were frequent, and routine post-PCI physiology guidance could effectively improve final FFR values in a considerable number of severely affected patients. The proportion of patients with final FFR ≥ 0.9 increased to 38.1% in the physiology-guided incremental optimization group compared with 28.1% in the blinded control group ($p = 0.099$). Additionally, the proportion of patients with final FFR ≤ 0.8 was 18.6% in the physiology-guided incremental optimization group compared with 29.8% in the blinded control group ($p = 0.045$)[30].

3.2 Intravascular ultrasound

Intravascular ultrasound (IVUS) is a medical imaging technique that utilizes high-frequency sound waves to generate images of the inside of blood vessels. IVUS is a catheter-based imaging modality, which means that an ultrasound catheter is inserted into the blood vessel of interest to capture images. IVUS, as the first intravascular imaging device, was introduced by Dr. Yock and his team at Stanford University in the 1980s.[73]

The physical principles of IVUS are based on the interaction of ultrasound waves with the tissues in the blood vessel. Ultrasound waves are high-frequency sound waves that are beyond the range of human hearing. The ultrasound catheter emits ultrasound waves that travel through the blood and tissue, and are then reflected back to the catheter. The time taken for the ultrasound waves to travel back to the catheter is used to calculate the distance to the tissue, which is then used to generate an image.

The ultrasound waves used in IVUS have frequencies typically ranging from 20 to 60 MHz, which allows for high-resolution imaging of structures within the blood vessel wall. The depth of imaging is determined by the frequency of the ultrasound wave, with higher frequencies allowing for shallower imaging but higher resolution. The image generated by IVUS shows the cross-sectional view of the blood vessel, including the lumen, plaque, and

the layers of the vessel wall. When an ultrasound pulse travels through two different tissues, such as fat and muscle, it is only partially transmitted and partially reflected. The extent of reflection depends on the difference in the mechanical impedance of the two materials. For instance, imaging highly calcified structures often results in acoustic shadowing, where the signal is almost completely reflected at the interface between the soft tissue and calcium. As the wave passes through multiple tissue interfaces, its energy is attenuated, or reduced. This attenuation is affected by various factors, such as the tissue properties, energy scattering by small objects, and tissue absorption. As a result, only a small portion of the transmitted signal returns to the transducer. The detected signal is then converted into electrical energy and sent to an external signal processing system for amplification, filtering, scan-conversion, and other user-controlled modifications, before being presented as a visual image[74,75].

IVUS is useful in clinical practice for evaluating the severity of stenosis, assessing the extent and characteristics of atherosclerotic plaques, and guiding interventional procedures.

There are two main types of intravascular ultrasound (IVUS) transducers: mechanical and solid-state.

- *Mechanical transducers* (the mechanically rotating) utilize a rotating transducer located at the catheter's tip to create ultrasound images. The transducer rotates at high speeds, up to 1800 rotations per minute, to provide a 360-degree cross-sectional image of the vessel. In order to prevent image degradation caused by even small air bubbles, mechanical transducer catheters require flushing with saline to provide a clear pathway for the ultrasound beam. Most mechanical systems feature a protective sheath that houses the rotating transducer while the imaging transducer is moved proximally and distally, allowing for smooth and uniform mechanical pullback[76].
- *Solid-state transducers* (the electronically switched multi-element array system), on the other hand, rely on a small array of fixed transducers located at the catheter's tip. These transducers create ultrasound images by electronically steering the ultrasound beam. The array can be programmed so that one set of elements transmits while a second set receives simultaneously[74].

Both types of transducers have their own advantages and limitations, and the choice of transducer depends on the specific clinical application and the preferences of the user.

3.2.1 Features of normal coronary artery seen on IVUS

A normal coronary artery visualized by IVUS typically displays three distinct layers, each with different echogenicity and thickness[75]:

1. *Intima:* The innermost layer of the arterial wall, which is in direct contact with the bloodstream. The intima appears as a thin, hyperechoic (bright) line on IVUS.
2. *Media:* The middle layer of the arterial wall, which consists of smooth muscle cells and elastic fibers. The media typically appears as a hypoechoic (darker) than the intima.
3. *Adventitia:* The outermost layer of the arterial wall, which is composed of connective tissue and contains small blood vessels (vasa vasorum) that supply the vessel wall. The adventitia appears as a quite hyperechoic (bright) band on IVUS.

In addition to these three layers, IVUS can also visualize the lumen of the coronary artery, which is the area surrounded by the arterial wall layers (Figure 1). The thickness of each layer can vary depending on the location within the artery and the age and health of the patient.

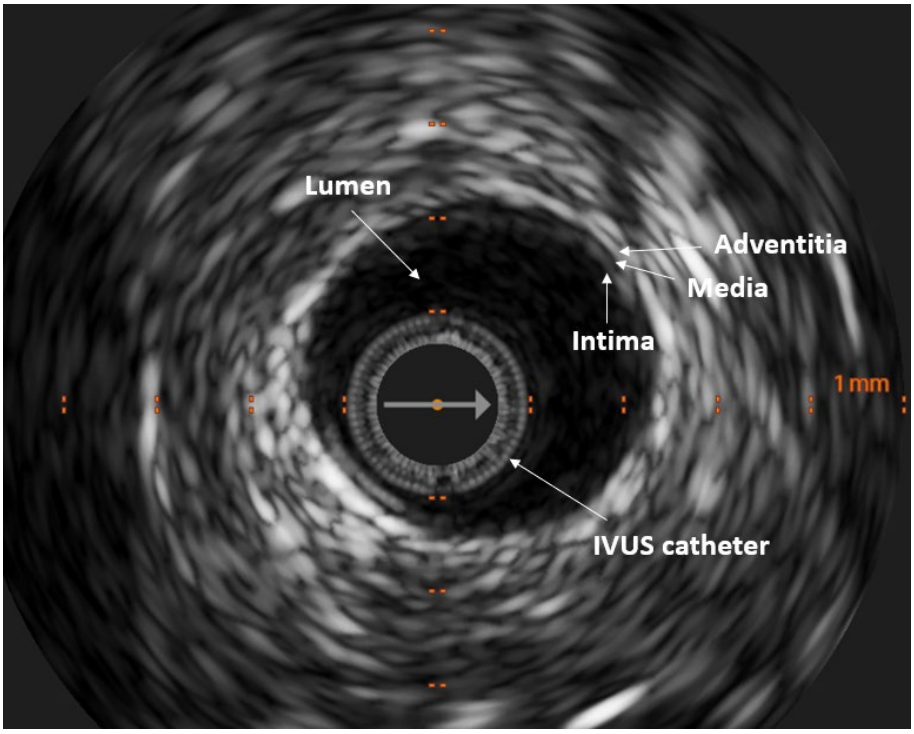


Figure 1. Intravascular ultrasound image demonstrating a normal segment of the coronary artery.

IVUS can provide detailed measurements of the arterial dimensions, including the lumen diameter (the diameter of the open space within the artery), the external elastic membrane (EEM) diameter (the diameter of the artery including the vessel wall), and the vessel area (the cross-sectional area of the artery) (Figure 2). These measurements can be used to assess the extent of plaque buildup and to monitor changes in the arterial wall over time.

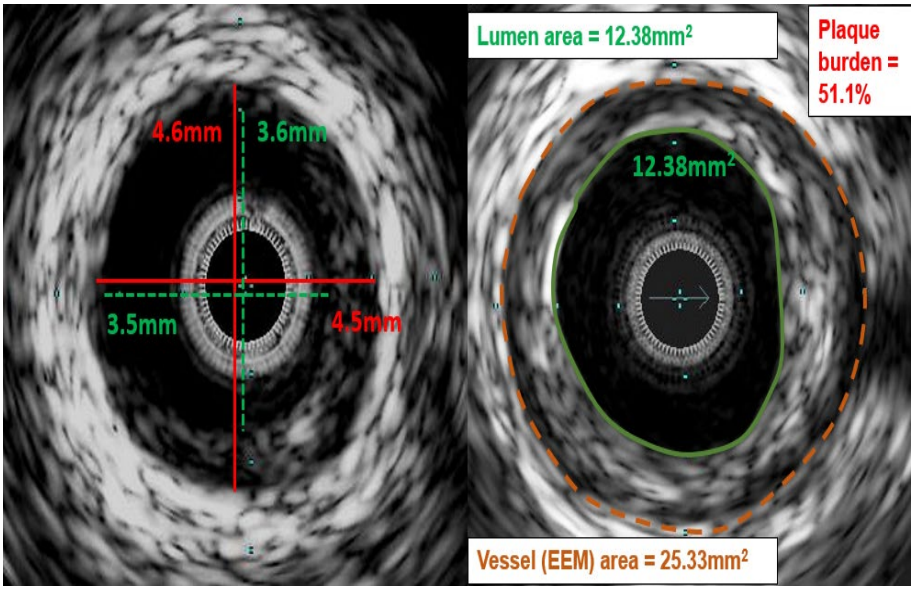


Figure 2. Intravascular ultrasound images demonstrating different measurements of the coronary artery. *Both images illustrate soft atherosclerotic plaque, with the left image showing measurements of the lumen diameter (green dashed line) and the external elastic membrane (EEM) diameter (red line), while the right image displays the lumen area (green circle) and the vessel area (brown circle). Plaque burden, expressed as a percentage, is calculated as 100 minus lumen area divided by vessel area, multiplied by 100%.*

3.2.2 Features of different plaque types seen on IVUS

Intravascular ultrasound can identify different types of coronary artery lesions and provide detailed information on the arterial wall and lumen. Specific IVUS characteristics are associated with each type of lesion, which can aid in accurate diagnosis and appropriate treatment selection.

Calcific lesions. On IVUS, calcified lesions appear as dense, highly reflective regions within the arterial wall (Figure 3). These regions typically have a low echolucent (dark) core and a high echogenic (bright) surface. High frequency ultrasound waves cannot penetrate calcium, resulting in a phenomenon called "acoustic shadowing." This means that IVUS is only able to detect the leading edge of the calcium and cannot accurately determine its thickness. In addition, calcium can cause reverberations or multiple reflections, which occur as the ultrasound oscillates between the transducer and calcium. These reflections can produce concentric arcs in the IVUS image at specific, repeatable distances. The calcified region may be extensive and extend throughout the length of the artery, or it may be focal and limited to a specific area[77,78,79].

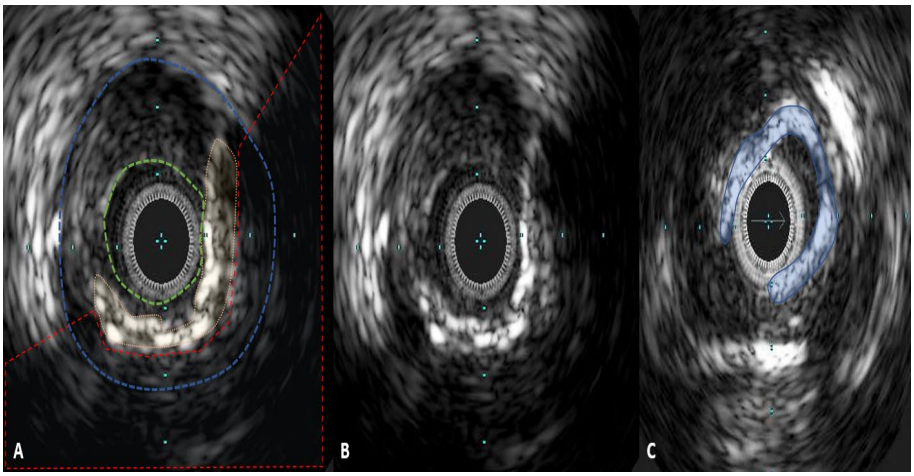


Figure 3. IVUS images demonstrating calcific lesions. *In image A, a severe lesion (with a plaque burden of 82.3%) is visible, with a 180° arc of superficial calcium (indicated by the brown line). The red line highlights the acoustic shadow caused by the calcium arc, while the green and blue lines mark the lumen and vessel areas, respectively. Image B shows the same view without the markings, and in image C, a severe lesion with an almost concentric arc of superficial calcium (indicated by the blue area) is visible.*

Fibrotic lesions. Fibrous plaques are the most commonly observed type of atherosclerotic lesion (Figure 4). Plaques that are primarily composed of fibrous tissue have an echogenicity that falls between that of echolucent soft atheromas and highly echogenic calcified plaques. On IVUS, fibrotic lesions typically appear as homogenous, hyperechoic regions within the arterial wall. These regions may have a thin fibrous cap, which can appear as a hyperechoic line separating the plaque from the arterial lumen. Generally, higher amounts

of fibrous tissue in the plaque correlate with greater echogenicity. However, very dense fibrous plaques can generate enough attenuation or acoustic shadowing to be mistakenly identified as calcified[77,78,79].

Lipid-rich lesions (soft plaque). The designation "soft" does not describe the structural properties of the plaque, but instead indicates the acoustic signal that results from its low echogenicity. On IVUS, lipid-rich lesions typically appear as large, hypoechoic regions within the arterial wall. These regions may have a thin fibrous cap, which can appear as a hyperechoic line separating the plaque from the arterial lumen. Soft plaques typically have a low amount of collagen and elastin[77,78,79].

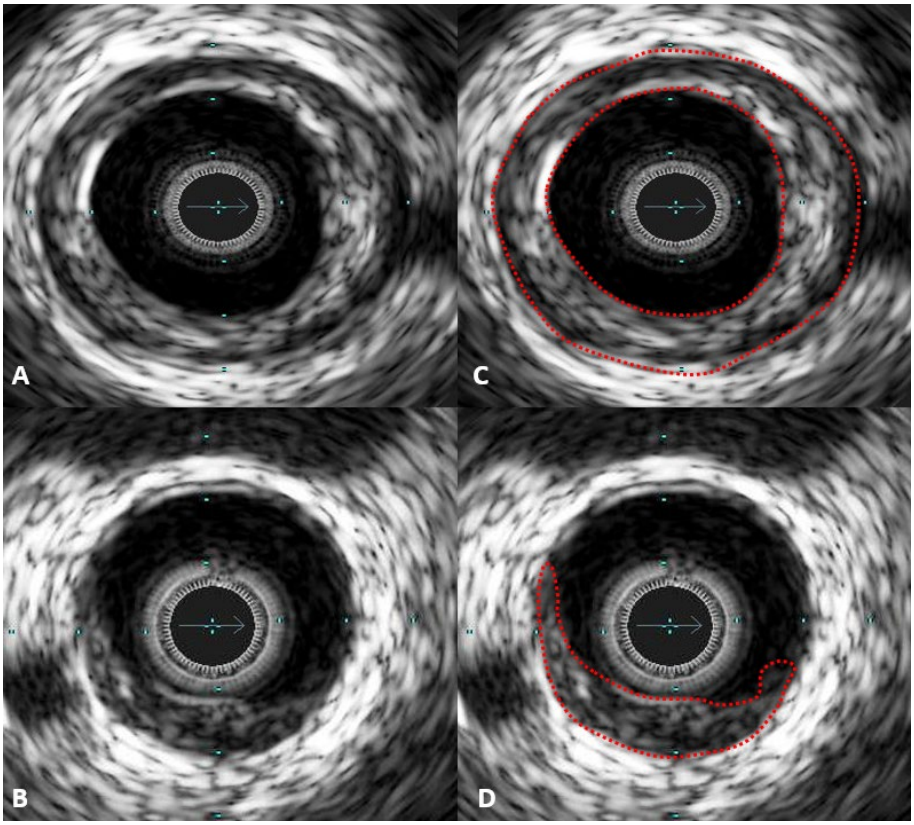


Figure 4. IVUS images demonstrating fibrotic lesions. *Images A and B show mild fibrotic lesions, with image A displaying a concentric pattern and image B showing an eccentric pattern. In pictures C and D, the plaque area is highlighted by red lines.*

Mixed lesions. Plaques that display more than one acoustical subtype are referred to as mixed plaques (Figure 5). These plaques can be described using various terms, such as "fibrocalcific" or "fibrofatty," depending on their composition.

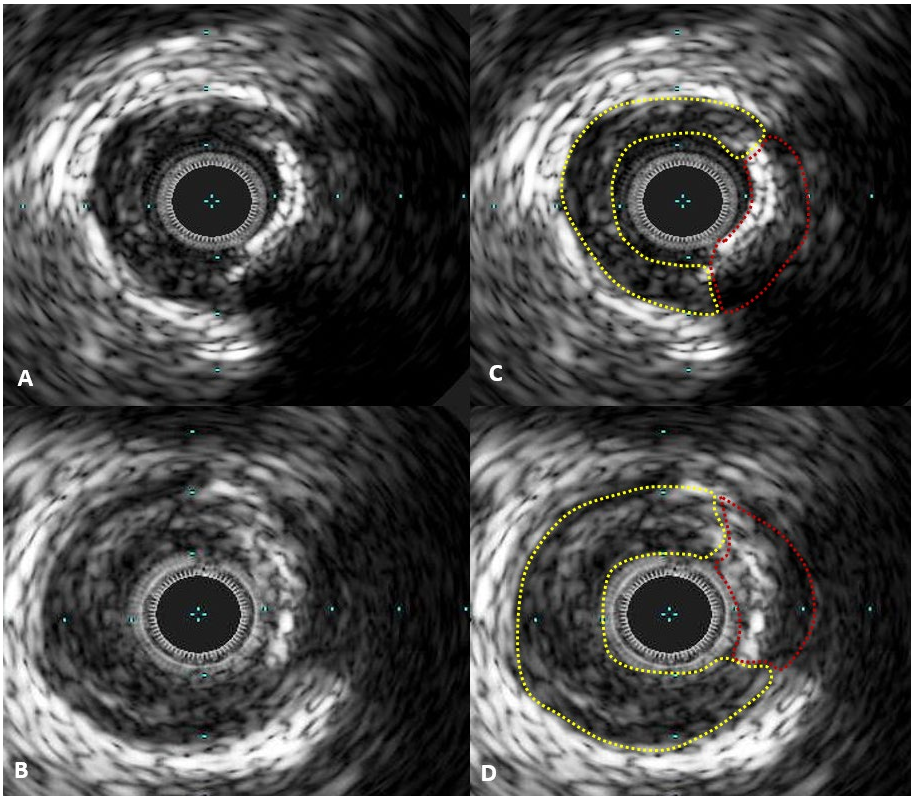


Figure 5. IVUS images demonstrating mixed lesions. *Images A and B demonstrate severe mixed (fibrocalcific) lesions. The location of soft plaque and calcium is marked by the yellow and red lines, respectively, in pictures C and D.*

Thrombotic lesions. On IVUS, thrombotic lesions are characterized by the presence of a thrombus within the lumen of the coronary artery. These lesions typically have a low echogenicity due to the presence of the thrombus, which can also produce acoustic shadowing. In some cases, a thrombotic lesion may be superimposed on top of a preexisting atherosclerotic plaque, further contributing to the complexity of the lesion[77,78,79].

3.2.3 IVUS as a tool to optimize PCI

Evaluation of the vessel prior to PCI.

To optimize outcomes in PCI, it is advisable to perform IVUS prior to stent implantation. Before stenting, intravascular imaging can evaluate the plaque's composition and distribution and determine if a more aggressive approach (such as cutting, or scoring balloons, rotational atherectomy or lithotripsy to induce calcium fractures) or a less aggressive approach (such as direct stenting) to lesion preparation is necessary. IVUS can also assist in selecting the appropriate stent size (diameter and length)[39,80].

When it comes to selecting the appropriate stent diameter, various approaches have been proposed. The most conservative method involves choosing a stent diameter based on the smallest reference lumen measurement. Alternatively, stent diameters could be selected based on the mean (average of proximal and distal) reference lumen measurement, the largest reference lumen measurement (proximal or distal), or the smallest reference EEM diameter. More aggressive approaches utilize a media-to-media measurement at the site of the minimal lumen diameter. From a practical standpoint, using the distal lumen reference (either EEM or lumen-based) is a simple and safe approach, followed by post-dilatation of the mid- and proximal part of the stent[80]. Intravascular ultrasound guidance has been found to result in larger stent diameters, greater angiographic minimum lumen diameter (MLD) and minimum stent area (MSA), and implantation of more and longer stents compared to angiographic guidance[81].

The proper selection of the sites for stent implantation and avoidance of the landing zones with plaque burden exceeding 50% hold immense clinical significance due to their association with stent edge restenosis following implantation of DES[82]. Furthermore, incomplete lesion coverage has been consistently identified as a predictor of stent failure (manifesting as stent thrombosis or restenosis), highlighting the crucial role of selecting the optimal stent length[83].

The imaging procedure should start at a point at least 20 mm distal to the lesion and end at the coronary ostium, allowing for the capture of the longest vessel segment feasible. In cases where the imaging catheter cannot cross the lesion before stenting, balloon pre-dilatation can be performed to facilitate image acquisition. Correlating intracoronary imaging findings with angiogram images is crucial for further angiography-guided interventions, such as the identification of stent landing zones.

Assessment of the stenting result and further optimization.

IVUS can reveal correctable anomalies in the stent and underlying vessel wall after stent implantation, including underexpansion, strut malapposition, geographic miss, and stent edge dissection, all of which have been linked to adverse outcomes after PCI[80].

- *Stent expansion* is assessed by minimum stent cross-sectional area (CSA) and underexpanded stent is a robust predictor of early stent thrombosis and restenosis following implantation of DES, according to multiple IVUS studies[84,85,86]. The CSA can be reported as an absolute measure or relative to a predefined reference area, which could be the proximal, distal, largest, or average reference area (Figure 6). Greater absolute stent expansion has been associated with improved clinical outcomes and lower stent failure risk, and it appears to be a more reliable predictor of future stent patency than relative expansion[87]. IVUS studies have shown that a stent CSA of 5.5 mm^2 provides the best discrimination of subsequent events in non-left main lesions[88], while cutoff values for left main lesions are higher (e.g., > 7 mm^2 for distal left main and > 8 mm^2 for proximal left main). For relative stent expansion, different targets for stent optimization have been proposed, including a minimum stent area greater than the distal reference lumen area or > 80% or > 90% of the average (proximal and distal) reference area. Recent IVUS trials have demonstrated that a MSA larger than the distal reference lumen area is linked with a minimal rate of adverse events[89].

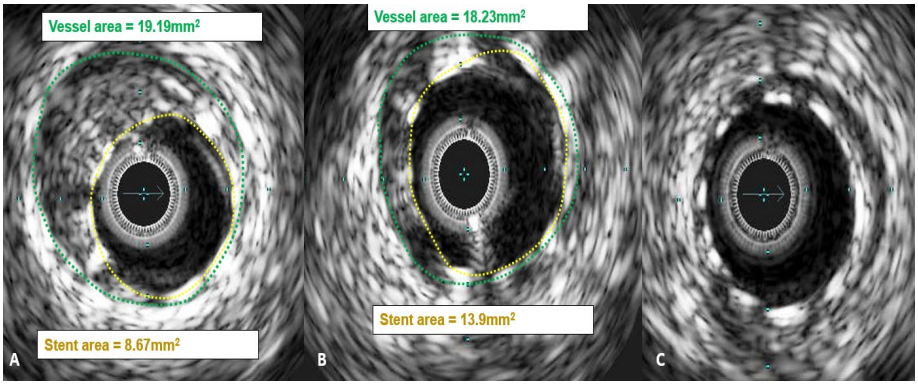


Figure 6. IVUS images showing stent expansion. *A – The stent area shows satisfactory absolute expansion, but the relative stent expansion in relation to the vessel area is suboptimal. B – After postdilating the stent using a larger balloon, both absolute and relative stent expansion have improved. C – Stent expansion is acceptable. All pictures show proper stent apposition.*

- *Stent malapposition* occurs when the stent struts do not contact the vessel wall (Figure 7). It can happen immediately after the procedure or later due to inflammation or remodeling of the vessel wall. Underexpansion and malapposition can happen together or separately. Studies have shown that if the distance between the struts and the vessel wall is less than 0.35 mm, the struts integrate fully with the vessel wall over time[90]. While underexpansion is a strong predictor of stent thrombosis or restenosis, acute malapposition alone may not lead to stent failure as it may resolve on its own[91]. However, malapposition has been frequently observed in very late stent thrombosis (>1 year post stent implantation)[92] and has been associated with increased thrombogenicity in laboratory studies[93]. Thus, it is important to avoid extensively malapposed struts during stent implantation and correct malapposition when feasible.

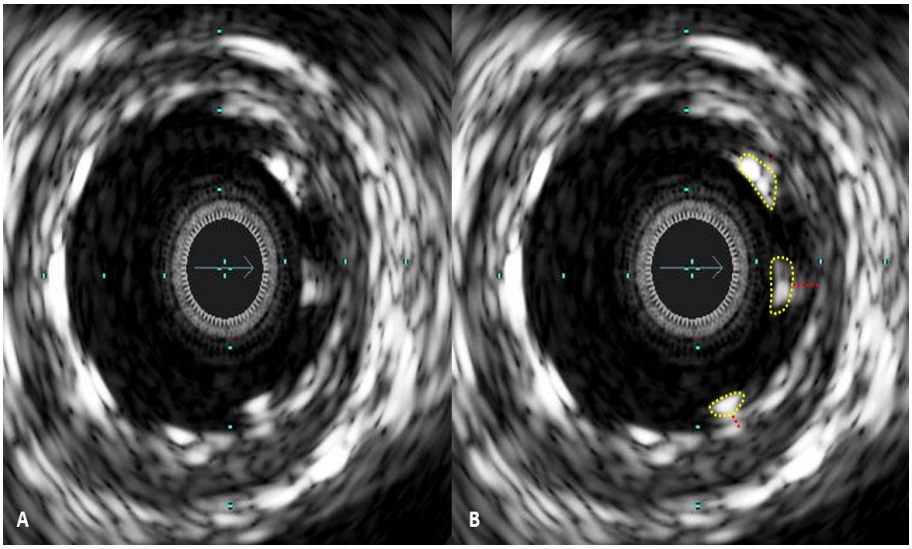


Figure 7. IVUS images demonstrating stent malapposition. *Picture A reveals stent struts that are not properly apposed against one side of the artery. Picture B demonstrates malapposed stent struts, which are highlighted with a yellow line, and the red lines illustrate the gap between the stent struts and the inner layer (intima) of the vessel wall.*

- *Stent edge dissection.* IVUS studies have found that deep (involving the medial layer), laterally extensive (> 60°), and long (> 2 mm) edge dissections are associated with early stent thrombosis[94]. Therefore, large dissections should be corrected by implanting additional stent.

However, minor edge dissections are unlikely to have clinical significance and may not need correction[95].

3.2.4 Impact of IVUS-guided stenting on clinical outcomes: a review of major trials

Several large randomized controlled trials have been conducted to compare patient outcomes between IVUS-guided PCI and angiography-guided PCI. While most of these trials have focused and proven IVUS benefit in optimizing complex coronary artery interventions, there is limited data on its efficacy in a wider subset of lesion types. Therefore, the ULTIMATE (Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation) trial is notable for its evaluation of IVUS-guided PCI versus angiography-guided PCI in an all-comers group of patients undergoing PCI.

During the trial, patients undergoing coronary revascularization were randomly assigned to either IVUS-guided PCI (n = 724) or angiography-guided PCI (n = 724). In the IVUS-guided PCI group operators tried to achieve certain IVUS characteristics, such as a minimal cross-sectional area of > 5.0 mm^2 (or 90% of distal reference lumen cross-sectional area), plaque burden at proximal and distal stent edges of < 50%, and no stent edge dissection involving media with length > 3 mm. The primary outcome of the study was target-vessel failure at one-year (cardiac death, MI, or target vessel revascularization). The incidence of the primary endpoint was 2.9% in the IVUS-guided PCI group, in contrast to 5.4% in the angiography-guided PCI group ($p = 0.019$). This difference was mainly due to the lower rate of repeat target vessel revascularization (TVR) in the IVUS group. For those who met the criteria for optimal IVUS-guided PCI (all criteria satisfied), it seemed that the use of IVUS offered a more substantial advantage compared to angiography-guided PCI[35]. These benefits persisted during long-term follow-up, with TVF occurring in 6.6% of the IVUS-guided PCI group and 10.7% of the angiography-guided PCI group at 3 years ($p = 0.01$)[36].

To sum up, the ULTIMATE trial found that in a heterogeneous population of patients receiving PCI, IVUS-guided PCI was linked to a lower incidence of target vessel failure over a 3-year span compared to angiography-guided PCI. Although the IVUS-guided PCI group had numerically lower rates of all composite outcomes, the most significant advantage appeared to be in the reduction of TVR.

IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) was a randomized controlled trial with the objective to compare the effectiveness of IVUS-guided and angiography-

guided PCI in patients undergoing DES implantation for long coronary artery lesions. The trial randomized patients with long coronary lesions (≥ 28 mm) to either IVUS-guided PCI (n = 700) or angiography-guided PCI (n = 700). The primary endpoint, which included cardiac death, myocardial infarction, or target lesion revascularization at 1 year, occurred in 2.9% of the IVUS-guided PCI group compared to 5.8% of the angiography-guided PCI group (p = 0.007). This difference was mainly due to a reduction in repeat target vessel revascularization (2.5% with IVUS-guided PCI vs. 5.0% with angiography-guided PCI (p = 0.02))[8]. The study followed up on patients for 5 years, and at this point, the primary endpoint occurred in 5.6% of the IVUS-guided PCI group versus 10.7% of the angiography-guided PCI group (p = 0.001), mainly due to the lower rate of ischemia-driven revascularization (4.8% of the IVUS-guided PCI group compared to 8.4% of the angiography-guided PCI group (p = 0.007))[9]. In conclusion, for patients with long coronary lesions, IVUS-guided PCI was more effective than angiography-guided PCI in reducing adverse cardiac events. The sustained benefit of IVUS was due to a decrease in target lesion revascularization.

Randomized clinical trials have indicated that IVUS-guided PCI can effectively reduce the need for repeat target lesion revascularization as compared to angiography guidance alone. However, the impact of IVUS on myocardial infarction and death rates during PCI remained uncertain, as the results of individual trials have not shown a statistically significant effect. In contrast, several meta-analyses have demonstrated that the use of IVUS during PCI is associated with a significant reduction in these more serious endpoints.

Darmoch et al. performed a meta-analysis, which analyzed 19 studies that included 27610 patients who underwent PCI, with 11513 patients in the IVUS-guided group and 16097 patients in the coronary-angiography-guided group. The authors found that, when compared to standard angiography-guided PCI, the use of IVUS guidance was associated with significantly lower risks of cardiovascular death (risk ratio (RR), 0.63; 95% CI, 0.54–0.73), myocardial infarction (RR, 0.71; 95% CI, 0.58–0.86), target lesion revascularization (RR, 0.81; 95% CI, 0.70–0.94), and stent thrombosis (RR, 0.57; 95% CI, 0.41–0.79)[96].

Elgendy et al. conducted a meta-analysis of seven randomized trials comparing IVUS-guided stent implantation to an angiography-guided approach in the era of DES. The study analyzed 3192 patients with a mean coronary lesion length of 32 mm, and found that at an average follow-up of 15 months, IVUS-guided PCI was associated with a lower risk of major adverse cardiac events (6.5% versus 10.3%; odds ratio (OR), 0.60; 95% confidence interval (CI), 0.46–0.77; P<0.0001), primarily due to a lower

incidence of ischemia-driven target lesion revascularization (4.1% versus 6.6%; OR, 0.60; 95% CI, 0.43–0.84; P=0.003). Additionally, the risk of cardiovascular mortality (0.5% versus 1.2%; OR, 0.46; 95% CI, 0.21–1.00; P=0.05), and stent thrombosis (0.6% versus 1.3%; OR, 0.49; 95% CI, 0.24–0.99; P=0.04) was also found to be lower in the IVUS-guided group[97].

3.3 Obstacles and unanswered questions in the percutaneous treatment of long lesions

Stent restenosis is an unfavorable outcome that often necessitates repeat revascularization when it is obstructive. The length of the stent plays an important role in the occurrence of restenosis, and therefore, stenting long lesions with long stents is naturally associated with a higher incidence of these negative events, especially when BMS were used routinely[98,99]. The introduction of DES has significantly reduced the incidence of stent restenosis; however, long DES implantation to treat these complex lesions still carries an increased risk of the need for repeat revascularization[100,101,102,103,104]. Thus, compared to shorter lesions, stent placement for diffusely diseased coronary segments is often avoided, and in some cases, only the most severe lesion is stented, leaving significant atheroma without a stent (known as “spot” stenting)[105,106]. Although this approach is appealing to minimize the stent length, it carries an elevated risk of implanting the stent in segments with high plaque volume, which is a risk factor for restenosis near the stent edges to occur. Additionally, this approach may lead to residual myocardial ischemia, which may not adequately improve the patient's symptoms. Another significant factor contributing to negative outcomes is the stent diameter. Smaller stents are associated with an increased risk for repeat revascularization[107,108,109]. This is particularly relevant for long LAD lesions, as this vessel tapers towards the distal segments. As a result, treating long LAD lesions that involve distal segments often requires using a small diameter stent in the distal to mid- part, which can lead to increased risk for the stent restenosis to develop.

In recent years, numerous clinical trials have been conducted to assess the effectiveness of drug-coated balloons (DCB) in treating de novo coronary artery lesions[110]. Previously, DCBs have been primarily used to treat stent restenosis. However, the results of trials comparing DCB to DES in the treatment of de novo coronary lesions have shown similar efficacy in terms of target lesion restenosis and thrombosis[111,112], thereby positioning DCB as an appealing alternative to treat coronary lesions without necessitating stent

implantation. For long LAD lesions, a "hybrid" approach[113] could be utilized, whereby stenting is performed for large proximal segments of the vessel, and balloon angioplasty using DCBs is utilized for smaller mid- to distal-segment lesions. This approach may offer an attractive treatment option for complex LAD lesions while minimizing the risk associated with using long stents.

Another important technical aspect to consider while treating long lesions is the adjuvant use of tools, such as fractional flow reserve or intravascular imaging, to optimize PCI and improve long term results. Although there is currently limited data on the role of functional optimization in optimizing stenting of long lesions, a recent analysis from a pooled patient group with long lesions from two robust randomized controlled trials (ULTIMATE and IVUS-XPL) has shown that intravascular imaging can not only reduce the frequency of repeat target lesion revascularization but also improve cardiac survival in this patient population. In this study authors compared IVUS guidance versus angiography guidance in 2577 patients who had undergone stent implantation with a length of at least 28 mm for long lesions. The primary endpoint of cardiac death at 3 years occurred in 12 patients (1.0%) in the IVUS-guided group compared to 28 patients (2.2%) in the angiography-guided group (HR: 0.43; 95% CI: 0.22-0.84; P = 0.011). Furthermore, there was a lower incidence of ischemia-driven target lesion revascularization in the IVUS-guided group (3.8%) than in the angiography-guided group (6.5%) (HR: 0.57; 95% CI: 0.40-0.82; P = 0.002)[114].

Despite the available evidence, several knowledge gaps persist regarding the percutaneous treatment of long coronary lesions. While recent trials suggest that the use of intravascular ultrasound can improve treatment outcomes in patients with long lesions, there is still not enough data on the impact of functional optimization in this specific lesion subset. Additionally, there is a scarcity of evidence on the effect of IVUS on functional results of long lesion PCI, and there have been no head-to-head comparison trials between these two distinct PCI optimization strategies.

4 METHODS

This is a single-center, prospective, observational study, which was conducted at Vilnius University Hospital, Santaros klinikos between July 1, 2019 and March 31, 2021. The study enrolled 80 consecutive patients who had functionally significant (FFR ≤ 0.8) long lesions necessitating a stent length of ≥ 30 mm. The study protocol involved the performance of IVUS-optimized PCI, with the results being evaluated using both IVUS and FFR. The study adhered to the principles set out in the Declaration of Helsinki and followed good clinical practice recommendations. An independent regional ethics committee approved the research protocol (approval number Nr.2019/6-1150-639). All patients provided their informed consent before participating in the trial. A flowchart outlining the study process is presented in Figure 8. Patients who met the following criteria were included in the study:

- age over 18 years;
- chronic coronary syndrome or acute coronary syndrome without ST segment elevation (unstable angina or myocardial infarction without ST segment elevation);
- functionally significant (FFR ≤ 0.8) lesion requiring a stent length of ≥ 30 mm amenable for percutaneous coronary intervention.

Patients were excluded from the study if they had:

- acute myocardial infarction with ST segment elevation;
- contraindications for dual antiplatelet therapy;
- life expectancy of ≤ 1 year;
- or known allergy to biolimus, sirolimus, everolimus, or zotarolimus.

The decision to perform percutaneous treatment for long lesions was based on various factors, including the Heart Team's decision, patient preference, single-vessel disease, or staged PCI after treating the culprit artery of previous ACS.

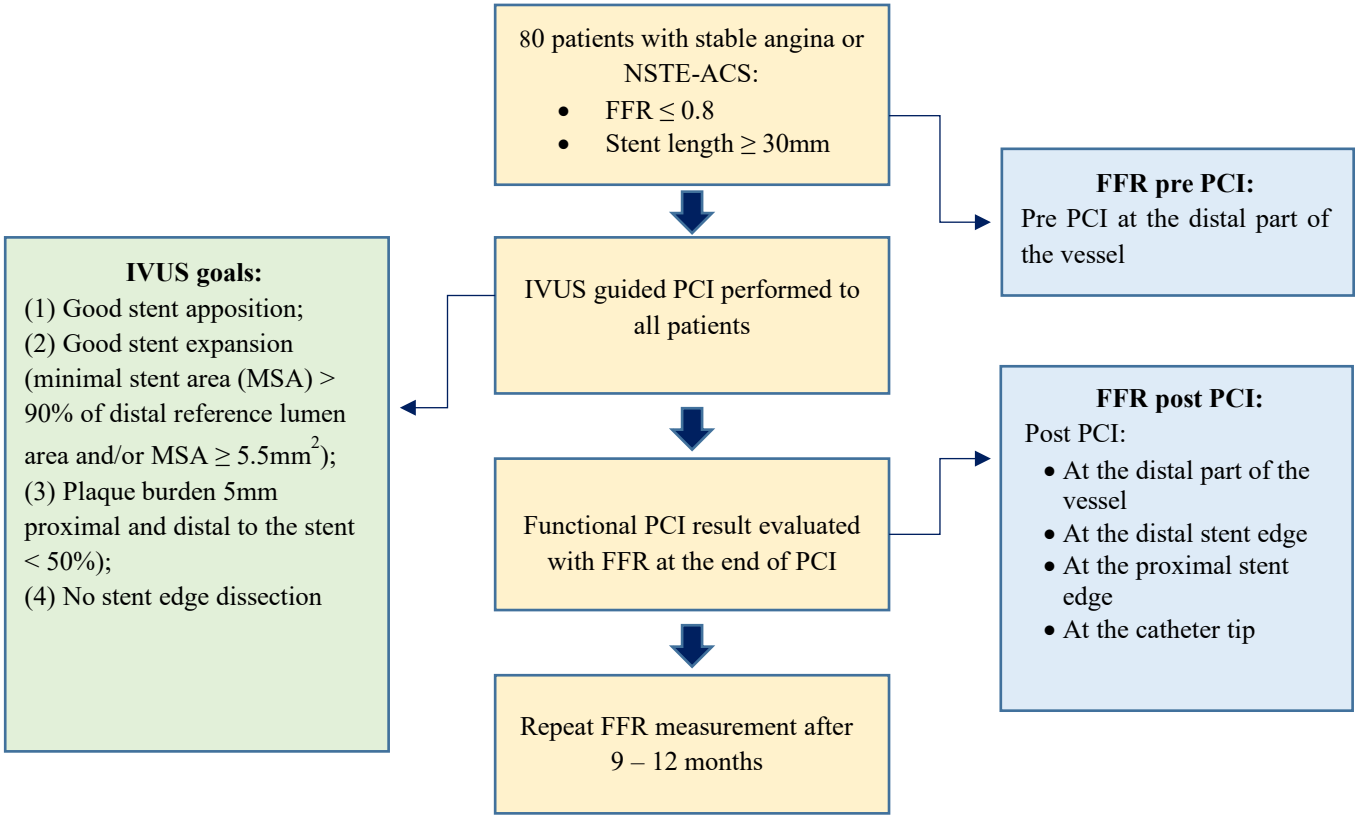


Figure 8. The flowchart of the clinical trial investigating the optimization of long lesions PCI with IVUS

IVUS – intravascular ultrasound; FFR – fractional flow reserve; NSTE-ACS – acute coronary syndrome without ST-segment elevation; PCI – percutaneous coronary intervention

To compare the outcomes of IVUS-optimized long lesion PCI with those of FFR-optimized PCI, a historical cohort of patients who underwent FFR-guided long lesion PCI was employed. This group included 74 patients who met the same inclusion and exclusion criteria and underwent PCI with long DES implantation at the same hospital, with FFR being used to optimize the functional outcome. The detailed results of this cohort were published previously[115]. A flowchart depicting this aspect of the study is presented in Figure 9.

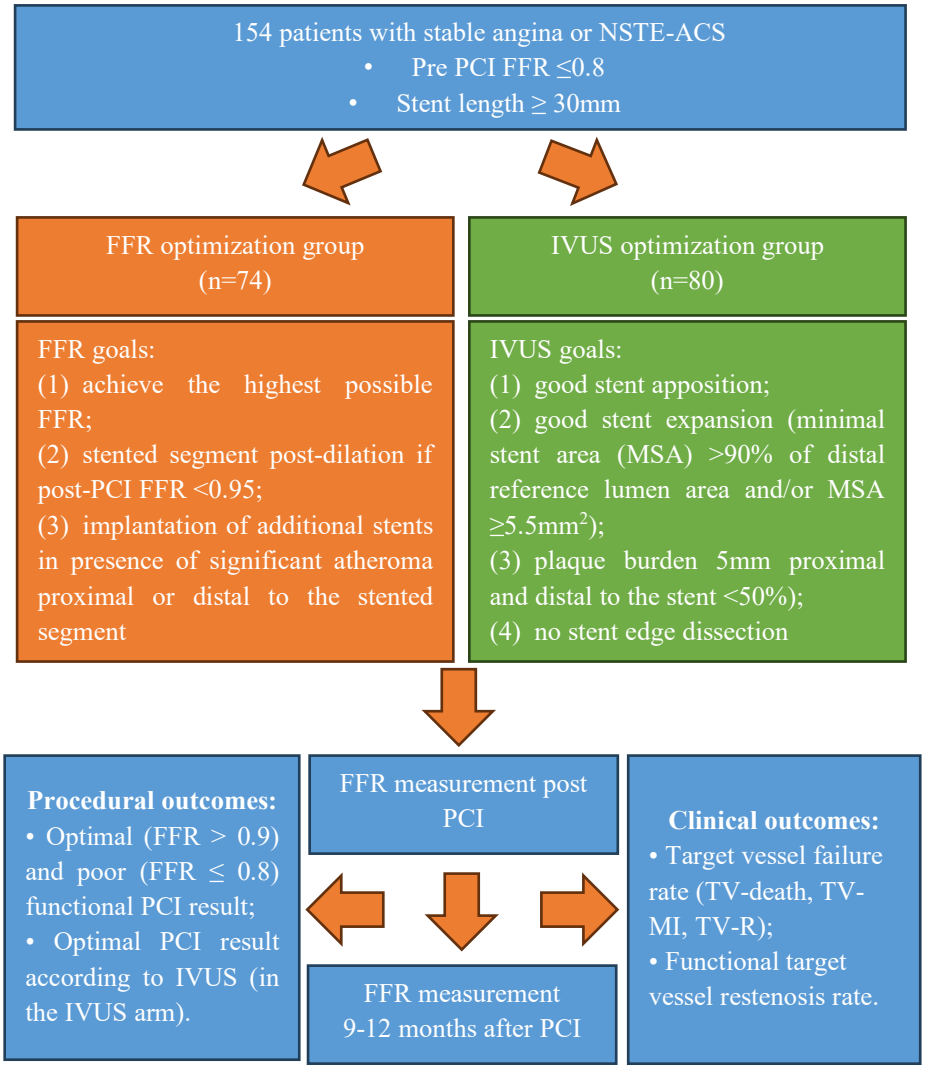


Figure 9. The flowchart of the clinical trial depicting the comparison of long lesions PCI optimization using FFR and IVUS.

IVUS – intravascular ultrasound; FFR – fractional flow reserve; NSTE-ACS – acute coronary syndrome without ST-segment elevation; PCI – percutaneous coronary intervention

4.1 Fractional flow reserve protocol

FFR measurements were obtained according to the standard practice. Following the insertion of a 6F introducer, typically through the right radial artery (in rare cases, the left radial artery or femoral artery was used), a 6F guide-catheter was employed to engage the coronary ostia. After flushing the guide-catheter with 10 ml of saline, a pressure-wire (Abbot Vascular) sensor was placed at the tip of the guide-catheter, and the aortic and pressure-wire pressures were equalized. If there was any coronary ostia disease, the equalization was conducted in the ascending aorta before engaging the ostia with the guide-catheter. Next, the pressure-wire sensor was placed at the distal third of the coronary artery, with a minimum distance of 20 mm from the most distal lesion. For situations where very distal segments were affected, the wire was advanced as far as reasonably achievable. Then, 200 mcg of intracoronary nitroglycerine was administered to the coronary artery, and the guide-catheter was disengaged from the ostium. To induce maximal hyperemia, adenosine was infused intravenously at a rate of 140 μg/kg/min. After reaching stable hyperemia, typically after 2 minutes of adenosine infusion, an FFR recording with a pull-back was performed. A value of FFR $\leq$ 0.8 was considered indicative of functionally significant disease. The following FFR measurements were taken before and after PCI (as shown in Figure 10):

1. Baseline (Pre-PCI FFR): This was specified as the evaluation of lesion significance prior to PCI.
2. Post-PCI measurements:

- Post-PCI FFR: This was measured in the same position as the pre-PCI FFR at the end of the PCI procedure, when the PCI result was considered acceptable and final. No further manipulations were performed afterwards.
- FFR gradients:
    - The FFR gradient across the stented segment (StentGradient) was specified as the difference between the FFR value just proximal to the stent and the FFR value just distal to the stent.
    - The FFR gradient distal to the stented segment (DistalGradient) was specified as the difference between the FFR value just distal to the stent and the post-PCI FFR.

3. The same FFR measurements were obtained at 9 – 12 months follow-up (Follow-up-FFR, Follow-up-StentGradient, Follow-up-DistalGradient).

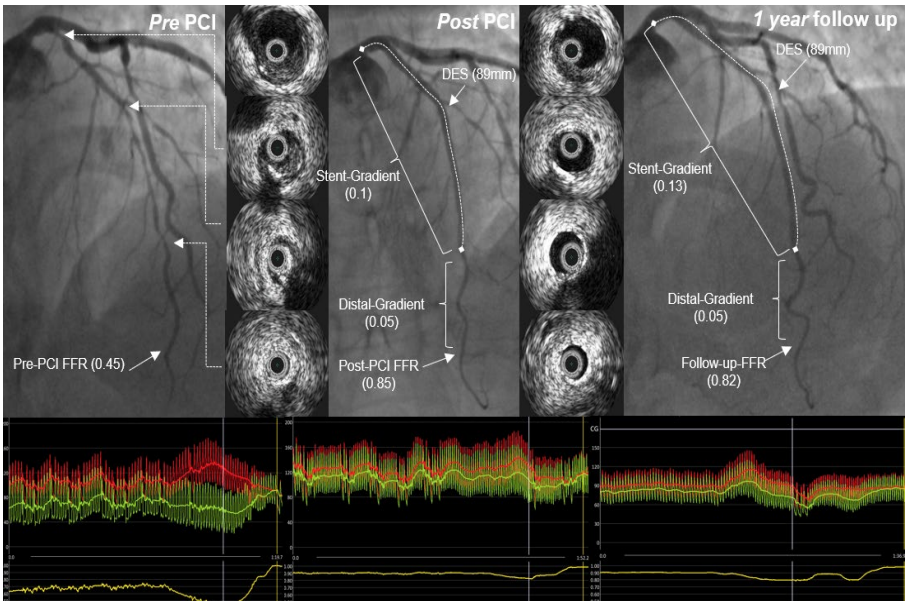


Figure 10. An example case from the IVUS-optimized PCI group. *The figure displays the pre- and post-PCI angiographic images of a left anterior descending artery, as well as the corresponding intravascular ultrasound pictures and fractional flow reserve (FFR) curves (below). One-year follow-up angiographic images are also presented. The same FFR measurement methods were used in the FFR-optimized PCI group.*

4.2 Percutaneous coronary intervention

All PCI procedures were performed by operators experienced in coronary physiology and imaging.

Following identification of a functionally significant long lesion, PCI was performed using the same 6F guide-catheter. Before the procedure, patients were given a loading dose of 300 mg aspirin and 600 mg clopidogrel or 180 mg ticagrelor if these medications were not taken regularly. Heparin was administered at a dose of 70-100 IU/kg prior to FFR measurements.

In the FFR-optimized group, PCI was performed under angiography control, and the decision regarding lesion predilatation, balloon and stent size, stent implantation sites, and postdilatation was made by the operator based on the angiographic images. After PCI and optimization, an FFR recording with a pull-back was performed. If the operator was not satisfied with the angiographic or functional result, additional optimization was performed (a detailed functional optimization description is provided in the FFR optimization protocol).

In the IVUS-optimized group, IVUS was performed before, during and after PCI. If the IVUS catheter could not be delivered due to tight stenosis, predilatation was performed, and IVUS was carried out afterwards. Information obtained from IVUS was used to select the PCI strategy (more detailed information about IVUS use during PCI can be found in the IVUS optimization protocol).

In both groups, a post-PCI FFR measurement with a pull-back was performed when the procedure was considered final, after which no further manipulations were allowed. A PCI procedure was considered angiographically successful when there was TIMI (Thrombolysis in Myocardial Infarction) 3 flow at the end of the procedure (*Grade 0 means no flow beyond the blockage, grade 1 means some flow but not full opacification, grade 2 means partial flow with slower entry/clearance, and grade 3 means complete and rapid flow*)[116] and the residual stenosis was ≤ 10%.

4.3 FFR PCI optimization protocol

The aim was to obtain the highest possible post-PCI FFR. Operators were advised to perform post-dilatation for all cases and it was necessary to perform additional post-dilatation if post-PCI FFR was less than 0.95. In case there was noticeable evidence of major atheroma either proximal or distal to the stented segment, operators were urged to enhance the functional outcome further by implanting additional stents. A final post-PCI FFR measurement with a pull-back was recorded when the angiographic and functional result was considered acceptable and final and no more interventions were performed afterwards.

4.4 IVUS PCI optimization protocol

IVUS was utilized to guide the PCI procedure, with the aim of achieving an optimal anatomical result. Before PCI, IVUS run was done to select the appropriate stent implantation locations with a plaque burden of less than 50% if possible and stent diameter calculated as distal EEM diameter minus 0.25 mm. The morphological plaque features revealed on IVUS assisted operators in choosing the appropriate lesion preparation tools, such as semi-compliant, non-compliant, or cutting balloons. An Eagle Eye Platinum IVUS catheter (Philips) was used for IVUS imaging.

The operators aimed to achieve an optimal anatomical PCI result assessed by IVUS, with specific criteria including:

1. good stent apposition;

2. good stent expansion (minimal stent area (MSA) > 90% of distal reference lumen area and/or MSA ≥ 5.5 mm^2);
3. plaque burden 5mm proximal and distal to the stent < 50%;
4. no stent edge dissection.

Following stent optimization, an IVUS assessment was conducted and regarded as conclusive when an optimal anatomical outcome was attained (all four IVUS criteria were satisfied) or no further anatomical enhancements were feasible.

4.5 Medical treatment after PCI

After PCI, patients received double antiplatelet therapy with aspirin and either clopidogrel or ticagrelor for six to twelve months, as per current guidelines[24,117,118]. If a patient had an indication for anticoagulant therapy, triple antithrombotic therapy (including anticoagulant, aspirin, and clopidogrel) was prescribed for one month, followed by double therapy (anticoagulant and clopidogrel) from 5 to 11 months. In addition, patients received other medications, such as statins, ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and diuretics, as per their clinical condition and current guidelines[24,117,118,119].

4.6 Procedural and clinical outcomes

Study outcomes were categorized as procedural and clinical outcomes.

Procedural outcomes included the following:

- The rate of achieving an optimal functional result for PCI, defined as an FFR value ≥ 0.9, and the rate of achieving a poor functional result, defined as an FFR ≤ 0.8, immediately after the PCI procedure and at 9 – 12 months follow-up.
- The rate of achieving an optimal PCI result as determined by IVUS in the group that underwent IVUS-guided stent implantation.

Clinical outcomes were as follows:

- Target vessel failure rate during one-year follow-up, defined as a combination of target vessel-related death (TV-death), target vessel-related spontaneous myocardial infarction (TV-MI), and any target vessel revascularization (TV-R).
- Functional target vessel restenosis rate at 9 – 12 months follow-up, defined as an FFR value ≤ 0.80.

TV-death referred to all cardiac deaths attributed to the target vessel, unless there was clear evidence of other causes.

TV-MI was defined as the presence of clinical symptoms, electrocardiographic changes, and/or imaging findings suggestive of myocardial infarction, combined with an increase in troponin I or troponin T to a level greater than the 99th percentile of the upper normal limit. A culprit lesion should be confirmed in the target vessel during coronary angiogram.

TV-R was defined as any percutaneous or surgical revascularization procedure at the previously stented vessel.

Patients in whom the post-PCI FFR was ≤ 0.80 immediately post-PCI were excluded from the follow-up analysis of functional restenosis.

4.7 Statistical analysis

Continuous variables were expressed as mean (± standard deviation) or as median [Q1-Q3], depending on their distribution. Student's t test was used to compare continuous variables with a normal distribution, while nonparametric Mann-Whitney U-test was used for those without. Categorical variables were reported as frequency and compared using the $\chi 2$ test. Univariate regression analysis was performed on clinically relevant variables to identify predictors of FFR ≤ 0.8 at 9 – 12 months follow-up. Variables with $p < 0.15$ were included in the multivariable regression analysis model.

5 RESULTS

5.1 Part I. Results from the group of patients undergoing PCI optimization with IVUS

The working conjecture was that post-PCI IVUS assesses primarily the target lesion, while post-PCI FFR evaluates the functional state of the entire target vessel, including non-stented segments. Therefore, we conducted a comparative analysis of clinical, procedural, and anatomical IVUS characteristics, as well as the occurrence of target vessel failure over a 12-month follow-up period between patients who achieved optimal functional result (post-PCI FFR ≥ 0.9) to those who experienced suboptimal functional outcome (post-PCI FFR < 0.9).

5.1.1 Comparison of optimal PCI outcomes based on physiological and anatomical assessment modalities

After IVUS-optimized long lesions PCI less than half (37.5%) of the patients achieved optimal physiological PCI result, defined as a post-PCI FFR value of 0.9 or higher. However, none of the patients exhibited residual ischemia, denoted by a post-PCI FFR value of 0.8 or lower. In contrast, optimal anatomical PCI outcomes, based on IVUS criteria, were achieved in a greater proportion of patients, at 68.4% (Figure 11). Only a quarter of the patients achieved both optimal FFR and IVUS result, underlining the difficulty in treating these complex lesions.

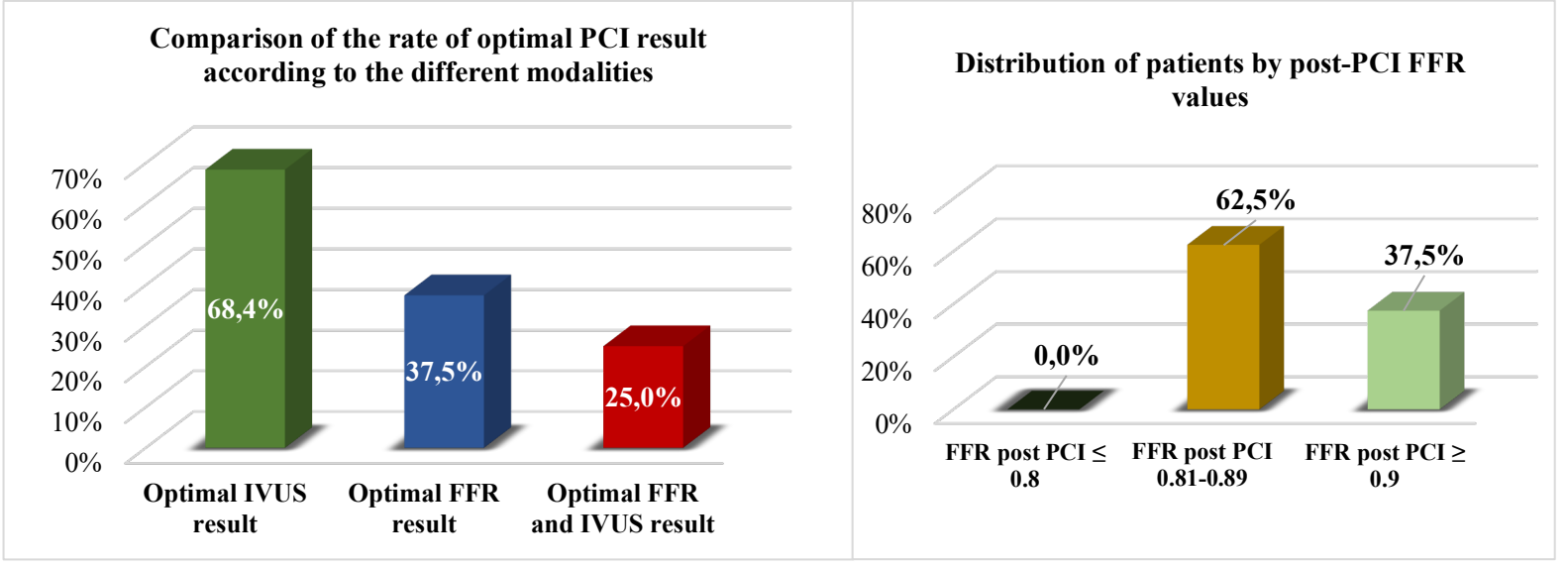


Figure 11. Comparison of the proportion of optimal PCI result achieved based on different modalities and the distribution of patients based on their post-PCI FFR values.

5.1.2 Baseline clinical characteristics

Table 1 displays the baseline clinical characteristics of the study participants. The average age of the patients was 66.2 ± 8.9 years, with 71.3% being male. There were no significant differences in the baseline clinical characteristics between the groups of patients who achieved optimal vs. suboptimal functional results.

Table 1. Comparison of baseline clinical characteristics in patients with post-PCI FFR ≥ 0.9 vs. < 0.9.

Characteristic	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
Age, years	66.2 ± 8.9	65.9 ± 9.2	66.4 ± 9.0	0.83
Male sex	57 (71.3)	22 (73.3)	35 (70.0)	0.75
Diabetes	15 (18.8)	6 (20.0)	9 (18.0)	0.82
Hypertension	74 (92.5)	27 (90.0)	47 (94.0)	0.51
Dyslipidemia	72 (91.1)	26 (89.7)	46 (92.0)	0.72
Chronic kidney disease	16 (20.0)	6 (20.0)	10 (20.0)	1
Active smoking	20 (25.0)	9 (30.0)	11 (22.0)	0.42
History of non-index vessel PCI	47 (58.8)	18 (60.0)	29 (58.0)	0.86
History of CABG	1 (1.3)	1 (3.3)	0 (0.0)	0.38
Previous MI	46 (57.5)	18 (60.0)	28 (56.0)	0.73
Indications for PCI				
Stable angina	30 (37.5)	10 (33.3)	20 (40.0)	0.58
Unstable angina	7 (8.8)	2 (6.7)	5 (10.0)	
NSTEMI	13 (16.3)	5 (16.7)	8 (16.0)	
Silent ischemia	4 (5.0)	3 (10.0)	1 (2.0)	
Staged PCI after STEMI	26 (32.5)	10 (33.3)	16 (32.0)	
LV ejection fraction, %	52.0 ± 5.2	51.5 ± 5.0	52.3 ± 5.3	0.27
Hemoglobin, g/l	139.7 ± 15.6	141.0 ± 14.9	138.8 ± 16.2	0.55
Creatinine, µmol/l	85.5 ± 22.0	81.5 ± 21.4	87.9 ± 22.3	0.21
Total cholesterol, mmol/l	5.2 ± 1.6	5.0 ± 1.3	5.2 ± 1.8	0.66
LDL, mmol/l	3.3 ± 1.3	3.3 ± 1.1	3.4 ± 1.4	0.74

Data is presented as mean ± standard deviation and number (percentage). PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft surgery; MI – myocardial infraction; NSTEMI – myocardial infraction without ST segment elevation; STEMI – myocardial infarction with ST segment elevation; LV – left ventricle; LDL – low-density lipoprotein

5.1.3 Characteristics related to PCI procedure

The PCI-related characteristics are presented in Table 2. Angiographically successful PCI was performed to all patients, with the left anterior descending artery (LAD) being the target vessel in 82.5% of cases. All patients in the functionally suboptimal PCI group had LAD treated, whereas LAD was treated in only half of the patients in the FFR ≥ 0.9 group (p=0.0001). There was no significant difference in the mean length of the stented segment between the two groups, with an average of 62.3 ± 18.0 mm. Similarly, the average stent diameter was comparable between the groups (3.4 ± 0.4 mm vs. 3.2 ± 0.3 mm, p=0.14). All patients underwent postdilation, and the balloon diameter used was similar in both groups.

Table 2. Comparison of procedural characteristics between patient groups with post-PCI FFR ≥ 0.9 and < 0.9.

Characteristic	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
No of diseased vessels				
1	12 (15.0)	4 (13.3)	8 (16.0)	0.91
2	35 (43.8)	14 (46.7)	21 (42.0)	
3	33 (41.3)	12 (40.0)	21 (42.0)	
Target vessel				
LAD	66 (82.5)	16 (53.3)	50 (100.0)	**0.0001**
LCx	7 (8.8)	7 (23.3)	0 (0.0)	
RCA	7 (8.8)	7 (23.3)	0 (0.0)	
Successful PCI	80 (100.0)	30 (100.0)	50 (100.0)	
Predilatation	80 (100.0)	30 (100.0)	50 (100.0)	
Largest predilation balloon diameter, mm	2.7 ± 0.3	2.7 ± 0.3	2.7 ± 0.3	0.91
Maximal predilation pressure, atm	15.4 ± 2.2	15.3 ± 1.9	15.4 ± 2.4	0.99
Number of stents implanted	1.85 ± 0.6	1.87 ± 0.6	1.84 ± 0.6	0.85
Average stent implantation pressure, atm	12.2 ± 1.6	12.7 ± 1.7	11.9 ± 1.4	**0.03**
Average stent diameter, mm	3.3 ± 0.4	3.4 ± 0.4	3.2 ± 0.3	0.14
Total stent length, mm	62.3 ± 18.0	61.8 ± 19.9	62.5 ± 17.0	0.85
Stent length ≥50 mm	53 (63.3)	17 (56.7)	36 (72.0)	0.16
Postdilatation	80 (100.0)	30 (100.0)	50 (100.0)	

Characteristic	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
Largest postdilation balloon, mm	4.2 ± 0.5	4.0 ± 0.5	4.2 ± 0.5	0.07
Maximal balloon pressure, atm	17.8 ± 2.9	18.3 ± 3.2	17.4 ± 2.7	0.09
Bifurcation two stent technique	7 (8.8)	1 (3.3)	6 (12.0)	0.25
Procedure time, min	77.4 ± 27.7	78.2 ± 39.7	76.9 ± 17.1	0.32
Contrast volume, ml	157.7 ± 41.4	150.7 ± 45.6	162.0 ± 38.4	0.18

Data is presented as mean ± standard deviation and number (percentage). LAD – left anterior descending artery; LCx – left circumflex artery; RCA – right coronary artery; PCI – percutaneous coronary intervention

5.1.4 Fractional flow reserve results

The baseline FFR value was 0.64 ± 0.1 in both patient groups. Following PCI, the mean FFR increased to 0.94 ± 0.04 in the group with optimal physiological result and to 0.86 ± 0.02 in the group with suboptimal physiological outcome. Patients who achieved a post-PCI FFR < 0.9 had higher distal (0.05 ± 0.03 vs 0.02 ± 0.02, p=0.0001) and trans-stent (0.08 ± 0.02 vs 0.04 ± 0.02, p=0.0001) gradients compared to those with FFR ≥ 0.9, as shown in Table 3.

Table 3. Comparison of FFR measurements between patient groups with post-PCI FFR ≥ 0.9 and < 0.9

Characteristic	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
FFR pre-PCI	0.64 ± 0.1	0.64 ± 0.12	0.64 ± 0.09	0.75
FFR post-PCI	0.89 ± 0.05	0.94 ± 0.04	0.86 ± 0.02	**0.0001**
Distal gradient	0.04 ± 0.03	0.02 ± 0.02	0.05 ± 0.03	**0.0001**
Trans-stent gradient	0.07 ± 0.03	0.04 ± 0.02	0.08 ± 0.02	**0.0001**

Data is presented as mean ± standard deviation and number (percentage). FFR – fractional flow reserve; PCI – percutaneous coronary intervention

5.1.5 Intravascular ultrasound findings

Table 4 presents the IVUS findings of the study. Nearly half of the patients underwent multiple IVUS assessments after PCI, indicating that 40% of the lesions necessitated further interventions to improve anatomical PCI outcome subsequent to the initial stent optimization. Patients with suboptimal FFR result had a significantly smaller distal reference lumen area (5.5 ± 1.7 mm^2

vs 6.5 ± 2.1 mm^2, p=0.03) and distal reference external elastic membrane area (8.3 ± 3.1 mm^2 vs 9.9 ± 3.6 mm^2, p=0.06) compared to those with FFR ≥ 0.9. However, the plaque burden at the distal site was similar in both groups. The minimal stent area tended to be larger in the FFR ≥ 0.9 group (6.3 ± 1.8 mm^2 vs 5.6 ± 1.8 mm^2), but this finding did not reach statistical significance (p=0.12). The IVUS demonstrated an optimal PCI outcome in 68% of patients, and this percentage was nearly the same in both groups. Patients who did not fulfill all four IVUS optimization criteria usually had plaque burden of ≥ 50% near the stent edges.

Table 4. Comparison of intravascular ultrasound findings between patient groups with post-PCI FFR ≥ 0.9 and < 0.9.

Characteristic	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
Number of IVUS runs				
2	50 (62.5)	19 (63.3)	31 (62.0)	0.98
3	27 (33.8)	10 (33.3)	17 (34.0)	
4	3 (3.8)	1 (3.3)	2 (4.0)	
Distal reference EEM diameter, mm	3.3 ± 0.5	3.4 ± 0.5	3.2 ± 0.5	0.12
Proximal reference EEM diameter, mm	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.5	0.28
Minimal lumen diameter, mm	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.93
Minimal lumen area, mm^2	2.5 ± 0.6	2.6 ± 0.7	2.5 ± 0.6	1
Calcium arc ≥180º	39 (48.8)	13 (43.3)	26 (52.0)	0.45
Distal reference lumen area, mm^2	5.9 ± 1.9	6.5 ± 2.1	5.5 ± 1.7	**0.03**
Distal reference EEM area, mm^2	8.9 ± 3.3	9.9 ± 3.6	8.3 ± 3.1	0.06
Distal reference plaque burden, %	32.6 ± 9.2	32.1 ± 9.6	32.9 ± 9.1	0.72
Proximal reference lumen area, mm^2	10.5 ± 2.8	10.6 ± 2.6	10.5 ± 3.0	0.7
Proximal reference EEM area, mm^2	18.2 ± 4.1	18.0 ± 4.6	18.4 ± 3.9	0.76
Proximal reference plaque burden, %	42.0 ± 8.4	40.4 ± 6.5	42.9 ± 9.2	0.28
Minimal stent diameter, mm	2.5 ± 0.4	2.6 ± 0.4	2.5 ± 0.4	0.25
Minimal stent area, mm^2	5.9 ± 1.9	6.3 ± 1.8	5.6 ± 1.8	0.12
Good stent expansion	73 (92.4)	26 (86.7)	47 (95.9)	0.13
Good stent apposition	79 (100.0)	30 (100.0)	49 (100.0)	
No stent edge dissection	79 (100.0)	30 (100.0)	49 (100.0)	
Plaque ≤ 50% near stent edges	56 (70.9)	21 (70.0)	35 (71.4)	0.89
Optimal IVUS result	54 (68.4)	20 (66.7)	34 (69.4)	0.8

Data is presented as mean ± standard deviation and number (percentage). IVUS – intravascular ultrasound; EEM – external elastic membrane.

5.1.6 Medical therapy and adverse events during follow-up

Antithrombotic therapy, either double or triple, was administered to all patients, and most of them were prescribed statin, beta-blocker, and ACE-inhibitor or ARB at discharge (Table 5).

Table 5. Comparison of medical treatment at discharge between patient groups with post PCI FFR ≥ 0.9 and < 0.9.

Medication	All (n=80)	FFR ≥ 0.9 (n=30)	FFR < 0.9 (n=50)	p
DAPT	72 (90.0)	28 (93.3)	44 (88.0)	0.65
OAC and antiplatelet	8 (10.0)	2 (6.7)	6 (12.0)	0.35
Statin	74 (92.5)	28 (93.3)	46 (92.0)	1
Beta-blocker	67 (83.8)	24 (80.0)	43 (86.0)	0.48
ACE-i/ARB	68 (85.0)	26 (86.7)	42 (84.0)	0.75

Data is presented as number (percentage). DAPT – double antiplatelet therapy; OAC – oral anticoagulant; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Over the 12-month follow-up duration, there were no occurrences of deaths or myocardial infarctions associated with the target vessel. The incidence rate of target vessel failure was 3.8% due to stent restenosis, and one patient died from cardiac causes (Table 6).

Table 6. Adverse events during one-year follow-up.

Adverse event	All patients
Target vessel related death	0 (0)
Target vessel related myocardial infarction	0 (0)
Target vessel revascularization	3 (3.8)
Target vessel failure	3 (3.8)
Cardiac death	1 (1.25)
All-cause death	1 (1.25)

5.1.7 Summary of part I results

The clinical features of 80 patients who underwent IVUS-optimized long lesions PCI were representative of typical CAD patients. The majority of patients were males, 66 years old, and had a history of hypertension and dyslipidemia, while 25% of them were smokers and 20% had diabetes. Chronic coronary syndrome was the most common indication for PCI, and the

LAD artery was the most frequently treated vessel. This finding could partially explain the infrequent attainment of optimal post-PCI FFR result.

Post-PCI IVUS was crucial in verifying the anatomical result, as it demonstrated the additional need for optimization in nearly half of the vessels. Although the rate of optimal IVUS result was high, the same frequency of optimal FFR result was not achieved, likely due to the most frequently treated LAD artery and the diffuse downstream disease.

The majority of patients received guideline-recommended medical treatment. The one-year event rate was acceptable and comparable to trials assessing shorter lesions' event rates. These findings offer assurance that, with IVUS optimization, even extremely lengthy coronary artery lesions, averaging a stented segment length of 62 mm, can be managed with a favorable one-year rate of target vessel failure and the absence of remaining myocardial ischemia.

5.2 Part II. Comparison of long lesions PCI optimization with IVUS vs. FFR

This section presents the results of the second part of the trial, which involved comparing the results of the IVUS-optimized long lesions PCI group to the historical cohort of patients, who underwent FFR-optimized long lesions PCI.

5.2.1 Baseline clinical characteristics

There were no significant differences in the baseline clinical characteristics between the FFR-optimized and IVUS-optimized groups, as shown in Table 7. However, there were fewer patients with a history of non-target vessel related myocardial infarction (MI) in the FFR-optimized group (39.2% vs. 57.5%, p=0.02). The average age of the patients was 66 years, with the majority being male (72%) and 75% of the patients undergoing PCI for chronic coronary syndrome.

Table 7. Comparison of baseline clinical characteristics in patients with FFR-optimized PCI vs. IVUS-optimized PCI.

Clinical characteristics	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	P
Age, years	66.3 ± 9.2	66.3 ± 9.6	66.2 ± 9.0	0.95
Male sex	111 (72.1)	54 (73.0)	57 (71.3)	0.81
Current smoker	35 (22.9)	15 (20.3)	20 (25.0)	0.51
Diabetes mellitus	31 (20.1)	16 (21.6)	15 (18.8)	0.66
Hypertension	141 (91.6)	67 (90.5)	74 (92.5)	0.66
Dyslipidemia	139 (90.8)	67 (90.5)	72 (91.1)	0.9
GFR <60 mL/min/1.73m^2	28 (21.5)	12 (16.2)	16 (20.0)	0.59
Previous non-target vessel myocardial infarction	75 (48.7)	29 (39.2)	46 (57.5)	**0.02**
Previous CABG	3 (1.9)	2 (2.7)	1 (1.3)	0.52
Number of diseased vessels				
Single vessel disease	23 (14.9)	11 (14.9)	12 (15.0)	0.49
Two vessel disease	74 (48.1)	39 (52.7)	35 (43.8)	
Triple vessel disease	57 (37.0)	24 (32.4)	33 (41.3)	
Indications for PCI				
Chronic coronary syndrome	115 (74.7)	55 (74.3)	60 (75.0)	0.92
NSTE-ACS	39 (25.3)	19 (25.7)	20 (25.0)	
LV ejection fraction, %	55.0 [50.0-55.0]	50.0 [45.0-55.0]	55.0 [50.0-55.0]	**0.02**
Hemoglobin, g/l	138.6 ± 16.4	136.7 ± 17.8	139.7± 15.6	0.34
Creatinine, µmol/l	89.9 ± 47.5	96.9 ± 71.0	85.5 ± 22.1	0.18
Total cholesterol, mmol/l	5.3 ± 1.5	5.6 ± 1.4	5.2 ± 1.6	0.18
LDL, mmol/l	3.4 ± 1.3	3.7 ± 1.2	3.3 ± 1.3	0.19

Data is presented as mean ± standard deviation, median [Q1-Q3] and number (percentage). FFR – fractional flow reserve, IVUS – intravascular ultrasound, GFR – glomerular filtration rate, PCI – percutaneous coronary intervention, CABG – coronary artery bypass graft surgery, NSTE-ACS – acute coronary syndrome without ST segment elevation, LV – left ventricle, LDL – low density lipoprotein.

5.2.2 Results associated with PCI

The left anterior descending artery was the most commonly treated vessel, accounting for 82% of the cases (Table 8). When employing the FFR optimization strategy for LAD treatment, there was a significantly lower incidence of left main artery coverage (3% vs. 16%, p=0.01). In both groups, pre-dilatation was routinely carried out, but the FFR-optimized group utilized smaller diameter balloons (2.5 [2.2-2.8] mm vs. 2.6 [2.5-2.9], p=0.001). Furthermore, the FFR-optimized group had notably shorter stented segments (49.0 [36.0-60.3] mm vs. 62.5 [48.0-76.0] mm, p=0.001) compared to the IVUS-optimized group. Post-dilatation was less frequent in the FFR group, and they used smaller diameter balloons for this purpose (3.5 [3.5-3.5] mm vs. 4.0 [3.8-4.5] mm, p=0.001). The contrast volume administered during the procedures was similar in both groups.

Table 8. Comparison of angiographic and percutaneous coronary intervention related characteristics in patients with FFR-optimized PCI vs. IVUS-optimized PCI.

Procedural characteristics	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	P
Target vessel				
LAD	127 (82.5)	61 (82.4)	66 (82.5)	0.83
LCx	15 (9.7)	8 (10.8)	7 (8.8)	
RCA	12 (7.8)	5 (6.8)	7 (8.8)	
PCI involving left main artery	15 (9.7)	2 (2.7)	13 (16.3)	**0.01**
Bifurcation two stent technique	10 (6.5)	3 (4.1)	7 (8.8)	0.24
Predilatation	149 (96.8)	69 (93.2)	80 (100.0)	**0.02**
Largest predilatation balloon diameter, mm	2.5 [2.5-2.75]	2.50 [2.2-2.8]	2.63 [2.5-2.9]	**<0.001**
Number of implanted stents	2 [1.0-2.0]	2 [1.0-2.0]	2 [1.0-2.0]	0.54
Total stent length, mm	56.0 [47.0-71.0]	49.0 [36.0-60.3]	62.5 [48.0-76.0]	**<0.001**
Total stent length ≧ 50mm	89 (57.8)	36 (48.6)	53 (66.3)	**0.03**
Average stent diameter, mm	3.25 [3.0-3.5]	3.25 [3.0-3.5]	3.25 [3.0-3.5]	0.36
Average stent diameter >3 mm	98 (63.6)	45 (60.8)	53 (66.3)	0.48
Maximal implantation pressure, atm	12.5 [12.0-15.0]	14.0 [13.9-16.0]	12.0 [11.5-12]	**<0.001**
Postdilatation	143 (92.9)	63 (85.1)	80 (100.0)	**<0.001**
Maximal postdilatation balloon diameter, mm	4.0 [3.5-4.0]	3.5 [3.5-3.5]	4.0 [3.8-4.5]	**<0.001**
Maximal postdilatation pressure, atm	18.0 [16.0-20.0]	18.0 [16.0-20.0]	18.0 [16.0-20.0]	0.29
Contrast volume, ml	164 ± 51.8	162.3 ± 61.6	157.7 ± 41.4	0.84
Contrast induced neprophaty	0	0	0	

Data is presented as mean ± standard deviation, median [Q1-Q3] and number (percentage). FFR – fractional flow reserve, IVUS – intravascular ultrasound, LAD – left anterior descending artery, LCx – left circumflex artery, RCA – right coronary artery, PCI – percutaneous coronary intervention.

5.2.3 Fractional flow reserve findings

The baseline pre-PCI FFR median value stood at 0.65 [0.55-0.71], and there were no statistically significant differences between the FFR-optimized and IVUS-optimized groups (Table 9). However, following the procedure, 12.3% of patients in the FFR-optimized group exhibited FFR values ≤ 0.8, whereas none of the patients in the IVUS-optimized group had values ≤ 0.8, constituting a significant difference (p=0.001) (Figure 12). Achieving the optimal functional PCI result (FFR post-PCI ≥ 0.9) was recorded in 35.1% of the FFR-optimized group and 37.5% of the IVUS-optimized group patients (p=0.87). Among these patients, 82% underwent coronary angiography with FFR assessment during the 9 – 12-month follow-up, revealing a higher ischemic burden (FFR ≤ 0.8) in the FFR-optimized group compared to the IVUS-optimized group (20% vs. 6%, p=0.02). During follow-up, the FFR pull-back examination demonstrated a smaller trans-stent gradient in the FFR-optimized group (0.06 vs. 0.08, p=0.04), but the distal gradient was larger (0.04 vs. 0.03, p=0.02) compared to the IVUS-optimized group

Table 9. Fractional flow reserve measurement immediately post-PCI and at 9-12 months follow-up

FFR characteristics	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	P
$FFR_{PRE\ PCI}$	0.64 [0.54-07.0]	0.63 [0.52-0.69]	0.66 [0.59-0.71]	0.08
$FFR_{POST\ PCI}$	0.88 [0.85-0.91]	0.88 [0.84-0.91]	0.88 [0.85-0.92]	0.6
Stent-Gradient	0.06 [0.04-0.08]	0.06 [0.04-0.07]	0.07 [0.05-0.09]	0.06
Distal-Gradient	0.03 [0.02-0.06]	0.04 [0.02-0.07]	0.03 [0.01-0.05]	0.06
FFR follow-up performed	126 (81.8)	61 (82.4)	65 (81.3)	0.85
$FFR_{AT\ FOLLOW-UP}$	0.87 [0.83-0.90]	0.87 [0.82-0.90]	0.87 [0.84-0.90]	0.47
Follow-up-StentGradient	0.07 [0.04-0.09]	0.06 [0.04-0.08]	0.08 [0.05-0.10]	0.04
Follow-up-DistalGradient	0.03 [0.02-0.06]	0.04 [0.03-0.07]	0.03 [0.02-0.04]	0.02

Data is presented as median [Q1-Q3] and number (percentage). FFR – fractional flow reserve.

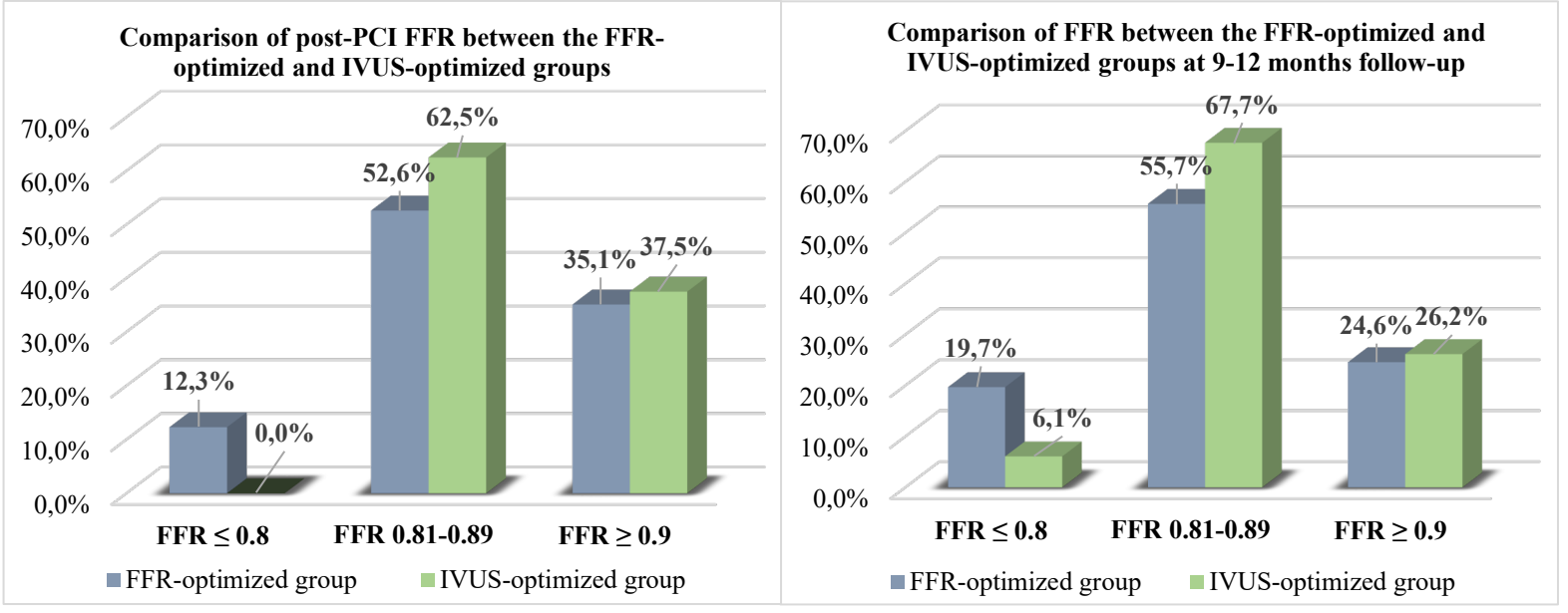


Figure 12. Post-PCI and 9-12 months FFR comparison in the target vessel between FFR-optimized and IVUS-optimized groups.

5.2.4 Medical treatment

Every patient received antithrombotic treatment, which varied between double and triple therapy – the IVUS-optimized group had a higher percentage of patients necessitating triple therapy. Upon discharge, most patients in both groups were prescribed a regimen consisting of statins, beta-blockers, and either ACE inhibitors or ARBs, with no notable distinction observed between the two groups (Table 10)

Table 10. Comparison of medical treatment at discharge between patient groups with different PCI optimization strategies.

Medication	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	p
DAPT	143 (92.9)	72 (97.3)	71 (88.8)	**0.01**
OAC and antiplatelet	11 (7.1)	2 (2.7)	9 (11.2)	**0.01**
Statin	139 (90.8)	64 (87.7)	75 (93.8)	0.19
Beta-blocker	127 (83.0)	60 (82.2)	67 (83.8)	0.80
ACE-i/ARB	132 (86.3)	64 (87.7)	68 (85.0)	0.63

Data is presented as number (percentage). DAPT – double antiplatelet therapy; OAC – oral anticoagulant; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker.

5.2.5 Follow-up results

The incidence of functional target lesion restenosis was observed to be numerically higher in the FFR-optimized group as compared to the IVUS-optimized group (13.5% versus 6.2%). However, this difference did not attain statistical significance (p=0.18). There were no deaths related to target vessel (TV) and no cases of spontaneous myocardial infarctions in either group during the one-year follow-up period. The FFR group demonstrated a numerically elevated rate of repeat target vessel revascularization (8.1% versus 3.8% in the IVUS group), but this difference also missed statistical significance (p=0.25) (Table 11).

Table 11. Clinical outcomes of the study during the 9-12 months follow-up period

Adverse event	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	P
Functional TL restenosis	13 (10.9)	8 (15.1)	5 (7.6)	0.18
TV related death	0	0	0	
TV related MI	0	0	0	
TV revascularization	9 (5.8)	6 (8.1)	3 (3.8)	0.25
TV failure	9 (5.8)	6 (8.1)	3 (3.8)	0.25
Cardiac death	2 (1.3)	1 (1.4)	1 (1.3)	0.95
All-cause death	2 (1.3)	1 (1.4)	1 (1.3)	0.95

Data is presented as number (percentage). TL – target lesion, TV – target vessel.

Angina on exertion at 9 – 12 months follow-up was more prevalent in the FFR-optimized group (62%) compared to the IVUS-optimized group (38%), p=0.001 (Table 12). In the FFR-optimized group, patients with anginal symptoms tended to experience them at lower loads compared to the IVUS group. However, it's worth noting that both PCI optimization strategies appeared to provide acceptable symptom relief, as evidenced by the limited number of patients classified as CCS (Canadian Cardiovascular Society) class III or IV. The majority of patients in both groups continued to take statins and their blood pressure was well controlled with medications.

Table 12. Symptom severity and medical treatment at 9 – 12 months follow-up

Characteristic	All patients (n=154)	FFR-optimized group (n=74)	IVUS-optimized group (n=80)	P
Angina severity (CCS class):				
0 (no angina)	58 (43.6)	17 (25.4)	41 (62.1)	0.001
I	38 (28.6)	22 (32.8)	16 (24.2)	NS
II	33 (24.8)	24 (35.8)	9 (13.6)	0.001
III	3 (2.3)	3 (4.5)	0	NS
IV	1 (0.8)	1 (1.5)	0	NS
Treatment with statins	107 (81.7)	50 (76.9)	57 (86.4)	0.16
Hypertension controlled with medications	117 (88.0)	57 (85.1)	60 (90.9)	0.28

Data is presented as number (percentage). CCS – Canadian Cardiovascular Society.

5.2.6 Factors predicting FFR ≤ 0.8 at follow-up

Based on the results of the multivariable regression analysis, it was found that an average stent diameter of ≤ 3mm was significantly associated with an increased likelihood of having FFR ≤ 0.8 at follow-up. Moreover, the adoption of an FFR optimization strategy was found to be associated with a higher probability of myocardial ischemia in the target vessel territory after 9 – 12 months following PCI, as compared to using IVUS to optimize PCI. These findings are presented in Table 13.

Table 13. Odds ratios for FFR ≤ 0.8 at the 9–12 months follow-up.

Factor	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Age	0.99	0.94-1.06	0.97			
Male gender	2.96	0.64-13.6	0.15	3.23	0.62-16.7	0.16
Active smoking	2.23	0.75-6.66	0.15	2.64	0.76-9.20	0.13
Diabetes	1.37	0.41-4.58	0.61			
Dyslipidemia	1.49	0.30-7.34	0.63			
GFR <60 mL/min/1.73m^2	0.31	0.04-2.48	0.27			
Target vessel LAD	1.55	0.33-7.25	0.58			
Total stent length ≥50mm	0.53	0.19-1.51	0.24			
Average stent diameter ≤3 mm	2.49	0.87-7.10	0.09	3.65	1.14-11.7	**0.03**
FFR optimization strategy (vs IVUS)	3.67	1.13-11.9	0.03	3.79	1.11-12.9	**0.03**

OR – odds ratio, CI – confidence interval, GFR – glomerular filtration rate, LAD – left anterior descending artery, FFR – fractional flow reserve, IVUS – intravascular ultrasound.

5.2.7 Summary of part II results

Although the present study was non-randomized, the baseline clinical characteristics were similar between the FFR-optimized and IVUS-optimized PCI groups. The patient population had a mean age of 66 years, with a male predominance (72%) and 75% of the patients undergoing PCI for chronic coronary syndrome. The LAD artery was the most commonly treated vessel in both groups, accounting for 82% of cases. There were several PCI-related differences between the two groups, with IVUS-optimized procedures resulting in a higher frequency of left main artery coverage during LAD stenting and a greater use of predilatation and postdilatation with larger balloon sizes and longer

stented segments. These differences may be explained by the additional visual information provided by IVUS, which facilitates more accurate selection of stent and balloon size as well as implantation sites with acceptable plaque burden.
Although the median post-PCI FFR did not differ significantly between the two groups, 12% of patients in the FFR-optimized group had an FFR ≤ 0.8, whereas no patient in the IVUS-optimized group had poor functional result. The trend for higher myocardial ischemia in the FFR-optimized group remained during follow-up, with multivariable regression analysis identifying FFR optimization strategy as a predictor of myocardial ischemia 9 – 12 months post-PCI. These findings were further supported by a higher prevalence of angina in the FFR-optimized group. Medical treatment was similar between the two groups. The rates of target vessel failure and functional restenosis were twice as high in the FFR-optimized group; however, the differences did not reach statistical significance due to the low event rates and a relatively small sample size.

6 DISCUSSION

To the best of the investigators' knowledge, this is the first trial to assess the functional results of IVUS-optimized PCI for long coronary lesions and to compare it with the group of patients who underwent FFR-optimized long lesions PCI. It should be noted that the main findings, as detailed below, were obtained in a patient cohort with very long coronary lesions (median total stent length of 56 mm, which is considerably longer than in the majority of previous long lesion PCI trials).

1. Following IVUS-optimized PCI for long lesions, fewer than half of the patients (37.5%) attained an optimal functional PCI outcome (FFR ≥ 0.9). However, none of the patients exhibited residual myocardial ischemia (FFR ≤ 0.8) after the PCI procedure. In contrast, when employing the FFR-optimized strategy, a comparable proportion achieved an optimal functional outcome, but a significantly higher percentage of patients (12.3%) had post-PCI FFR values ≤ 0.8.
2. An optimal anatomical PCI result (according to IVUS criteria) was achieved in two-thirds of the patients.
3. Only one-quarter of patients had both an optimal FFR and IVUS result in the IVUS-optimized group.
4. Repeat FFR measurements recorded 9 – 12 months post-PCI revealed a significantly smaller myocardial ischemia burden (FFR ≤ 0.8) in the IVUS-optimized group (6%) than in the FFR-optimized group (20%).
5. The incidence of target vessel failure during the 12-month follow-up was numerically lower in the IVUS-optimized group (3.8%) than in the FFR-optimized group (8.1%).

6.1 Evaluating functional PCI results in the light of previous trials

The findings from this study reveal that in patients with long coronary artery lesions, the proportion of individuals achieving a post-PCI FFR value ≥ 0.9 was similar in both the IVUS-optimized group (37.5%) and the FFR-optimized group (35.1%). This frequency of optimal post-PCI outcomes aligns with previous research, such as the TARGET-FFR trial, which utilized a physiology-guided PCI optimization approach and achieved a post-PCI FFR value ≥ 0.9 in 38.1% of patients. Interestingly, in the TARGET-FFR trial, 18.6% of patients still had a post-PCI FFR value ≤ 0.8 despite the use of FFR to optimize functional outcomes[30]. In our study, none of the patients in the IVUS-optimized group exhibited residual ischemia, whereas 12% in the FFR-optimized group had post-PCI FFR values ≤ 0.8. It's worth noting that the

TARGET-FFR trial had a different distribution of target vessels (with the left anterior descending artery as the target vessel in 57% of patients compared to 83% in our study) and a significantly shorter average length of the stented segment (31 mm vs. 56 mm) compared to our trial. It's plausible to argue that had the TARGET-FFR trial included patients with a target vessel distribution and stenosis length similar to our study, their functional PCI outcomes might have been less favorable compared to their reported results. Notably, for only 13% of patients in the TARGET-FFR trial IVUS was employed, and it is conceivable that with more frequent utilization of intravascular imaging, the functional outcomes could have been better, as demonstrated in our study.

Another study demonstrated that with the help of functional optimization strategy, but without routine intravascular imaging, a proportion of patients with post-PCI FFR values ≤ 0.8 were reduced from 21% to 8%, and 43% had post-interventional FFR values > 0.9[62].

Retrospective analysis by Kimura et al. reported a similar proportion of patients with post-PCI FFR values > 0.9, but a higher percentage of patients with post-PCI FFR values ≤ 0.8 (18.6%) than in our study[32]. The patients in aforementioned study underwent IVUS-guided PCI, however, the study protocol lacked clearly defined criteria for IVUS optimization, whereas our study applied strict PCI optimization according to IVUS criteria, which may explain the absence of residual ischemia in the IVUS-optimized group, particularly in the treatment of longer coronary artery lesions. We also found that LAD artery lesions were associated with a lower post-PCI FFR value, consistent with previous studies.

Finally, Hwang et al. have proposed varying post-PCI FFR cutoff values based on the target vessel, recommending 0.82 for the LAD and 0.88 for non-LAD vessels[70]. Applying these cutoffs to our study would have resulted in achieving an optimal functional PCI outcome in over 90% of lesions.

In general, prior trials investigating post-PCI FFR in the era of drug-eluting stents have consistently highlighted the importance of conducting post-PCI measurements. These trials have shown that a significant proportion of patients (ranging from 8% to 30%) experience residual myocardial ischemia despite angiographically successful PCI[30,31,62]. It's worth noting that our study focused on treating long coronary artery lesions with an average stent length of 56 mm, whereas the mentioned trials involved substantially shorter lesions, and the percentage of LAD as the target vessel was lower. Both the length of the lesion and the involvement of the LAD artery have been identified as independent predictors of suboptimal functional PCI outcomes[31,32]. Consequently, given the treatment of long lesions, primarily in the LAD, a 12% rate of residual ischemia in the FFR-optimized group might be

considered acceptable. Nevertheless, the use of IVUS in our study effectively eliminated this issue, resulting in zero cases of residual ischemia.

6.2 Factors contributing to suboptimal functional PCI result

Various factors can contribute to suboptimal functional PCI outcomes, including insufficient stent expansion, stent malapposition, residual focal lesions, dissections near stent edges, or diffuse disease downstream. It is often challenging to detect these issues solely through angiography. Therefore, conducting post-PCI FFR measurements with a pull-back approach can assist in pinpointing regions with a notable gradient change and provide guidance for post-dilatation or the potential need for additional stent placement, thereby enhancing the overall functional PCI outcome, as shown in the TARGET-FFR trial[30]. However, incorporating intravascular imaging could offer more insight into the underlying mechanism of ischemia and potentially enhance PCI optimization.

Few potential components may account for the significantly lower incidence of poor functional PCI outcome in the IVUS-optimized group relative to the FFR-optimized group in the present study. Since the length of the stented segment was significantly longer in the IVUS-optimized group (63 mm versus 49 mm), it is plausible that more of the significant atheroma was covered with stent. Notably, stent prolongation appeared to affect both the proximal and distal ends, as evidenced by a higher rate of left main coverage with stent during LAD treatment and a smaller distal FFR gradient (indicative of the functional significance of the unstented distal segment) in the IVUS-optimized group. Furthermore, postdilatation was performed more frequently and with bigger balloon sizes in the IVUS group, which may have contributed to better stent expansion. However, the IVUS group also exhibited a trend towards a higher trans-stent gradient, which could be attributable to the longer stented segment or not ideal stent expansion in particular cases. These observations are hypothesis-generating, as the FFR-optimized group did not undergo intravascular ultrasound.

Using intravascular imaging selectively for lesions with suboptimal functional result (post-PCI FFR < 0.9) is a viable alternative to optimize cost-effectiveness. This approach was put to the test in the FFR-REACT study, which involved 291 patients with post-PCI FFR values < 0.9. Patients were randomly assigned to either an IVUS-guided optimization group or a control group. IVUS-guided PCI optimization led to a notable improvement in post-PCI FFR, with a mean increase from 0.82 ± 0.06 to 0.85 ± 0.05 ($P < 0.001$), and it resulted in achieving post-PCI FFR > 0.90 in 20% of the treated vessels.

However, despite these improvements, this strategy did not significantly lower the rate of TVF at the one-year follow-up, primarily due to lower-than-anticipated event rates[120].

6.3 Optimizing PCI through IVUS in long coronary artery lesions

In accordance with our study protocol, IVUS was implemented both before and after PCI in all IVUS-optimized group patients. The criteria for determining an optimal PCI outcome through IVUS were comparable to those utilized in the ULTIMATE trial[35], with the exception that our study established a larger desirable minimal stent area (5.5 vs. 5.0 mm^2), which is in line with an expert consensus document of the European Association of Percutaneous Cardiovascular Intervention[80].

In our study, we observed that the optimal result for PCI as per IVUS criteria was achieved in 68.4% of patients, and this proportion remained consistent between patient groups with optimal (FFR $\geq$ 0.9) and suboptimal (FFR < 0.9) functional outcomes. When patients failed to meet all four IVUS optimization goals, it was frequently due to $\geq$ 50% plaque burden near the stent edges, which emphasizes the difficulties in locating an appropriate stent landing zone within a diffusely diseased artery.

Our results indicate that an optimal IVUS outcome was achieved more frequently than to the 53% rate reported in the ULTIMATE trial[35]. However, it should be noted that the ULTIMATE trial encompassed all lesion types, whereas our study focused solely on long coronary lesions.

Two randomized controlled trials have conducted comparisons between IVUS-guided PCI and angiography-guided interventions for long coronary artery lesions. In the IVUS-XPL trial, which enrolled 1400 patients with long lesions (defined as stent lengths $\geq$ 28 mm, with an average stented segment length of 39 mm), the IVUS optimization criteria used were less stringent than those applied in our study. Specifically, they aimed for a minimal stent area larger than the cross-sectional area of the lumen at the distal reference segment, and this led to achieving an optimal IVUS result in only 54% of patients[8].

Similarly, Kim et al. conducted a study involving 543 patients who were randomly assigned to either IVUS-guided or angiography-guided PCI for long coronary artery lesions (stents $\geq$ 28 mm in length)[121]. However, this study did not establish predefined PCI optimization criteria based on IVUS findings, and the authors acknowledged that the potential value of IVUS information might not have been fully realized. It is worth mentioning that the average implanted stent length in this study was 32 mm, which closely resembles the

lengths seen in the IVUS-XPL trial and is considerably shorter than the 63 mm length observed in our study (IVUS-optimized group). Consequently, our study cohort encompasses patients with very long coronary artery lesions when compared to the majority of other studies.

6.4 One-year outcomes of FFR vs. IVUS optimization strategies and a comparison with previous trials

Previous trials have demonstrated poor outcomes following treatment of long coronary lesions. Despite the routine use of intravascular ultrasound, Honda et al reported a one-year target vessel revascularization (TVR) rate of 8% after implantation of ultra-long DES (> 50 mm)[11]. Similarly, the analysis of the GRAND-DES registry (a patient-level pooled registry consisting of 17286 patients from five Korean multicenter DES registries) showed a two-year target vessel failure (TVF) rate of 8.1% when stents > 40 mm were used[12]. Our study's results showed an identical one-year TVF rate (8.1%) in the FFR optimization strategy. However, IVUS guidance was associated with a numerically lower event rate of 3.8%, although this difference was not statistically significant due to low event rate and inadequate power to compare hard endpoints. The smaller incidence of TVR in the IVUS optimization group compared to the Honda et al. trial may be partially attributed to the different criteria for IVUS optimization used in the studies, as the criteria were less stringent in the Honda et al study, and IVUS was not routinely used in the GRAND-DES registry.

Our findings offer assurance that favorable short-term rates of target vessel failure (TVF) can be attained even when addressing extremely long coronary artery lesions. Notably, the TVF rate in our IVUS-optimized group closely aligns with rates observed in other trials utilizing IVUS for PCI guidance. For instance, over a 12-month follow-up period, the ULTIMATE trial reported a TVF rate of 2.9% in the IVUS group (in comparison to 5.4% in the angiography group)[35]. Similarly, the IVUS-XPL trial exhibited a 2.9% TVF rate in the IVUS group (versus 5.8% in the angiography group)[8] and Kim et al.'s study showcased a 4.0% TVF rate in the IVUS group (as opposed to 8.1% in the angiography group)[121]. It's essential to note that the length of the stented segment in these trials was considerably shorter than in our study.

Moreover, it's important to note that many trials typically rely solely on clinical follow-up, potentially leading to the under recognition of some TVF events. In contrast, our study involved the majority of patients undergoing repeat coronary angiography with FFR measurements during the follow-up period. As a result, the TVF rate we have reported might appear somewhat

higher compared to what one might expect in everyday clinical practice, particularly since certain TVR events were observed in clinically asymptomatic patients.

6.5 Contemporary challenges and future directions

Long coronary artery lesions represent a significant challenge in contemporary medical practice. Although optimal medical therapy can improve patient outcomes and relieve symptoms, it may be insufficient to adequately control symptoms in cases of severe ischemia, particularly with very long LAD lesions. On the other hand, revascularization by PCI or CABG is associated with a high incidence of adverse events, as was demonstrated in clinical trials examining outcomes of long lesion PCI and CABG[11,12,72].

The utilization of PCI optimization tools like FFR and IVUS has the potential to reduce target vessel failure when compared to PCI guided solely by angiography. Their adoption, particularly IVUS, is highly advisable. Our findings suggest that while IVUS-guided PCI did not significantly increase the percentage of patients achieving optimal functional PCI outcome, it did significantly diminish the presence of residual myocardial ischemia after treating long lesions when compared to optimization based on FFR. Furthermore, IVUS-guided optimization was associated with a satisfactory one-year target vessel failure rate, even in the context of very long coronary artery lesions.

Despite these advancements, a substantial randomized controlled trial comparing imaging-guided and possibly hybrid PCI approach (using drug-eluting stents and drug-coated balloons) to surgical revascularization is still warranted to determine the optimal treatment modality for this complex clinical scenario.

6.6 Limitations

The limitations of our study must be acknowledged in order to interpret the findings properly. Firstly, this was a single-center non-randomized trial, which may limit the generalizability of the results. Although both groups had similar baseline clinical characteristics, the study design did not fully control for potential confounding variables that could have influenced the outcomes. Secondly, the sample size was relatively small, which have limited the ability to detect statistically significant differences in the hard end-points. To address this limitation, a large randomized controlled trial with adequate statistical power would be needed.

Thirdly, the functional optimization protocol in the historical FFR-optimized group lacked a more detailed approach on how to respond to post-PCI FFR pull-back findings, as demonstrated in recent trials. However, its simplicity makes it easier to implement in daily practice.

Finally, the IVUS optimization criteria for stent expansion (MSA >90% of the distal reference lumen area and/or MSA $\geq 5.5mm^2$) employed in our study might not be the most suitable for long lesions. This is because it could potentially overestimate stent expansion, particularly in the larger proximal section of the long lesion. A potentially more appropriate approach could involve dividing the lesion length into two or three segments and assessing expansion separately for the distal portions of those segments. However, this was not feasible in our study because the IVUS console used only allowed for manual pull-back, therefore it was not possible to estimate the precise lesion length on IVUS and divide it into segments accordingly.

7 CONCLUSIONS

1. Following IVUS-optimized long lesions PCI, less than half of the patients achieved an optimal functional PCI result (FFR $\geq$ 0.9); nevertheless, none of the patients had residual myocardial ischemia (FFR $\leq$ 0.8) after PCI.
2. After 9 – 12 months post-PCI, more than one-quarter of patients, for whom IVUS was used to optimize PCI, maintained an optimal FFR in the target vessel, with only a few patients developing myocardial ischemia.
3. Although the median post-PCI FFR and the rate of optimal functional result did not differ between the two PCI optimization strategies, the IVUS-optimization strategy resulted in significantly lower rates of residual myocardial ischemia immediately post-PCI and at the 9 – 12 months follow-up.
4. The IVUS-optimized group had a numerically lower incidence of target vessel failure and functional target lesion restenosis rate compared to the FFR-optimized group at follow-up.

8 RECOMMENDATIONS FOR CLINICAL PRACTICE

- It is recommended to use fractional flow reserve not only to evaluate baseline myocardial ischemia, but also to assess the functional result of PCI, since a considerable number of lesions may still induce myocardial ischemia even after angiographically successful PCI.
- The routine use of intravascular ultrasound is strongly encouraged in the treatment of long coronary artery lesions, as it reduces the rate of poor functional PCI result and is associated with numerically lower rates of target vessel failure and functional restenosis.
- It is recommended to employ both FFR (for assessing baseline ischemia and evaluating the functional PCI outcome) and IVUS (for procedure optimization), however, should the operator opt for using only one additional tool, the findings of the present study suggest that IVUS should be chosen, particularly when there is evidence of myocardial ischemia.
- Further research is still needed to determine the optimal treatment modality for long coronary artery lesions. However, IVUS-optimized PCI is a promising option for managing this complex clinical scenario.

9 SUMMARY (SANTRAUKA)

1. TIRIAMOJI PROBLEMA IR DARBO AKTUALUMAS

Vainikinių arterijų (VA) ilgi/difuziniai susiaurėjimai yra priskiriami sudėtingiems pažeidimams, o jų gydymas išlieka iššūkiu ir šių dienų kardiologijoje. Ilgo VA pažeidimo apibrėžimas skiriasi priklausomai nuo naudojamų diagnostikos kriterijų, tačiau paprastai jis laikomas pažeidimu, kurio ilgis yra mažiausiai 20 milimetrų[7]. Visgi naujesniuose tyrimuose ilgiems VA pažeidimams apibrėžti dažniau pasirenkamas didesnis - 28 mm – slenkstis[8,9,10]. Atliekant ilgų VA pažeidimų perkutaninę koronarinę intervenciją (PKI) dažnai implantuojami ilgi arba persidengiantys stentai, todėl didėja periprocedūrinio miokardo infarkto rizika (dėl šoninės šakos užsidarymo po stentu). Taip pat tokių pažeidimų intervencinis gydymas dažnai susijęs su suboptimaliu funkciniu rezultatu bei dažnesniais su gydyta kraujagysle susijusiais nepageidaujamais įvykiais, tokiais kaip pakartotinės revaskuliarizacijos poreikis, miokardo infarktas ir mirtis[11,12,13]. Todėl ilgiems vainikinių arterijų pažeidimams gydyti dažnai pasirenkama aorto-koronarinių jungčių suformavimo operacija (AoKJO), nors trūksta įrodymų, kurie pagrįstų šios strategijos pranašumą.

Vainikinių arterijų angiografijos ir PKI metu naudojamos papildomos priemonės, tokios kaip frakcijinis tėkmės rezervas (FFR) ir intravaskulinio atvaizdavimo tyrimai (intravaskulinis ultragarsas (IVUS) bei optinė koherentinė tomografija (OCT)), ne tik palengvina vainikinių arterijų patologijos identifikavimą bei sprendimo dėl revaskuliarizacijos poreikio priėmimą, bet ir leidžia optimizuoti PKI, taip dažnu atveju pagerinant jos rezultatą ir sumažinant nepageidaujamų įvykių riziką atokiuoju laikotarpiu.

FFR yra fiziologinis indeksas, naudojamas vainikinių arterijų susiaurėjimo hemodinaminiam-funkciniam reikšmingumui įvertinti. FFR tai distalinio (vainikinės arterijos distalinėje dalyje, už susiaurėjimų) ir proksimalinio (aortoje, ties kateteriu) kraujo spaudimų santykis maksimalios hiperemijos metu. FFR vertės svyruoja nuo 0 iki 1, kai FFR vertė 1 nurodo normalią kraujotaką, o 0.80 ir mažesnė nurodo funkciškai reikšmingą pažeidimą. Atliktų tyrimų duomenimis FFR pritaikymas yra susijęs su geresniais klinikiniais rezultatais[21,22] ir mažesnėmis sveikatos priežiūros išlaidomis[23], todėl pagrindinėse miokardo revaskuliarizacijos gairėse rekomenduojama jį pasitelkti vertinant vidutinio dydžio susiaurėjimų funkcinį reikšmingumą[24,25]. Nors FFR yra laikomas „auksiniu standartu“ vertinant susiaurėjimo hemodinaminį reikšmingumą, jis nėra reguliariai matuojamas po atliktos PKI, siekiant įvertinti funkcinį PKI rezultatą, nepaisant įrodymų, rodančių stiprų

ryšį tarp FFR verčių ≤ 0.80 po PKI ir nepageidaujamų įvykių[26,27,28,29]. Ankstesnių tyrimų duomenimis liekamoji miokardo išemija (FFR ≤ 0.8) nustatoma net iki 30% atvejų po angiografiškai sėkmingos PKI[13,30,31,32]. Šie nuviliantys rezultatai buvo gauti gydant trumpo ir vidutinio ilgio pažeidimus, todėl ilgų vainikinių arterijų pažeidimų PKI dažnai yra susijusi su dar prastesniais funkciniais rezultatais. Daugėja klinikinių tyrimų, pagrindžiančių FFR matavimo po PKI naudą siekiant optimizuoti funkcinį intervencijos rezultatą. TARGET-FFR (Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention) atsitiktinių imčių klinikiniame tyrime vien tik angiografijos kontrolėje atliktos PKI buvo palygintos su intervencijomis, kurių metu buvo pritaikyta laipsniško optimizavimo strategija panaudojant FFR. Tyrimo metu įrodyta, kad PKI optimizacijai pasitelkus FFR, po PKI buvo reikšmingai rečiau nustatoma liekamoji miokardo išemija (FFR ≤ 0.8), lyginant su pacientais, kuriems PKI atlikta vien tik angiografijos kontrolėje. Šie rezultatai dar kartą pabrėžia fiziologijos vaidmenį optimizuojant funkcinį PKI rezultatą[30].

Intravaskuliniai atvaizdavimo tyrimai (IVUS ir OCT) tai dar viena priemonė, kurios svarba vertinant vainikinių arterijų pažeidimų morfologinius pakitimus ir optimizuojant PKI įrodyta klinikiniuose tyrimuose. Nustatyta, kad tiek intravaskulinis ultragarsas, tiek optinė koherentinė tomografija suteikia tikslesnės ir išsamesnės informacijos apie vainikinių arterijų anatomiją ir pažeidimų morfologiją, lyginant vien su angiografijos rodmenimis[33,34]. Taip pat šie intravaskuliniai atvaizdavimo tyrimai gali būti naudojami vertinant stento išsiplėtimą ir prigludimą prie kraujagyslės sienelės vidinio sluoksnio (apoziciją), aterosklerotinės plokštelės tūrį šalia stento ir padėti aptikti reikšmingas disekacijas ties stentų ribomis. Atsitiktinių imčių klinikiniuose tyrimuose ir metaanalizėse įrodyta intravaskulinių atvaizdavimo tyrimų nauda pagerinant PKI rezultatus, įskaitant geresnę stento apoziciją ir išsiplėtimą bei sumažinant nepageidaujamų įvykių dažnį atokiuoju laikotarpiu[9,10,35,36,37,38,39,40].

Apibendrinant, FFR ir intravaskulinių atvaizdavimo tyrimų panaudojimas atliekant PKI sumažina nepageidaujamų įvykių riziką lyginant su intervencijomis, atliktomis vien tik angiografijos kontrolėje. Tačiau lyginant šias dvi PKI optimizacijos strategijas tarpusavyje kartais galima aptikti tam tikrų prieštaraujančių parodymų: pavyzdžiui, optimali stento implantacija vizualizuota IVUS būdu nebūtinai užtikrina optimalų funkcinį rezultatą, išmatuotą FFR būdu, ir atvirkščiai. Todėl optimali PKI optimizacijos strategija iki šiol lieka neaiški, kadangi atliktuose tyrimuose buvo vertinamos arba FFR, arba intravaskulinių atvaizdavimo tyrimų strategijos atskirai su angiografijos kontrole ir dažniausiai gydant trumpus – vidutinio ilgio

susiaurėjimus. Šiandien vis dar trūksta minėtų priemonių palyginamųjų studijų, ypač gydant ilgus vainikinių arterijų pažeidimus.

2. TYRIMO NAUJUMAS

- Pirmą kartą įvertinti ilgų vainikinių arterijų pažeidimų PKI, atliktų intravaskulinio ultragarsinio tyrimo kontrolėje, funkciniai rezultatai.
- Pirmą kartą įvertinti ilgų vainikinių arterijų pažeidimų PKI, atliktų intravaskulinio ultragarsinio tyrimo kontrolėje, atokieji (9 – 12 mėn. po atliktos PKI) funkciniai rezultatai.
- Pirmą kartą tarpusavyje palygintos dvi skirtingos PKI optimizacijos strategijos (IVUS ir FFR) gydant ilgus vainikinių arterijų pažeidimus.

3. TYRIMO TIKSLAS IR UŽDAVINIAI

Tyrimo hipotezė:

Ilgų vainikinių arterijų pažeidimų PKI, atlikta pasitelkiant IVUS, pagerina funkcinį PKI rezultatą ir sumažina liekamosios miokardo išemijos dažnį atokiuoju laikotarpiu bei yra susijusi su retesniais nepageidaujamais įvykiais ir funkcine gydytos kraujagyslės restenoze, lyginant su FFR optimizacijos strategija.

Tyrimo tikslas:

Įvertinti funkcinį perkutaninės koronarinės intervencijos rezultatą gydant difuzinius/ilgus vainikinių arterijų pažeidimus intravaskulinio ultragarsinio tyrimo kontrolėje ir palyginti pasiektą rezultatą su intervencijomis atliktomis frakcijinio tėkmės rezervo kontrolėje.

Tyrimo uždaviniai:

1. Įvertinti optimalaus (FFR > 0.9) ir išeminio (FFR ≤ 0.8) funkcinio PKI rezultato dažnį po ilgų vainikinių arterijų pažeidimų PKI IVUS kontrolėje.
2. Įvertinti ilgalaikį funkcinį PKI rezultatą išmatuojant FFR praėjus 9 – 12 mėn. nuo ilgų pažeidimų gydymo IVUS kontrolėje.
3. Palyginti funkcinius IVUS optimizacijos grupės rezultatus su FFR optimizacijos („istorinės“) grupės rezultatais.

4. Palyginti su gydyta kraujagysle susijusių nepageidaujamų įvykių dažnį ir funkcinės gydytos kraujagyslės restenozės dažnį per vienerių metų stebėjimo laikotarpį tarp dviejų PKI optimizacijos strategijų.

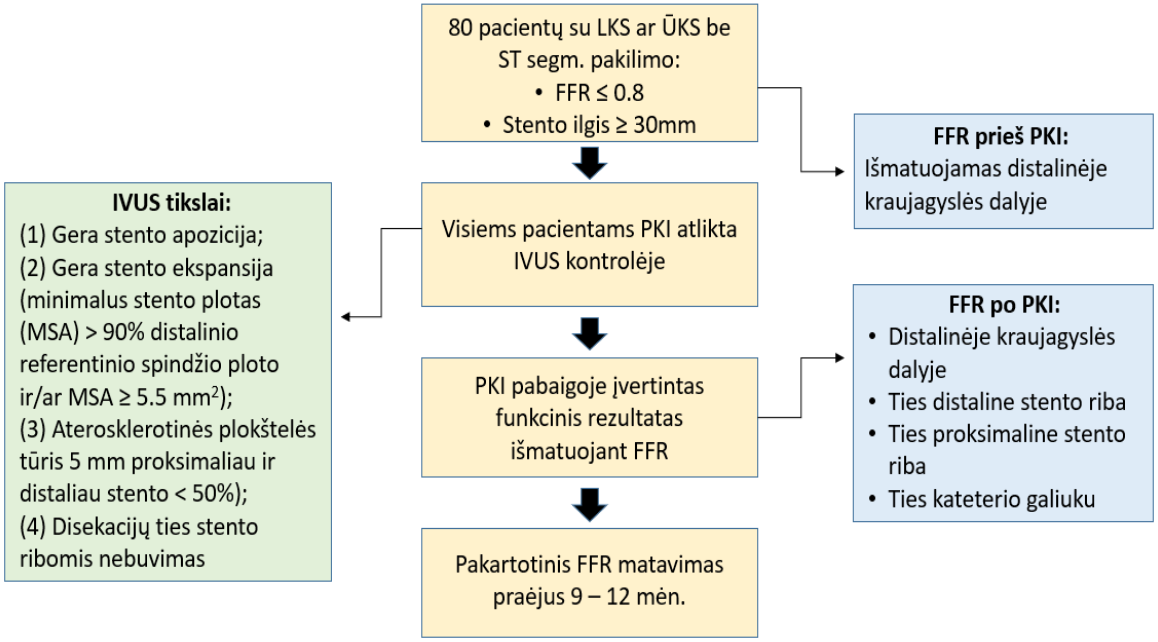
Ginamieji teiginiai

- IVUS panaudojimas atliekant ilgų vainikinių arterijų pažeidimų PKI sumažina išeminio (FFR ≤ 0.8) funkcinio rezultato dažnį iš kart po atliktos intervencijos ir praėjus 9 – 12 mėn., lyginant su PKI atliktomis FFR kontrolėje.
- Su gydyta kraujagysle susijusių nepageidaujamų įvykių ir funkcinės gydytos kraujagyslės restenozės dažniai per vienerių metų stebėjimo laikotarpį yra mažesni IVUS optimizacijos grupėje, lyginant su FFR optimizacijos grupe.

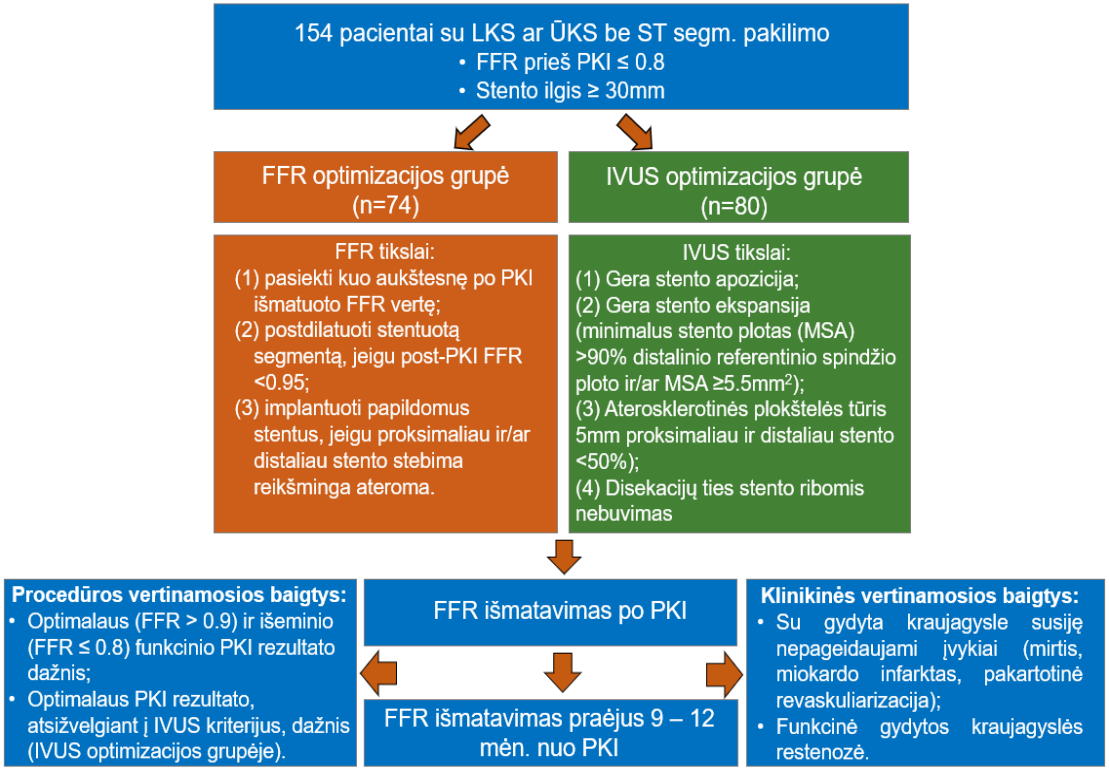
4. TYRIMO METODIKA

Tyrimas atliktas Vilniaus universiteto ligoninės Santaros klinikose. Tyrimą sudarė dvi dalys:

1. Pirmąją, prospektyvinę tyrimo dalį, sudarė 80 pacientų, kuriems 2019 m. liepos 1 d. – 2021 m. kovo 31 d. nustatyti hemodinamiškai reikšmingi (FFR ≤ 0.8) ilgi vainikinių arterijų pažeidimai, kuriems gydyti reikalingas ≥ 30 mm ilgio stentas. Visiems pacientams PKI atlikta IVUS kontrolėje, įvertinant funkcinį PKI rezultatą FFR būdu iš kart po atliktos PKI ir praėjus 9 – 12 mėn. Tyrimo metu buvo laikomasi Helsinkio deklaracijoje nustatytų principų ir geros klinikinės praktikos rekomendacijų. Vilniaus regioninis biomedicininių tyrimų etikos komitetas patvirtino tyrimo protokolą (Nr. 2019/6-1150-639). Visi pacientai prieš dalyvaudami tyrime pasirašė informuoto asmens sutikimo formą.
2. Antrąją tyrimo dalį sudarė IVUS optimizacijos pacientų grupės rezultatų palyginimas su FFR optimizacijos grupe („istorinė“ grupė), kuriems PKI taip pat buvo atlikta Vilniaus universiteto ligoninės Santaros klinikose ir optimizuota pasitelkiant FFR. Tyrimo eigą apibūdinančios schemos pateiktos 1 ir 2 pav.



1 pav. Pirmosios tyrimo dalies schema.



2 pav. Antrosios tyrimo dalies schema

Įtraukimo kriterijai:

- amžius daugiau nei 18 metų;
- lėtinis koronarinis sindromas (LKS) arba ūminis koronarinis sindromas (ŪKS) be ST segmento pakilimo (nestabilioji krūtinės angina arba ūminis miokardo infarktas be ST segmento pakilimo);
- hemodinamiškai reikšmingas (FFR $\leq$ 0.8) vainikinės arterijos susiaurėjimas, tinkamas perkutaninei koronarinei intervencijai ir kuriam gydyti reikalingas $\geq$ 30 mm ilgio stentas.

Ekskliudavimo kriterijai:

- ūminis miokardo infarktas su ST segmento pakilimu;
- kontraindikacijos dvigubai antiagregacinei terapijai;
- tikėtina gyvenimo trukmė trumpesnė nei 1 metai;
- žinoma alergija biolimusui, sirolimusui, everolimusui ar zotarolimusui.

FFR matavimų protokolas

FFR matavimų protokolas buvo pritaikytas visiems pacientams. FFR matavimai buvo atliekami pagal standartinę metodiką. Hiperemijai sukelti buvo naudojama intraveninio adenozino infuzija (140 µg/kg/min). FFR vielos (Abbott Vascular, Plymouth, MN, USA) jutiklis buvo įvedamas į distalinį vainikinės arterijos trečdalį, mažiausiai 20 mm distaliau nuo labiausiai nutolusio pažeidimo. Prieš atliekant matavimus į vainikinę arteriją buvo suleidžiama 200 mcg intrakoronarinio nitroglicerino. Pasiekus stabilią hiperemiją, paprastai praėjus 2 min. nuo adenozino infuzijos pradžios, buvo atliekami FFR matavimai. FFR vertė $\leq$ 0.8 buvo laikoma hemodinamiškai reikšminga, rodančia funkciškai reikšmingą pažeidimą. Šie FFR matavimai buvo atliekami prieš ir po PKI:

1. Bazinis lygmuo (Pre-PKI FFR) - pažeidimo hemodinaminio reikšmingumo įvertinimas prieš atliekant PKI.

2. Matavimai po PKI:

• Post-PKI FFR - matavimas atliktas procedūros pabaigoje, kuomet PKI rezultatas buvo laikomas priimtinu ir galutiniu. Matavimas atliktas toje pačioje vietoje kaip ir Pre-PKI FFR.

• FFR gradientai:

• FFR gradientas stentuotame segmente (StentoGradientas) – skirtumas tarp FFR vertės, esančios ties proksimaline stento riba, ir FFR vertės, esančios ties distaline stento riba.

• Distaliau stento esantis FFR gradientas (DistalinisGradientas) – skirtumas tarp FFR vertės, esančios ties distaline stento riba, ir Post-PKI FFR vertės.

3. Tie patys FFR matavimai buvo atlikti praėjus 9 – 12 mėn. nuo atliktos PKI (Stebėjimo-FFR, Stebėjimo-StentoGradientas, Stebėjimo-DistalinisGradientas).

FFR optimizacijos grupėje buvo galima atlikti daugiau nei vieną FFR matavimą po PKI, jeigu buvo atliekama papildoma PKI optimizacija. Paskutinis FFR matavimas buvo traktuojamas kaip Post-PKI FFR vertė. IVUS optimizacijos grupėje Post-PKI FFR buvo matuojamas vienintelį kartą, pačioje procedūros pabaigoje, užbaigus PKI optimizaciją pagal IVUS kriterijus. Po galutinio FFR matavimo papildomos intervencijos nebuvo atliekamos.

FFR optimizacijos protokolas

PKI tikslas buvo pasiekti aukščiausią įmanomą FFR po PKI. Operatoriams buvo patarta visais atvejais atlikti stentų post-dilataciją, kuri buvo būtina, jeigu Post-PKI FFR vertė buvo mažesnė nei 0.95. Jei ties proksimaline ar distaline stento riba buvo stebima reikšminga ateroma, operatoriai buvo raginami dar labiau pagerinti funkcinį rezultatą implantuojant papildomą stentą/us. Galutinis FFR matavimas (Post-PKI FFR) kartu su vielutės atitraukimu buvo atliekamas, kai angiografinis ir funkcinis rezultatas buvo laikomas priimtinu ir galutiniu.

IVUS optimizacijos protokolas

PKI buvo atliekamos IVUS kontrolėje, stengiantis pasiekti optimalų anatominį PKI rezultatą. Iš pradžių IVUS buvo atliekamas prieš PKI, siekiant parinkti tinkamas stento implantacijos vietas, kuriose, jei įmanoma, aterosklerotinės plokštelės tūris būtų mažesnis nei 50%. Stento diametras buvo parenkamas pagal distalinės išorinės elastinės membranos (IEL) dydį (iš IEL diametro dydžio atėmus 0.25 mm). IVUS vaizdavimui buvo naudojamas Eagle Eye Platinum IVUS kateteris (Philips, Cambridge, MA, USA).

Operatoriai stengėsi pasiekti optimalų anatominį PKI rezultatą pagal IVUS, taikant šiuos tikrus kriterijus:

1) gera stento apozicija;

2) gera stento ekspansija (minimalus stento plotas (MSA) > 90% distalinio referentinio spindžio ploto ir/ar MSA ≥ 5.5 mm^2);
3) aterosklerotinės plokštelės tūris 5 mm proksimaliau ir distaliau stento < 50%;
4) disekacijų ties stento ribomis nebuvimas.

Po stento implantacijos ir optimizavimo buvo atliekamas IVUS tyrimas, pagal jo rodmenis PKI rezultatas buvo papildomai optimizuojamas (po to vėl pakartojant IVUS tyrimą) arba buvo laikomas galutiniu, kuomet buvo pasiekti visi keturi IVUS optimizacijos kriterijai (optimalus anatominis rezultatas) arba papildoma optimizacija nebuvo įmanoma.

Medikamentinis gydymas

Visiems pacientams po atliktos PKI buvo skiriama dviguba antiagregacinė terapija aspirinu ir klopidogreliu arba tikagreloru nuo 6 iki 12 mėn. kaip rekomenduojama Europos Kardiologų Draugijos gairėse. Jeigu pacientui buvo indikuotinas gydymas antikoaguliantais, tuomet vieną mėnesį buvo skiriamas trigubas antitrombozinis gydymas (įskaitant antikoaguliantą, aspiriną ir klopidogrelį), po to – nuo 5 iki 11 mėnesių – dviguba terapija (antikoaguliantas ir klopidogrelis). Taip pat pacientams buvo skiriami ir kiti vaistai, tokie kaip statinai, AKF inhibitoriai, beta adrenoblokatoriai, mineralokortikoidų receptorių antagonistai ir diuretikai, atsižvelgiant į jų klinikinę būklę ir galiojančias gydymo gaires.

Vertinamosios baigtys

Vertinamosios baigtys buvo suskirstytos į procedūros ir klinikines.

Procedūros vertinamosios baigtys:

- Optimalaus (FFR > 0.9) ir išeminio (FFR ≤ 0.8) funkcinio PKI rezultato dažnis iš kart po PKI ir praėjus 9 – 12 mėn.;
- Optimalaus PKI rezultato, atsižvelgiant į IVUS kriterijus, dažnis (IVUS optimizacijos grupėje).

Klinikinės vertinamosios baigtys:

- Su gydyta kraujagysle susijusių nepageidaujamų įvykių (TVF) dažnis per vienerių metų stebėjimo laikotarpį. Tai sudėtinė baigtis, kurią sudarė su gydyta kraujagysle susijusi mirtis, miokardo infarktas ir pakartotinė gydytos kraujagyslės revaskuliarizacija;
- Funkcinė gydytos kraujagyslės restenozė per vienerių metų stebėjimo laikotarpį.

Su gydyta kraujagysle susijusi mirtis buvo priskiriama visoms širdinėms mirtims, nebent buvo akivaizdžių kitos priežasties įrodymų.

Su gydyta kraujagysle susijęs miokardo infarktas apibrėžiamas kaip klinikinių simptomų, išeminių elektrokardiografinių pokyčių ir (arba) išeminių radinių vaizdiniuose tyrimuose derinys, kartu esant troponino I arba troponino T padidėjimui iki lygio, didesnio nei 99-oji viršutinės normos ribos procentilė. Taip pat vainikinių arterijų angiografijos metu turėjo būti identifikuotas reikšmingas gydytos kraujagyslės pažeidimas.

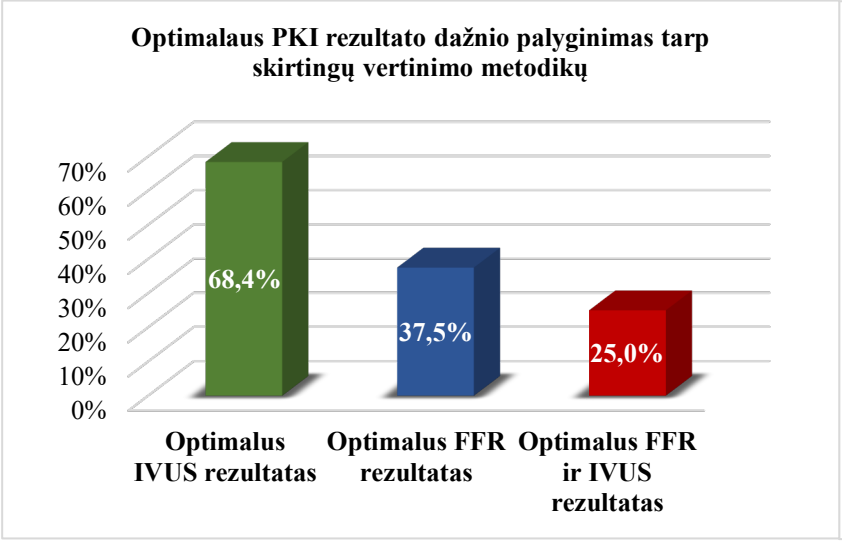
Pakartotinė gydytos kraujagyslės revaskuliarizacija – tai bet kokia perkutaninė ar chirurginė revaskuliarizacijos procedūra tyrimo metu stentuotoje kraujagyslėje.

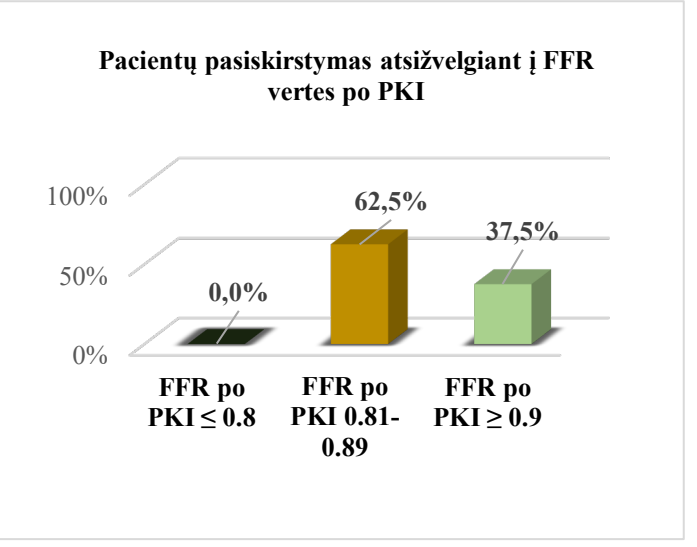
Funkcinė gydytos kraujagyslės restenozė – apibrėžiama, kaip stebėjimo laikotarpiu gydytoje kraujagyslėje išmatuota ≤ 0.8 FFR vertė. Pacientai, kurių FFR iškart po PKI buvo ≤ 0.8, nebuvo įtraukti funkcinės restenozės analizę.

5. REZULTATAI

Pirmosios tyrimo dalies (IVUS optimizacijos grupės pacientų) pagrindiniai rezultatai

Po IVUS pagalba optimizuotų ilgų pažeidimų PKI mažiau nei pusei (37.5 %) pacientų pavyko pasiekti optimalų funkcinį PKI rezultatą (Post-PKI FFR ≥ 0.9), tačiau nė vienam iš pacientų nebuvo nustatyta liekamoji miokardo išemija gydytoje kraujagyslėje (FFR ≤ 0.8). Optimalus anatominis PKI rezultatas, remiantis IVUS kriterijais, buvo pasiektas didesnei daliai pacientų – 68.4 % (1 lentelė). Tik ketvirtadaliui pacientų pavyko pasiekti optimalų ir FFR, ir IVUS rezultatą (3 pav.)





3 pav. IVUS optimizacijos grupės rezultatai.

1 Lentelė. Intravaskulinio ultragarsinio tyrimo duomenys.

Charakteristika	IVUS optimizacijos grupė (n = 80)
IVUS atlikimo kartai:	
2	50 (62.5)
3	27 (33.8)
4	3 (3.8)
Distalinio referentinio segmento IEM diameteras, mm	3.3 ± 0.5
Proksimalinio referentinio segmento IEM diameteras, mm	4.6 ± 0.5
Minimalus spindžio diametras, mm	1.8 ± 0.2
Minimalus spindžio plotas, mm^2	2.5 ± 0.6
Kalcio lankas ≥ 180°	39 (48.8)
Distalinio referentinio segmento spindžio plotas, mm^2	5.9 ± 1.9
Distalinio referentinio segmento IEM plotas, mm^2	8.9 ± 3.3
Distalinio referentinio segmento aterosklerotinės plokštės tūris, %	32.6 ± 9.2
Proksimalinio referentinio segmento spindžio plotas, mm^2	10.5 ± 2.8
Proksimalinio referentinio segmento IEM plotas, mm^2	18.2 ± 4.1
Proksimalinio referentinio segmento aterosklerotinės plokštės tūris, %	42.0 ± 8.4
Minimalus stento diametras, mm	2.5 ± 0.4
Minimalus stento plotas, mm^2	5.9 ± 1.9
Gera stento ekspansija	73 (92.4)
Gera stento apozicija	79 (100.0)
Disekacijų ties stento ribomis nebuvimas	79 (100.0)
Aterosklerotinės plokštės tūris ≤ 50% ties stento ribomis	56 (70.9)
Optimalus IVUS rezultatas	54 (68.4)

IVUS – intravaskulinis ultragarsinis tyrimas; IEM – išorinė elastinė membrana

Pirmosios tyrimo dalies rezultatų apibendrinimas

80 pacientų, kuriems ilgų pažeidimų PKI buvo atlikta IVUS kontrolėje, klinikinės charakteristikos gerai atspindėjo koronarine širdies liga sergančius pacientus. Vidutinis pacientų amžius buvo 66 metai, daugumą sudarė vyrai, sergantys pirmine arterine hipertenzija ir dislipidemija, 25% buvo rūkantys ir 20% sirgo cukriniu diabetu. Lėtinis koronarinis sindromas buvo dažniausia PKI indikacija, o priekinė tarpskilvelinė šaka (PTŠ) – dažniausiai gydyta kraujagyslė.

IVUS vaidmuo optimizuojant PKI rezultatą buvo itin svarbus, kadangi beveik pusei pacientų prireikė papildomų manipuliacijų siekiant pagerinti anatominį PKI rezultatą. Nors optimalaus PKI rezultato dažnis, atsižvelgiant į IVUS kriterijus, santykinai buvo didelis, tačiau optimalus funkcinis rezultatas buvo pasiektas rečiau,

tikėtina, dėl vyraujančių PTŠ pažeidimų ir difuzinės ligos nestentuotuose segmentuose.

Daugumai pacientų buvo skirtas dabartinėse gairėse rekomenduojamas medikamentinis gydymas. Nepageidaujamų įvykių dažnis per vienerių metų stebėjimo laikotarpį (3.8%) buvo priimtinas ir panašus į nustatytą ankstesniuose klinikiniuose tyrimuose, kuriuose PKI taip pat buvo atliktos IVUS kontrolėje, tačiau kuriuose vyravo trumpesni pažeidimai. Atsižvelgiant į gautus rezultatus galima teigti, kad net ir labai ilgi vainikinių arterijų pažeidimai (vidutinis stentuoto segmento ilgis 62 mm), pasitelkus IVUS gali būti gydomi PKI būdu, tikintis visiškai panaikinti miokardo išemiją ir per vienerius metus retai susidurti su nepageidaujamais įvykiais.

Antrosios tyrimo dalies (IVUS optimizacijos ir FFR optimizacijos grupių pacientų palyginimas) pagrindiniai rezultatai

Bazinės klinikinės charakteristikos

Bazinės klinikinės charakteristikos tarp IVUS ir FFR optimizacijos grupių ženkliau nesiskyrė (2 lentelė), išskyrus dažnesnį ne su gydyta kraujagysle susijusį miokardo infarkto anamnezėje paplitimą IVUS grupėje (58%), lyginant su FFR grupe (39%), p=0.02.

2 lentelė. Bazinės klinikinės charakteristikos.

Klinikinės charakteristikos	Visi pacientai (n = 154)	FFR-optimizacijos grupė (n = 74)	IVUS-optimizacijos grupė (n = 80)	p
Amžius, metai	66.3 ± 9.2	66.3 ± 9.6	66.2 ± 9.0	0.95
Vyriška lytis	111 (72.1)	54 (73.0)	57 (71.3)	0.81
Rūkymas	35 (22.9)	15 (20.3)	20 (25.0)	0.51
Cukrinis diabetas	31 (20.1)	16 (21.6)	15 (18.8)	0.66
Arterinė hipertenzija	141 (91.6)	67 (90.5)	74 (92.5)	0.66
Dislipidemija	139 (90.8)	67 (90.5)	72 (91.1)	0.9
Lėtinė inkstų liga (GFG < 60 mL/min/1.73 m^2)	28 (21.5)	12 (16.2)	16 (20.0)	0.59
Persirgtas miokardo infarktas (kitoje VA)	75 (48.7)	29 (39.2)	46 (57.5)	0.02
Anksčiau atlikta AoKJO	3 (1.9)	2 (2.7)	1 (1.3)	0.52
Vainikinių arterijų liga:				
Vienos kraujagyslės	23 (14.9)	11 (14.9)	12 (15.0)	0.49
Dviejų kraujagyslių	74 (48.1)	39 (52.7)	35 (43.8)	
Trijų kraujagyslių	57 (37.0)	24 (32.4)	33 (41.3)	
PKI indikacijos:				
Lėtinis koronarinis sindromas	115 (74.7)	55 (74.3)	60 (75.0)	0.92
ŪKS be ST segmento pakilimo	39 (25.3)	19 (25.7)	20 (25.0)	
KS išstūmio frakcija, %	55.0 [50.0–55.0]	50.0 [45.0–55.0]	55.0 [50.0–55.0]	0.02
Hemoglobinas, g/l	138.6 ± 16.4	136.7 ± 17.8	139.7± 15.6	0.34
Kreatininas µmol/l	89.9 ± 47.5	96.9 ± 71.0	85.5 ± 22.1	0.18
Bendras cholesterolis, mmol/l	5.3 ± 1.5	5.6 ± 1.4	5.2 ± 1.6	0.18
MTL-cholesterolis, mmol/l	3.4 ± 1.3	3.7 ± 1.2	3.3 ± 1.3	0.19

FFR – frakcijinis tėkmės rezervas; IVUS – intravaskulinis ultragarsinis tyrimas; GFG – glomerulų filtracijos greitis; VA – vainikinė arterija; AoKJO – aorto-koronarinių jungčių suformavimo operacija; PKI – perkutaninė koronarinė intervencija; ŪKS – ūminis koronarinis sindromas; KS – kairiojo skilvelio; MTL – mažo tankio lipoproteinas.

Pagrindiniai rezultatai, susiję su PKI procedūra, FFR matavimais, medikamentiniu gydymu ir nepageidaujamais įvykiais pateikti 3 – 6 lentelėse ir 4 pav.

3 lentelė. Perkutaninės koronarinės intervencijos duomenys.

Charakteristikos	Visi pacientai (n = 154)	FFR-optimizacijos grupė (n = 74)	IVUS-optimizacijos grupė (n = 80)	p
Gydyta kraujagyslė:				
PTŠ	127 (82.5)	61 (82.4)	66 (82.5)	0.83
JŠ	15 (9.7)	8 (10.8)	7 (8.8)	
DVA	12 (7.8)	5 (6.8)	7 (8.8)	
Kartu atlikta KVA kamieno PKI	15 (9.7)	2 (2.7)	13 (16.3)	0.01
Pre-dilatacija	149 (96.8)	69 (93.2)	80 (100.0)	0.02
Didžiausio pre-dilatacijai naudoto baliono diametras, mm	2.5 [2.5–2.75]	2.50 [2.2–2.8]	2.63 [2.5–2.9]	<0.001
Implantuotų stentų skaičius	2 [1.0–2.0]	2 [1.0–2.0]	2 [1.0–2.0]	0.54
Bendras stentuoto segmento ilgis, mm	56.0 [47.0–71.0]	49.0 [36.0–60.3]	62.5 [48.0–76.0]	<0.001
Vidutinis stentų diametras, mm	3.25 [3.0–3.5]	3.25 [3.0–3.5]	3.25 [3.0–3.5]	0.36
Maksimalus stento implantacijos slėgis, atm	12.5 [12.0–15.0]	14.0 [13.9–16.0]	12.0 [11.5–12]	<0.001
Post-dilatacija	143 (92.9)	63 (85.1)	80 (100.0)	<0.001
Didžiausias post-dilatacijai naudoto baliono diametras, mm	4.0 [3.5–4.0]	3.5 [3.5–3.5]	4.0 [3.8–4.5]	<0.001
Didžiausias post-dilatacijos slėgis, atm	18.0 [16.0–20.0]	18.0 [16.0–20.0]	18.0 [16.0–20.0]	0.29
Kontrasto kiekis, ml	164 ± 51.8	162.3 ± 61.6	157.7 ± 41.4	0.84

FFR – frakcijinis tėkmės rezervas; IVUS – intravaskulinis ultragarsinis tyrimas; PTŠ – priekinė tarpskilvelinė šaka; JŠ – juosianti šaka; DVA – dešinioji vainikinė arterija; KVA – kairioji vainikinė arterija.

4 lentelė. Frakcijinio tėkmės rezervo tyrimo duomenys.

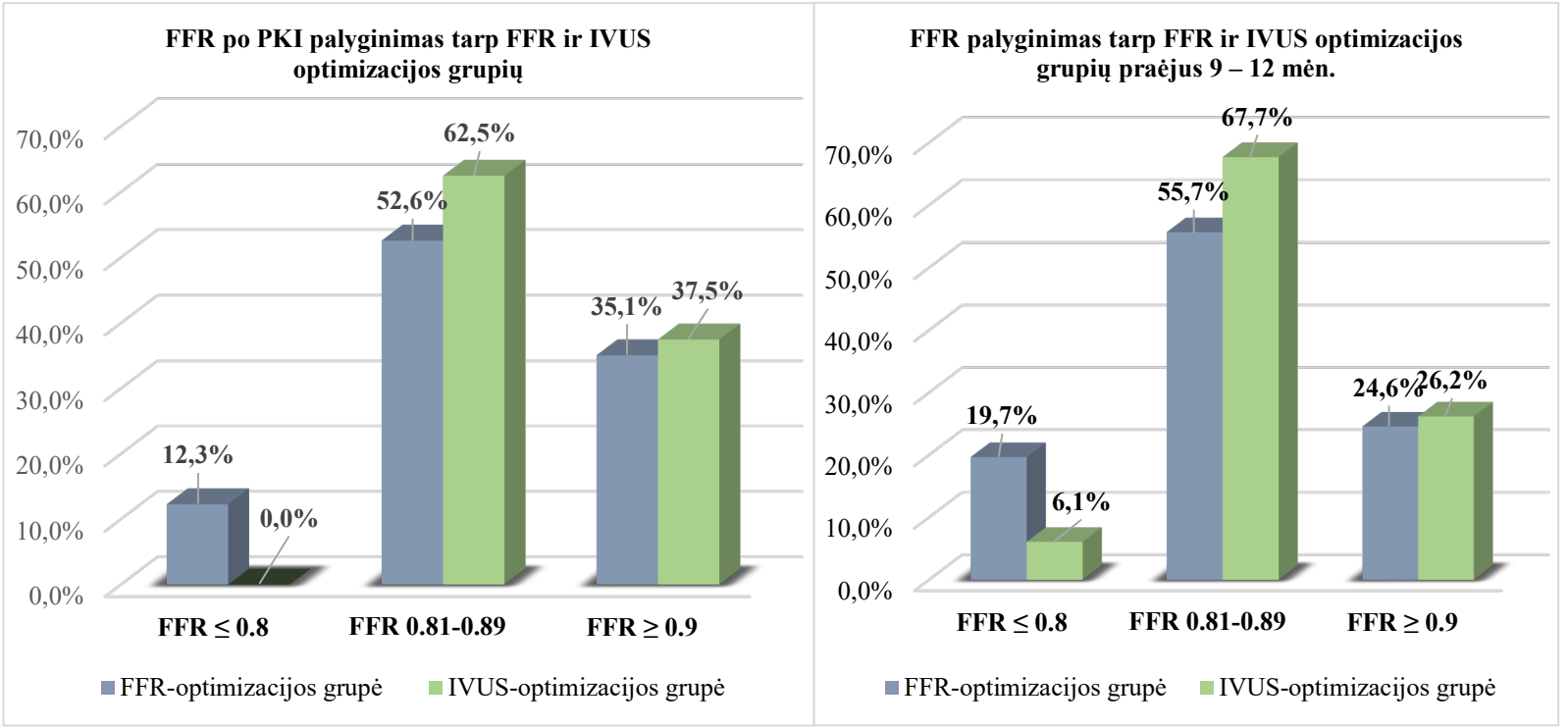
FFR charakteristikos	Visi pacientai (n = 154)	FFR-optimizacijos grupė (n = 74)	IVUS-optimizacijos grupė (n = 80)	p
$FFR_{PRIEŠ\ PKI}$	0.64 [0.54–07.0]	0.63 [0.52–0.69]	0.66 [0.59–0.71]	0.08
$FFR_{PO\ PKI}$	0.88 [0.85–0.91]	0.88 [0.84–0.91]	0.88 [0.85–0.92]	0.6
Stento gradientas	0.06 [0.04–0.08]	0.06 [0.04–0.07]	0.07 [0.05–0.09]	0.06
Distalinis gradientas	0.03 [0.02–0.06]	0.04 [0.02–0.07]	0.03 [0.01–0.05]	0.06
FFR atlikimas stebėjimo laikotarpiu	126 (81.8)	61 (82.4)	65 (81.3)	0.85
Stebėjimo FFR	0.87 [0.83–0.90]	0.87 [0.82–0.90]	0.87 [0.84–0.90]	0.47
Stebėjimo stento gradientas	0.07 [0.04–0.09]	0.06 [0.04–0.08]	0.08 [0.05–0.10]	0.04
Stebėjimo distalinis gradientas	0.03 [0.02–0.06]	0.04 [0.03–0.07]	0.03 [0.02–0.04]	0.02

FFR – frakcijinis tėkmės rezervas; IVUS – intravaskulinis ultragarsinis tyrimas.

5 lentelė. Medikamentinis gydymas.

Vaistai	Visi pacientai (n = 154)	FFR-optimizacijos grupė (n = 74)	IVUS-optimizacijos grupė(n = 80)	p
Dviguba antiagregacinė terapija	143 (92.9)	72 (97.3)	71 (88.8)	0.01
Triguba antitrombotinė terapija	11 (7.1)	2 (2.7)	9 (11.2)	0.01
Statinai	139 (90.8)	64 (87.7)	75 (93.8)	0.19
Beta-blokatoriai	127 (83.0)	60 (82.2)	67 (83.8)	0.80
AKF-i/ARB	132 (86.3)	64 (87.7)	68 (85.0)	0.63

FFR – frakcijinis tėkmės rezervas; IVUS – intravaskulinis ultragarsinis tyrimas; AKF-i – angiotenziną konvertuojančio fermento inhibitoriai; ARB – angiotenzino receptorių blokatoriai.



4 pav. Funkcinio PKI rezultato palyginimas tarp FFR ir IVUS optimizacijos grupių.

6 lentelė. Nepageidaujami įvykiai.

Nepageidaujamas įvykis	Visi pacientai (n = 154)	FFR-optimizacijos grupė (n = 74)	IVUS-optimizacijos grupė (n = 80)	p
Funkcinė gydytos kraujagyslės restenozė	13 (10.9)	8 (15.1)	5 (7.6)	0.18
Su gydyta kraujagysle susijusi mirtis	0	0	0	
Su gydyta kraujagysle susijęs miokardo infarktas	0	0	0	
Pakartotinė gydytos kraujagyslės revaskuliarizacija	9 (5.8)	6 (8.1)	3 (3.8)	0.25
Su gydyta kraujagysle susijusi bendrinė nepageidaujama baigtis (mirtis, MI, pakartotinė revaskuliarizacija)	9 (5.8)	6 (8.1)	3 (3.8)	0.25
Širdinė mirtis	2 (1.3)	1 (1.4)	1 (1.3)	0.95
Mirtis dėl bet kokios priežasties	2 (1.3)	1 (1.4)	1 (1.3)	0.95

FFR – frakcijinis tėkmės rezervas; IVUS – intravaskulinis ultragarsinis tyrimas; MI – miokardo infarktas.

Antrosios tyrimo dalies rezultatų apibendrinimas

Bazinės pacientų klinikinės charakteristikos buvo panašios tarp IVUS optimizacijos ir FFR optimizacijos PKI grupių. Vidutinis pacientų amžius buvo 66 metai, vyravo vyrai (72%), o dažniausia PKI indikacija buvo lėtinis koronarinis sindromas (75%). Priekinė tarpskilvelinė arterija buvo dažniausiai gydyta kraujagyslė – 82% atvejų. PKI metu tarp dviejų PKI optimizacijos strategijų buvo stebėti šie skirtumai: IVUS optimizacijos grupėje gydant PTŠ dažniau buvo stentuojamas ir kairės vainikinės arterijos kamienas, taip pat IVUS grupėje buvo naudoti didesni balioniniai kateteriai ir stentuoti ilgesni segmentai, dažniau atliekant jų post-dilataciją, lyginant su FFR optimizacijos grupe. Tikėtina, kad šiuos skirtumus nulėmė papildoma informacija gauta atlikus IVUS tyrimą: papildoma vizualinė informacija leido tiksliau parinkti naudojamų balionų bei stentų dydžius, taip pat – stentų implantavimo vietas, kurios turėtų mažesnį aterosklerotinės plokštelės tūrį.

Nors po PKI išmatuoto FFR mediana tarp dviejų grupių statistiškai reikšmingai nesiskyrė, 12% pacientų FFR optimizacijos grupėje po atliktos

PKI FFR išliko ≤ 0.8, tuo tarpu nė vienam pacientui, kuriam PKI buvo optimizuota pasitelkus IVUS, nebuvo nustatyta išeminė FFR vertė. Praėjus 9 – 12 mėn. nuo PKI FFR optimizacijos grupėje taip pat buvo dažniau nustatoma gydytos kraujagyslės sąlygota miokardo išemija, lyginant su IVUS optimizacijos grupe (atitinkamai 20% ir 6%, p=0.03). Daugumai pacientų buvo skirtas optimalus medikamentinis gydymas. Su gydyta kraujagysle susijusių nepageidaujamų įvykių (8.1% ir 3.8%) ir funkcinės gydytos kraujagyslės restenozės (15.1% ir 7.6%) dažniai per vienerių metų stebėjimo laikotarpį buvo dvigubai didesni FFR optimizacijos grupėje, tačiau skirtumai nepasiekė statistinio reikšmingumo.

6. IŠVADOS

1. Optimalus funkcinis rezultatas (FFR ≥ 0.9) buvo pasiektas mažiau nei pusei pacientų, kuriems PKI optimizacijai buvo panaudotas IVUS, tačiau nei vienam pacientui nebuvo nustatyta liekamoji miokardo išemija po atliktos PKI.

2. Praėjus 9 – 12 mėn. nuo PKI daugiau nei ketvirtadaliui pacientų IVUS optimizacijos grupėje gydytoje kraujagyslėje išliko funkciškai optimali FFR vertė, tik keliems pacientams išsivystė miokardo išemija.

3. FFR po PKI mediana ir optimalaus funkcinio rezultato dažnis tarp IVUS ir FFR PKI optimizacijos strategijų nesiskyrė, tačiau IVUS optimizacijos grupėje liekamosios miokardo išemijos atvejų iš karto po PKI ir atokiuoju laikotarpiu buvo reikšmingai mažiau nei FFR optimizacijos grupėje.

4. IVUS grupėje buvo stebima tendencija retesniems su gydyta kraujagysle susijusiems nepageidaujamiems įvykiams ir funkcinei gydytos kraujagyslės restenozei, lyginant su FFR grupe, per vienerių metų stebėjimo laikotarpį.

7. REKOMENDACIJOS KLINIKINEI PRAKTIKAI

- Frakcijinio tėkmės rezervo tyrimą rekomenduojama naudoti ne tik siekiant įvertinti bazinę miokardo išemiją, tačiau taip pat ir po atliktos PKI, siekiant nustatyti funkcinį intervencijos rezultatą, kadangi reikšmingai daliai pažeidimų net ir angiografiškai sėkmingai atlikta PKI nepanaikina miokardo išemijos.

- Intravaskulinis ultragarsinis tyrimas turėtų būti kuo dažniau naudojamas atliekant ilgų vainikinių arterijų pažeidimų PKI, kadangi jo panaudojimas sumažina liekamosios miokardo išemijos dažnį ir yra susijęs su retesne nepageidaujamų įvykių gydytoje kraujagyslėje dažnio tendencija.
- Siekiant maksimaliai optimizuoti PKI rekomenduojama naudoti ir FFR (įvertinti bazinei miokardo išemijai ir funkciniam intervencijos rezultatui), ir IVUS (anatominei intervencijos optimizacijai). Jeigu būtų svarstomas vienos PKI optimizacijos priemonės panaudojimas, siūloma pasirinkti IVUS, ypač esant jau nustatytai miokardo išemijai kitais, neinvaziniais tyrimais.
- Vis dar reikalingi papildomi tyrimai, siekiant išsiaiškinti ilgų vainikinių arterijų pažeidimų optimalų gydymo būdą, tačiau PKI pasitelkiant IVUS yra daug žadanti opcija gydant šiuos kompleksinius vainikinių arterijų pažeidimus.

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11 LIST OF PUBLICATIONS

The main findings of the doctoral dissertation were published in the following articles:

Budrys P, Peace A, Baranauskas A, Davidavicius G. Intravascular Ultrasound vs. Fractional Flow Reserve for Percutaneous Coronary Intervention Optimization in Long Coronary Artery Lesions. *Diagnostics*. 2023; 13(18):2921. https://doi.org/10.3390/diagnostics13182921

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Theses and presentations of the main findings of the doctoral dissertation:

Budrys P, Baranauskas A, Davidavičius G. Frakcijinio tėkmės rezervo ir intravaskulinio ultragarsinio tyrimo įtaka funkciniam perkutaninės koronarinės intervencijos rezultatui gydant ilgus vainikinių arterijų pažeidimus, 16-oji Lietuvos jaunųjų mokslininkų konferencija Bioateitis: gamtos ir gyvybės mokslų perspektyvos (2023-11-23), Vilnius, Lithuania.

Budrys P, Petrylaite M, Baranauskas A, Davidavicius G. Evaluation of the residual myocardial ischemia after PCI to long diffuse left anterior descending artery lesions: comparison of IVUS vs FFR, ESC 2023, Amsterdam, Netherlands.

Budrys P, Baranauskas A, Davidavicius G. Comparison of Fractional Flow Reserve vs Intravascular Ultrasound Guided Percutaneous Coronary Intervention in the Treatment of Long Coronary Artery Lesions: One Year Invasive Follow-Up, TCT 2022, Boston, USA.

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