VILNIUS UNIVERSITY

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# THE EFFECTIVENESS OF MYOCARDIAL REVASCULARIZATION IN PATIENTS WITH DIFFUSE CORONARY ATHEROSCLEROSIS

Summary of doctoral dissertation
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VILNIAUS UNIVERSITETAS

ARVYDAS BARANAUSKAS

# MIOKARDO REVASKULIARIZACIJOS EFEKTYVUMO ĮVERTINIMAS VYRAUJANT DIFUZINIAM ATEROSKLEROZINIAM ŠIRDIES VAINIKINIŲ ARTERIJŲ PAŽEIDIMUI

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ABBREVIATIONS

BMS – bare metal stent

DAPT – dual antiplatelet therapy

DES – drug eluting stent

DS – diameter stenosis

FFR – fractional flow reserve

IVUS – intravascular ultrasound

LAD – left anterior descending artery

LLL – late lumen loss

MACE – major adverse cardiovascular events

MLD – minimal luminal diameter

NSD – nominal stent diameter

OCT – optical coherence tomography

PCI – percutaneous coronary intervention

QCA – quantitative coronary angiography

RVD – reference vessel diameter

STEMI – ST-elevation myocardial infarction

SD – standard deviation

TIMI – Thrombolysis In Myocardial Infarction

TVR – target vessel revascularization

# 1. Introduction

## 1.1. Clinical relevance

There is still a controversy in the treatment of long coronary lesions. In case of diffuse coronary artery disease the optimal extent of percutaneous coronary intervention (PCI) is not well established and is usually operator dependent. The evaluation of the post-PCI result by angiography alone is not accurate in the majority of the cases when diffuse coronary artery disease is present. There are almost no data on the long term functional result (residual ischemia in the target vessel territory) after PCI on long coronary lesions in the newer generation drug eluting stents (DES) era.

Fractional flow reserve (FFR) guided PCI has been shown to improve clinical outcomes in patients when compared to angiographic guided PCI at long-term follow-up. In patients with stable coronary artery disease the rate of death, myocardial infarction, or urgent revascularization at 2 years among those who underwent FFR-guided PCI with contemporary drug-eluting stents is less than half the rate among patients who received medical therapy alone (1).

There is a growing awareness of the poor accuracy of coronary angiography for identifying lesions responsible for myocardial ischemia and the inaccuracy of noninvasive stress testing, especially in patients with multivessel coronary artery disease (2,3). De Bruyne B et al. reported that in patients with coronary artery stenosis in another vessel, approximately half of coronary arteries without angiographic focal stenosis have a graded, continuous decline in coronary pressure along their length, especially during hyperemia. This decline in pressure was not observed in the normal arteries of subjects without atherosclerosis. The presence and severity of this coronary pressure gradient could not be predicted from the angiogram (4).

The poor correlation between FFR and arterial diameters reflects the failure of standard coronary angiography to account for the hemodynamic effects of diffuse disease (4). Furthermore, there is an increasing body of evidence that FFR measured after PCI is a strong independent predictor of major adverse cardiovascular events (MACE). According to Agarwal SK et al., the use of FFR after PCI in patients undergoing pre-PCI FFR modified treatment in approximately 20% of lesions (5). Pijls at al. have shown that

the higher the post-PCI FFR following bare metal stent implantation, the lower the MACE rate at 6 months follow-up (6). In support of this, a more recent meta-analysis by Johnson et al. again shows that the higher the FFR after PCI, the better the prognosis (7). Specifically, it seems that the optimal PCI result is achieved when the FFR value after PCI is >0.95, comparable to that found in angiographically normal coronary arteries (8).

Despite hints of the clinical value of post-PCI FFR, it is rarely performed in clinical practice and clinical guidelines and expert consensus documents are silent on the use of post-PCI FFR (9).

Earlier data with bare metal stents and first generation drug eluting stent indicates that the total stent length is associated with a risk of stent restenosis and thrombosis (10–12). First-generation DES have also been associated with the increased rates of very late (>1 year) stent thrombosis (13,14). Long coronary lesion stenting was shown to be associated with increased MACE in the first-generation DES era (15). Reported 2-year MACE rates were highest in patients with long lesions in small vessels (10.4%), intermediate in patients with either long lesions or small vessels but not both (8.2%), and lowest in patients with short lesions in large vessels (5.6%) (16). MACE rates remain remarkably high when long stents are used (16,17). Therefore, we cannot be sure that the functional result achieved after PCI is equally acceptable when long (>30 mm) or ultra long (>50 mm) stenting is carried out.

The assessment of restenosis has traditionally been done using angiographic follow-up or increasingly, clinically driven restenosis. This may not be ideal when we consider that the angiographic result after PCI may not be functionally acceptable. One might speculate that the traditional evaluation of restenosis may well underestimate the actual rates of target vessel revascularization (TVR) especially in long lesions treated with long drug eluting stents.

### 1.2. Study hypothesis

After stenting long coronary lesions functional revascularization result remains suboptimal (FFR≤0.8) despite good angiographic result achieved (residual stenosis <20%).

Because of the diffuse neointimal proliferation in long stented segment, the functional restenosis at follow-up can be measurable in patients without angiographically apparent restenosis.

### 1.3. The aim of this study

To evaluate functional, angiographic and clinical results of FFR guided PCI on long coronary lesions using 2nd or newer generation DES.

### 1.4. Study tasks

To evaluate the functional result immediately after PCI and at 9-month follow-up in long coronary lesions treated with long 2nd or newer generation DES.

To ascertain how often a functionally optimal result of FFR>0.95 can be achieved.

To compare the rate of functional and angiographic restenosis at 9-month follow-up.

To evaluate 2-year clinical result after treating long coronary lesions and the influence of the total 2nd or newer generation DES length on long term target vessel revascularization rate.

### 1.5. What is new

Little is known about the functional (haemodynamic) revascularization effect in patients with diffuse coronary artery disease. Currently there is no study that has used FFR to assess the functional PCI result and restenosis at a long-term follow-up in patients with long coronary lesions in newer generation DES era. The data of this study could help to establish optimal treatment strategies in patients with diffuse coronary atherosclerosis.

## 2. Methods

This was a prospective, “all comers” single center study. The study protocol was approved by the local Ethics Committee, and informed consent was obtained in all cases. The database was created to store the patient data.

Consecutive patients admitted to Vilnius University Hospital Santaros Klinikos with stable angina pectoris or an acute coronary syndrome were screened for inclusion after coronary angiography and FFR measurement. Patients were included if they had a lesion in a major epicardial vessel where FFR value was ≤0.8 and it was envisaged that a stent ≥30 mm in length would be necessary. Patients with ST-elevation myocardial infarction (STEMI), in whom long term dual antiplatelet therapy was contraindicated with an expected survival <1 year, or with an allergy to biolimus, everolimus or zotarolimus, were excluded from the study.

### 2.1. Coronary angiography, FFR measurement and PCI procedure

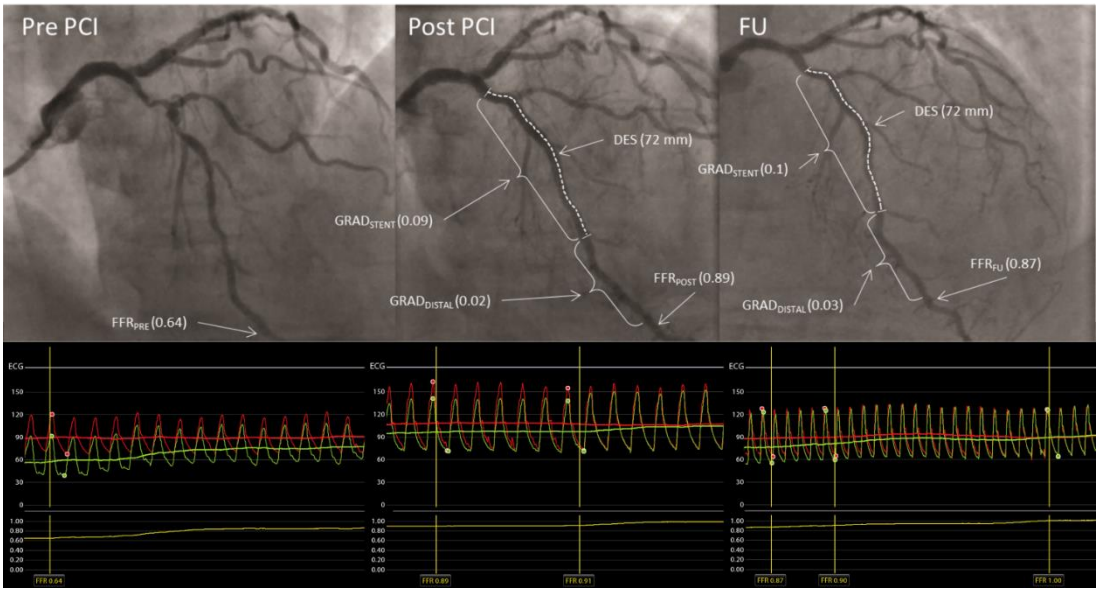
For transradial catheterization, an arterial puncture was made by means of the modified Seldinger technique. Once the sheath was in the place, an intra-arterial vasodilator was given (0.1 mg of isosorbide dinitrate). Intravenous heparin was used (usual dose, 70-100 units/kg; maximum total dose, 10000 units). Transfemoral catheterization could be performed if prefered by the operator.

As the access was obtained, after intracoronary administration of 0.1 mg of isosorbide dinitrate, selective coronary angiography was performed in different views (at least two orthogonal views for each segment of the coronary) using hand injections.

The 0.014-inch Pressure Wire (SJM™) was advanced to the tip of the guiding catheter and the pressures were equalized to ensure that the pressure recorded through the guiding catheter and the Pressure Wire were identical at that position. The wire was then advanced into the most distal part of the vessel. After the pressures had been recorded under baseline conditions, coronary hyperemia was induced by the intravenous administration of adenosine (140 mcg/kg/min). FFR was calculated as the ratio of distal coronary pressure to aortic pressure during maximal hyperemia. In the patients, in whom steady-state hyperemia was induced by intravenous adenosine, the pressure wire was slowly pulled back from the most distal to the proximal part of the artery by manual pullback. The following measurements were performed before and after PCI (Figure 1):

1. Baseline ($FFR_{PRE}$) – defined as evaluation of lesion significance prior to PCI, with the pressure wire sensor positioned at the beginning of the distal segment of the artery.
2. After PCI:
    a. $FFR_{POST}$ – after PCI the FFR was measured in the same position as $FFR_{PRE}$ positioned at the beginning of the distal segment.
    b. FFR gradient:
        i. FFR gradient across the stent ($GRAD_{STENT}$) was defined as difference between FFR value just proximal to the stent and FFR value just distal to the stent.
        ii. FFR gradient distal to stent ($GRAD_{DISTAL}$) was defined as difference between FFR value just distal to the stent and FFR value at the beginning of the distal segment.
        iii. Total gradient was defined as difference between FFR value just proximal to the stent and FFR value at the beginning of the distal segment.
3. The same FFR values were obtained at 9-month follow-up ($FFR_{FU}$, $GRAD_{StentFU}$, $GRAD_{DistalFU}$).

Figure 1. FFR measurement (example).



If the patient was not on long-term dual antiplatelet therapy (DAPT), a loading dose of a P2Y12 inhibitor was given. All patients should have been pretreated with aspirin.

All study lesions were treated with Biolimus A9 (Biomatrix Flex, Biosensors, Newport Beach, California), Everolimus (Xience Xpedition, Abbott Vascular, IL) or Zotarolimus (Resolute Integrity, Medtronic Vascular, Santa Rosa, CA) drug eluting stents using the standard PCI technique. In this study the operators were encouraged to post dilate in every case.

After the PCI result was deemed adequate (TIMI III flow with a residual angiographic diameter stenosis of ≤20%), the FFR measurement was repeated and the final angiograms taken. An optimal functional result was defined as FFR value after PCI of >0.95. A desirable result was defined as FFR value of >0.90 to 0.95. Where $FFR_{POST}$ was <0.95, further post dilatation was mandatory. If there was a clear evidence of atheroma beyond the stented segment, the operator was encouraged to try to optimise the functional result further by implanting another stent more distally.

The value of cardiac biomarkers (Troponin I) was evaluated 12-24 hours after index PCI procedure for periprocedural MI screening.

After PCI all patients had medical therapy optimised as tolerated with all receiving dual antiplatelet therapy for a period of 12 months.

### 2.2. Definition of stent length

Based on previous work stent length was defined as long (30 to 49 mm; L-DES) and ultra-long defined as (≥50 mm; UL-DES) (17).

### 2.3. Follow-up

Patients were planned to undergo angiographic, FFR and clinical follow-up at 9 months and aditional evaluation for clinical endpoints at 12 months and 2 years.

9-month follow-up was carried out during a visit to hospital with the clinical examination, control coronary angiography and FFR measurement (described in detail above).

The following clinical endpoints (MACE events) were evaluated:

1. Target vessel revascularization (TVR) – defined as any repeated percutaneous intervention of the target vessel or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion (18).
2. Non-target vessel revascularization – defined as any percutaneous intervention or bypass surgery of the non-target vessel.
3. Myocardial infarction:
    a. periprocedural;
    b. target vessel related;
    c. non-target vessel related.
4. Definite stent thrombosis – defined as stent thrombosis, confirmed by coronary angiography or autopsy.
5. Death:
    a. cardiac;
    b. non-cardiac.

On angiographic evaluation, the same angiographic views were recorded as in the post-PCI stage. Angiographic restenosis was defined as a >50% diameter stenosis at a follow-up, as measured by quantitative coronary angiography (QCA).

The same FFR measurements as in the post-PCI stage were performed in the target vessel (described in detail above). FFR value ≤0.80 found at 9 months follow-up was defined as functional restenosis. Patients in whom the $FFR_{POST}$ was ≤0.80 immediately after PCI, were excluded from the follow-up analysis of functional restenosis.

2-year follow-up was carried out as a telephone call to the patient or patient‘s general practitioner (in case the patient was unavailable). The same clinical endpoints as at 9 months were evaluated.

### 2.4. Quantitative coronary angiography (QCA)

QCA was retrospectively measured in all cases according to a standard protocol using QAngio XA 7.3 (Medis® medical imaging systems) software. The angiographic images taken before PCI, after PCI and at a follow-up stage were analyzed. The following variables were assessed and used for further statistical analysis:

1. Minimal luminal diameter (MLD) – the smallest in-segment lumen diameter derived from two orthogonal views.
2. Reference vessel diameter (RVD) – an average of the diameter of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views.
3. Percent diameter stenosis (% DS) – the value calculated as 100 x (1 – MLD/RVD) using the mean values determined by QCA from two orthogonal views.
4. Acute gain – MLD assessed immediately after the PCI procedure minus MLD assessed before PCI.
5. Late lumen loss (LLL) – minimal luminal diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the PCI procedure.

### 2.5. Statistical analysis

Analysis was performed according to the intention-to-treat principle. Normal distribution was tested using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were compared using Student's t-test and presented as mean ± standard deviation (SD), otherwise, nonparametric Wilcoxon's signed-rank tests were used. Categorical variables were compared by using $\chi^2$ or Fisher exact test and are presented as numbers or percentages. Multiple groups were compared by using a non-parametric Kruskal-Wallis test. Binary logistic regression analysis was performed to assess the associations of dichotomous dependent variables and independent variables. P value <0.05 was considered significant. Statistical analysis was performed with SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Patient and procedure characteristics

A total of 74 patients were enrolled. All patients had significant (FFR≤0.8) lesions in at least one of the major coronary arteries. 71.6% of the patients presented with stable angina, 28.4% with acute coronary syndrome without ST segment elevation. The mean patient age was 67.8±9.9 years, 73% of the patients were male. 21.6% of the patients had

diabetes mellitus, 90.5% hypertension, 81.1% hyperlipidemia. In 83.8% of the cases multivessel disease was present, 36.5% of the patients already had a previous revascularization event. Baseline demographic, clinical, lesion, and procedural characteristics are listed in detail in tables 1, 2 and 3 respectively.

Angiographic and functional assessment by FFR was performed in all 74 patients immediately before and after stent implantation. 61 lesions (82.4%) were in the left anterior descending artery (LAD), with the bigger proportion of LAD lesions in the longer stent (UL-DES) group (70.3% vs 94.6%, p=0.01). The mean lesion length was 39.04±14.11 mm. 1.80±0.62 stents per lesion were implanted. The mean stent length was 50.7 mm±14.6 mm ranging between 30 mm to 98 mm with a median stent length of 49 mm indicating that this was indeed a cohort with long diffuse coronary artery disease. 37 patients (50.0%) had total stent length between 30 and 49 mm (L-DES group), 37 (50.0%) ≥50 mm (UL-DES group). The postdilatation with a non-compliant baloon to optimize stent deployment was performed in 82.4% of cases.

Patients were screened for procedure related myocardial damage. A slight postprocedural elevation of cardiac biomarker values was observed in all cases, 5 of them (6.8%) were classified as a PCI related MI according to the consensus criteria (19).

Table 1. Clinical characteristics of the patients.

| | **All patients n=74** | **L-DES (≤50 mm) n=37** | **UL-DES (>50 mm) n=37** | **P value** |
|---|---|---|---|---|
| Age, years | 67.8±9.9 | 66.8±8.6 | 68.7±9.9 | 0.63 |
| Male sex | 54 (73) | 30 (81.1) | 24 (64.9) | 0.12 |
| Current smoker | 15 (20.3) | 11 (29.7) | 4 (10.8) | 0.04 |
| Diabetes mellitus | 16 (21.6) | 7 (18.9) | 9 (24.3) | 0.57 |
| Hypertension | 67 (90.5) | 32 (86.5) | 35 (94.6) | 0.23 |
| Hyperlipidemia | 60 (81.1) | 32 (86.5) | 28 (75.7) | 0.43 |
| Previous revascularization | 27 (36.5) | 19 (51.4) | 8 (21.6) | 0.02 |
| Previous myocardial infarction | 27 (36.5) | 17 (45.9) | 10 (27.0) | 0.09 |
| Multivessel disease | 62 (83.8) | 33 (89.2) | 29 (78.4) | 0.35 |
| Stable angina | 53 (71.6) | 27 (72.3) | 26 (70.3) | 0.79 |
| ACS | 21 (28.4) | 10 (27.0) | 11 (29.7) | 0.64 |
| LV ejection fraction | 49.29±7.77 | 48.96±8.34 | 49.60±7.35 | 0.78 |

Values are mean ± SD or n (%). ACS – acute coronary syndrome; LV – left ventricle.

Table 2. Procedural and QCA characteristics of the patients.

| | All patients n=74 | L-DES (≤50 mm) n=37 | UL-DES (>50 mm) n=37 | P value |
|---|---|---|---|---|
| **Pre-PCI** | | | | |
| RVD (mm ± SD) | 2.47±0.39 | 2.56±0.40 | 2.37±0.37 | 0.05 |
| MLD (mm ± SD) | 0.98±0.24 | 1.06±0.23 | 0.91±0.22 | 0.01 |
| Diameter stenosis (%) | 59.90±8.88 | 58.38±9.00 | 61.48±8.61 | 0.17 |
| **Post-PCI** | | | | |
| RVD (mm ± SD) | 3.08±0.46 | 3.09±0.43 | 3.06±0.49 | 0.81 |
| MLD (mm ± SD) | 2.59±0.40 | 2.64±0.41 | 2.55±0.40 | 0.39 |
| Diameter stenosis (%) | 15.66±5.18 | 14.70±5.52 | 16.64±4.69 | 0.14 |
| Acute gain (mm ± SD) | 1.61±0.41 | 1.58±0.42 | 1.64±0.41 | 0.57 |
| **Follow-up** | | | | |
| RVD (mm ± SD) | 2.95±0.49 | 3.06±0.53 | 2.84±0.42 | 0.07 |
| MLD (mm ± SD) | 2.35±0.46 | 2.46±0.52 | 2.23±0.36 | 0.04 |
| Diameter stenosis (%) | 20.29±8.27 | 19.45±8.75 | 21.17±7.79 | 0.41 |
| LLL (mm ± SD) | 0.24±0.41 | 0.17±0.35 | 0.32±0.46 | 0.17 |
| | | | | |
| Target Vessel LAD | 61 (82.4) | 26 (70.3) | 35 (94.6) | 0.01 |
| Stent length, mm | 50.72±14.6 | 39.0±5.6 | 62.4±10.7 | <0.001 |
| Average stent diameter, mm | 3.21±0.36 | 3.36±0.35 | 3.18±0.32 | 0.08 |
| Maximal implantation pressure, atm | 14.09±2.74 | 14.03±2.3 | 14.11±2.9 | 0.90 |
| Post-dilatation | 61 (82.4) | 29 (78.4) | 32 (86.5) | 0.21 |
| Maximal post-dilatation pressure, atm | 18.31±3.67 | 17.65±3.50 | 18.97±3.75 | 0.18 |

Values are mean ± SD or n (%). LAD – left anterior descending; atm – atmospheres.

Table 3. Stents used by type.

| Stent type | No. (%) |
|---|---|
| Biolimus A9 eluting with biodegradable polymer | 107 (80.5) |
| Zotarolimus eluting with durable polymer | 16 (12.0) |
| Everolimus eluting with durable polymer | 10 (7.5) |

### 3.2. Baseline and post-PCI functional assessment

At baseline, the mean $FFR_{PRE}$ was 0.61±0.11. The mean $FFR_{POST}$ immediately after the PCI increased to 0.88±0.06 ($p<0.001$) and was numerically higher in the L-DES group as compared to UL-DES (0.89 ± 0.07 vs. 0.87 ± 0.04; $p=0.05$). An optimal FFR value of >0.95 was achieved in only 9/74 patients (12.2%). Only 12/74 (16.2%) had a desirable $FFR_{POST}$ of 0.91 to 0.95 inclusive. Finally, 53/74 (71.6%) had FFR values ≤0.90. In 8/74 (10.8%) of the patients the FFR remained haemodynamically significant at ≤0.8 (mean

$FFR_{POST}$ 0.77±0.04, mean stent length 50±15mm) indicating significant inducible ischaemia (Table 4).

Table 4. FFR at baseline, post-PCI, and at 9 months follow-up.

| | **All patients n=74** | **L-DES (≤50 mm) n=37** | **UL-DES (>50 mm) n=37** | **P value** |
|---|---|---|---|---|
| **Baseline ($FFR_{PRE}$)** | 0.61±0.11 | 0.64±0.11 | 0.57±0.11 | 0.007 |
| **Post PCI** | n=74 | n=37 | n=37 | |
| $FFR_{POST}$ | 0.88±0.06 | 0.89±0.07 | 0.87±0.04 | 0.05 |
| $GRAD_{STENT}$ | 0.06±0.03 | 0.04±0.03 | 0.07±0.03 | 0.001 |
| $GRAD_{DISTAL}$ | 0.05±0.05 | 0.04±0.05 | 0.06±0.05 | 0.25 |
| **Follow-up** | n=61 | n=31 | n=30 | |
| $FFR_{FU}$ | 0.85±0.08 | 0.86±0.08 | 0.85±0.09 | 0.48 |
| $GRAD_{StentFU}$ | 0.07±0.07 | 0.05±0.05 | 0.09±0.08 | 0.04 |
| $GRAD_{DistalFU}$ | 0.05±0.04 | 0.05±0.05 | 0.04±0.03 | 0.38 |

### 3.3. $FFR_{POST}$ in relation to stent length

At baseline, the mean $FFR_{PRE}$ value was significantly lower in the UL-DES group compared to the L-DES group (0.57±0.11 versus 0.64±0.11, p=0.007)). Post PCI, the $FFR_{POST}$ value remained numerically lower in the UL-DES group compared to the L-DES (0.89±0.07 vs. 0.87±0.04, p=0.05). An optimal FFR value of >0.95 was not achieved in any of the UL-DES patients (Figure 2, Table 4). A desirable $FFR_{POST}$ value of >0.90 was achieved in only 21/74 patients (28.4%) of which 19 of those were from patients in the L-DES group and only 2 from the UL-DES group suggesting that even a desirable result is difficult to achieve in patients receiving Ultra Long stents. There was a low and inverse correlation between stent length and FFR after PCI (r = -0.297, p = 0.018) (Table 5).

Figure 2. Post-PCI functional results by FFR categories.

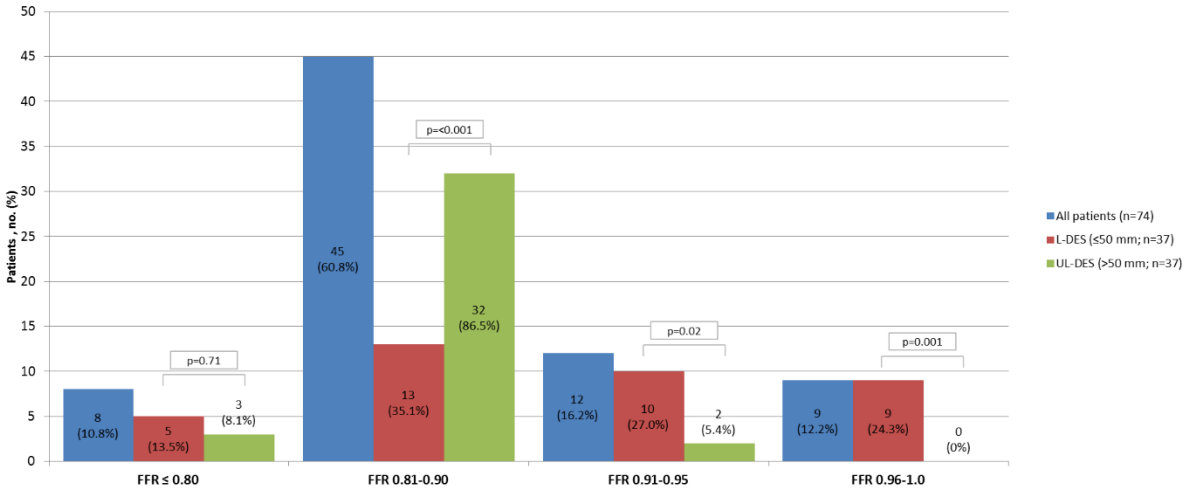



Table 5. The correlation between QCA measurements and functional results.

| | | FFR POST | | FFR FU | | GRAD Stent POST | | GRAD Stent FU | |
|---|---|---|---|---|---|---|---|---|---|
| | | ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** | ***r*** | ***p*** |
| **MLD** | baseline | -0.031 | 0.811 | -0.015 | 0.909 | -0.059 | 0.648 | -0.140 | 0.287 |
| | POST | 0.115 | 0.369 | 0.160 | 0.222 | -0.084 | 0.516 | -0.233 | 0.074 |
| **RVD** | baseline | 0.138 | 0.280 | 0.172 | 0.189 | -0.150 | 0.243 | -0.207 | 0.113 |
| | POST | 0.101 | 0.433 | 0.147 | 0.264 | -0.049 | 0.703 | -0.168 | 0.200 |
| **Diameter stenosis** | baseline | 0.123 | 0.337 | 0.147 | 0.264 | -0.032 | 0.804 | 0.002 | 0.989 |
| | POST | -0.064 | 0.620 | -0.051 | 0.700 | 0.185 | 0.149 | 0.226 | 0.083 |
| **Total stent lenght** | | -0.297 | **0.018** | -0.024 | 0.858 | **0.480** | **<0.001** | **0.460** | **<0.001** |

*r* – Correlation coefficient; MLD – minimal luminal diameter; RVD – reference vessel diameter

### 3.4. FFR gradient

In the entire cohort the mean FFR $GRAD_{Stent}$ was 0.06±0.03 and FFR $GRAD_{Distal}$ was 0.05±0.05. The total gradient in patients that achieved an optimal result of $FFR_{POST}$ of >0.95 after PCI was 0.02±0.02. Patients who remained haemodynamically significant after PCI (i.e. FFR≤0.8) had total gradient of 0.19±0.09. In these patients the $GRAD_{Distal}$ was significantly higher than $GRAD_{Stent}$ (0.11±0.07 vs. 0.08±0.02, p<0.0001)

(see Table 6), possibly indicating a more diffuse disease. $GRAD_{Stent}$ was significantly higher in the UL-DES group compared to the L-DES group (0.07±0.03 vs. 0.04±0.03; p=0.001).

Table 6. $GRAD_{Stent}$ and $GRAD_{Distal}$ by FFR categories.

| | **All patients** | **≤0.8** | **0.81-0.9** | **0.91-0.95** | **>0.95** | **P value** |
|---|---|---|---|---|---|---|
| **Post-PCI** | n=74 | | | | | |
| $GRAD_{Stent}$ | 0.06±0.03 | 0.08±0.02 | 0.07±0.03 | 0.04±0.02 | 0.01±0.01 | <0.001 |
| $GRAD_{Dist}$ | 0.05±0.05 | 0.11±0.07 | 0.05±0.04 | 0.03±0.03 | 0.01±0.01 | <0.001 |
| **Follow-up** | n=61 | | | | | |
| $GRAD_{StentFU}$ | 0.07±0.07 | 0.08±0.05 | 0.09±0.08 | 0.04±0.01 | 0.02±0.01 | <0.001 |
| $GRAD_{DistalFU}$ | 0.05±0.04 | 0.10±0.06 | 0.05±0.03 | 0.04±0.02 | 0.01±0.02 | <0.001 |

### 3.5. At 9-month follow-up

At 9 months, coronary angiography was repeated in 64/74 (86.5%) patients with functional follow (FFR measurement) in 61/74 (82.4%) (Figure 3). The FFR values of these 61 patients were compared after PCI and at 9 months. A desirable FFR value of >0.90 decreased to 14/61 patients (23%) at 9-month follow-up. A proportion of patients remained to have haemodynamically significant disease increased to 12/61 patients (19.7%) (Figure 4). Restenosis rate was 3/64 (4.7%) by angio and 8/53 (15.1%) by functional assessment (Figure 5).

TVR rate was 6/74 (8.1%). One patient died during the first 9 months of the follow-up.

Figure 3. Patient flow chart.

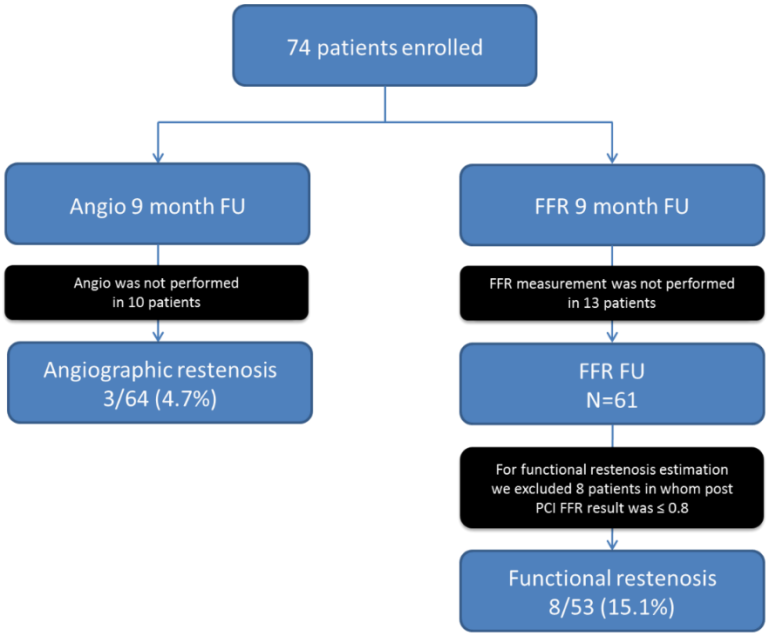



Figure 4. Functional results at follow up by FFR categories.

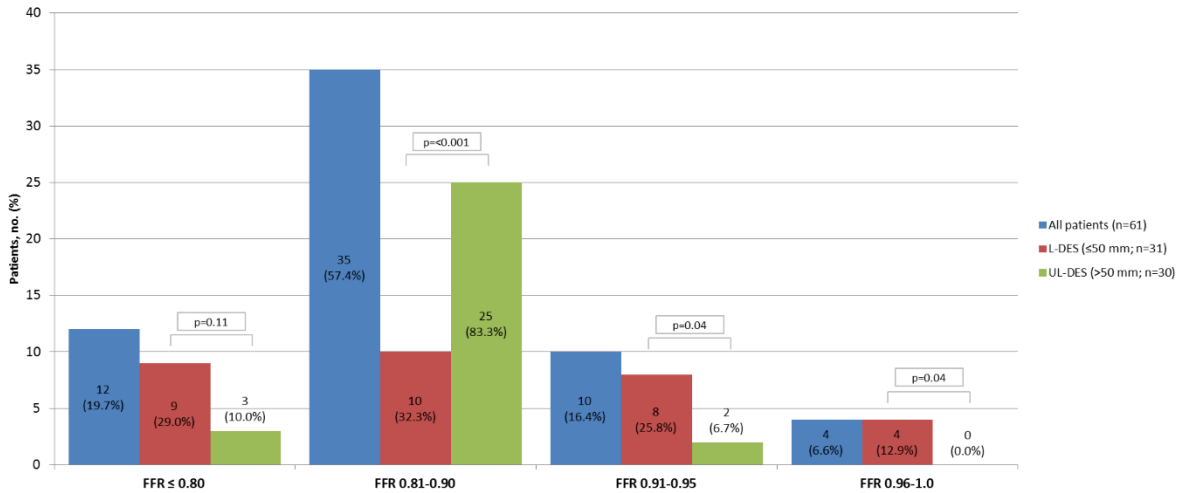
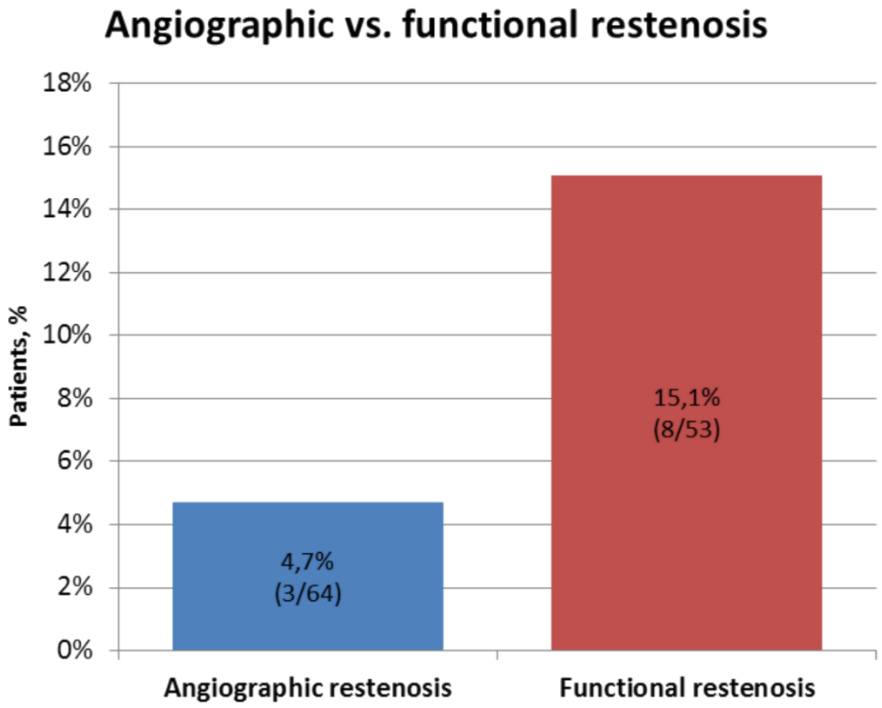


Figure 5. Angiographic vs functional restenosis.




### 3.6. At 2-year follow-up

6 (8.1%) of the patients had ischemia driven TVR, all within the first 12 months (Figure 6). There were no definite stent thromboses and target vessel related acute coronary syndromes in the study group. At 2 years, the total MACE rate was 29.7%. Three (4.1%) cardiac deaths were reported, none of them was target vessel related (Table 7).

Table 7. Clinical endpoints at follow-up.

| Clinical endpoints (N=74) | Up to 12 months, no. (%) | At 12-24 months, no. (%) | At 24 months, no. (%) |
|---|---|---|---|
| Death | 2 (2.7%) | 1 (1.3%) | 3 (4.1%) |
| Cardiac | 2 (2.7%) | 1 (1.3%) | 3 (4.1%) |
| Non-cardiac | 0 (0%) | 0 (0%) | 0 (0%) |
| Myocardial infarction | 5 (6.8%) | 2 (2.7%) | 7 (9.5%) |
| Periprocedural MI | 5 (6.8%) | - | 5 (6.8%) |
| Target vessel related MI | 0 (0%) | 0 (0%) | 0 (0%) |
| Non-target vessel related MI | 0 (0%) | 2 (2.7%) | 2 (2.7%) |
| Definite stent thrombosis | 0 (0%) | 0 (0%) | 0 (0%) |
| Target vessel revascularization | 6 (8.1%) | 0 (0%) | 6 (8.1%) |
| Other vessel revascularization | 5 (6.8%) | 3 (4.0%) | 8 (10.8%) |
| Major adverse cardiac events | 18 (24.3%) | 4 (5.4%) | 22 (29.7%) |

The regression analysis was performed to evaluate the influence of the total stent length, reference vessel diameter, stent diameter, presence of diabetes on the clinical endpoints. There was no association between neither of these variables and MACE or TVR rates at 24 months. No independent predictors of TVR were identified (Table 8). There was a trend towards a higher TVR rate in patients with overlapping DES vs single DES implanted, though not statistically significant (9,6% vs 4,5%, p=0.6) (Figure 7).

Figure 6. TVR and total MACE during 2-year follow-up.

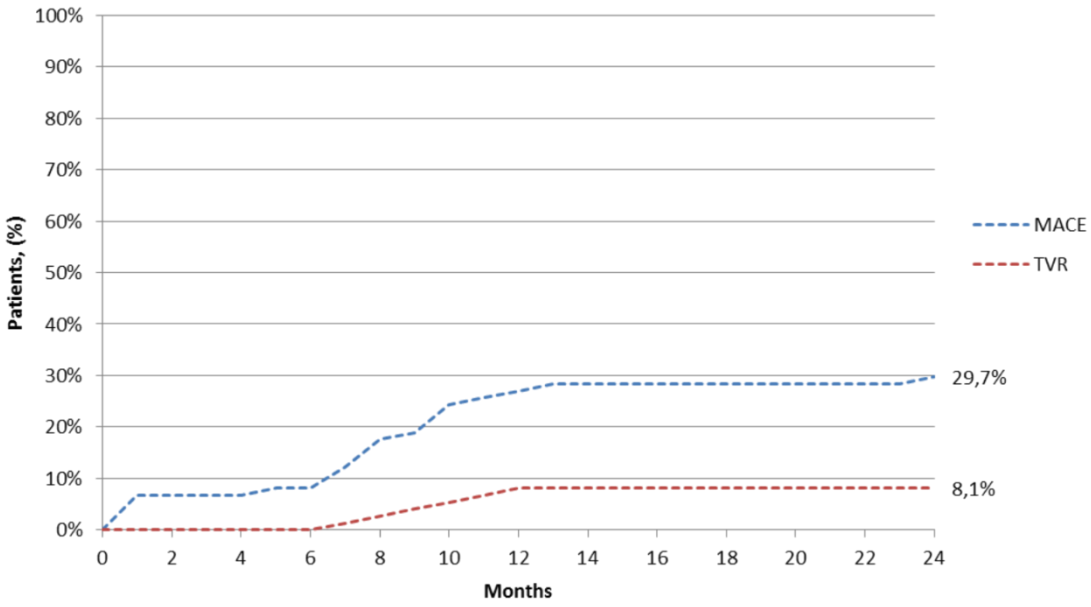



Figure 7. TVR rate in patients with overlapping DES vs single DES implanted.

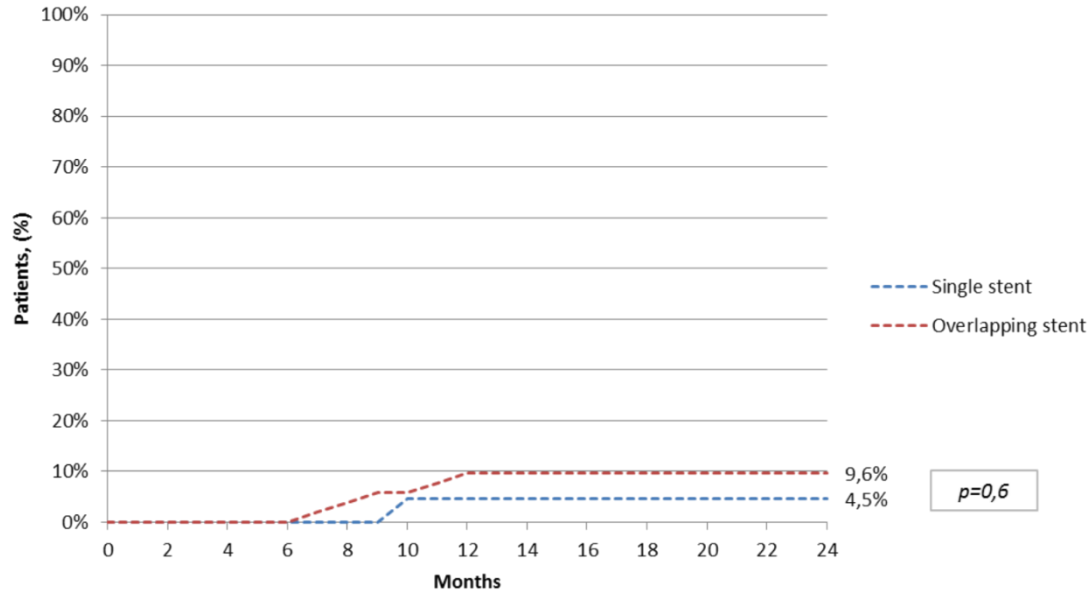


Table 8. Independent Predictors of a 2-Year TVR.

| Variable | OR (95% CI) | P value |
|---|---|---|
| Total stent lenght (per 10-mm increase) | 0.96 (0.86-1.01) | 0.41 |
| Overlapping stent | **2.23 (0.25-20.32)** | **0.48** |
| Bifurcation lesion | **3.44 (0.59-20.15)** | **0.17** |
| RVD (per 0.2-mm increase) | 0.74 (0.03-18.04) | 0.85 |
| MLD (per 0.5-mm increase) | 0.43 (0.02-8.96) | 0.58 |
| NSD (per 0.25-mm increase) | 0.03 (0.00-4.63) | 0.17 |
| Diabetes Mellitus | **1.93 (0.32-11.62)** | **0.47** |

RVD – reference vessel diameter; MLD – minimal luminal diameter; NSD – nominal stent diameter; MACE – major adverse cardiovascular event; TVR – target vessel revascularization.

### 3.7. QCA analysis at baseline, after PCI and at 9-month follow-up

QCA analysis was performed with the dedicated QAngio XA 7.3 (Medis® medical imaging systems) software (Table 2). The pre-PCI reference vessel diameter (RVD) was 2.47±0.39 mm, and was lower in UL-DES group as compared with L-DES (2.37±0.37 mm vs 2.56±0.40 mm respectively, p=0.05). A mean diameter stenosis was 59.9±8.9%. The post-PCI RVD was 3.08±0.46 mm, acute gain 1.61±0.41 mm, without significant difference between L-DES and UL-DES groups.

At the follow-up, the mean RVD was 2.95±0.49 mm and was similar in L-DES and UL-DES groups. Mean minimal lumen diameter (MLD) was 2.35±0.46 and was lower in UL-DES group (2.23±0.36 vs 2.46±0.52, p=0.04).

Angiographic in-stent late lumen loss was 0.24±0.41 mm, with a statistically non-significant trend to be higher in the UL-DES group (0.32±0.46 mm vs 0.17±0.35 mm, p=0.17).

## 4. Discussion

There are several key findings of this study, the first of which is that achieving an optimal post-PCI FFR result of >0.95 is only possible in a limited number of cases equating to 12.2%. In particular, an optimal FFR result of >0.95 could not be achieved in

any patient who was treated with >50mm of stent. Furthermore, the use of long and ultra-long stents resulted in a high proportion of patents with residual haemodynamically significant ischaemia defined as a FFR≤0.80, despite optimisation of the stent during the procedure. Finally, the rate of functional restenosis at 9 months follow-up was shown to be approximately 3 times higher than angiographic restenosis in this cohort.

This study evaluated the functional results that can be achieved in patients treated with 2nd or newer generation drug eluting stents for diffuse long coronary artery lesions. This data shows that achieving a functionally optimal or even desirable result in long coronary artery disease using long coronary stents can be very difficult, even when using newer generation drug eluting stents. Previous work shows that the measurement of the post-PCI FFR is an important predictor of MACE. Pijls et al. have shown that the higher the FFR value after PCI the lower the rate of MACE (6). This has been subsequently corroborated from a metanalysis done by Johnson et al. suggesting that FFR provides important prognostic information (7).

There are several key differences between our findings and those seen in previous studies. Crucially, the metanalysis by Johnson et al. shows that only 27% of the patients treated received a drug eluting stent as opposed to all patients in our cohort. Obviously, the former is not reflective of current practice as 2nd generation drug eluting stents and beyond are now more widely used, largely driven by the fact that angiographic restenosis is less of an issue compared to the levels of angiographic restenosis seen during the era of BMS and even 1st generation DES (20). Looking at the predictive value of FFR in the first studies, the stent length ranges on average between 16 and 20 mm and desirable results were achieved in a very significant proportion of patients who had PCI (6,21,22).

There are several lines of evidence to suggest that the optimal PCI result is achieved when the post-PCI FFR value is >0.95, comparable to that found in angiographically normal coronary arteries (0.97+/-0.02 [0.92-1.0]) (4). Moreover, the evidence also shows that optimal FFR values >0.95 are associated with lower rates of MACE (6,7,21,22). Pijls et al. showed that the 6 month MACE rate in patients receiving bare metal stents was 4.9% when the FFR value was >0.95 compared to 5.5% when the FFR value was between 0.91-0.95. MACE rates increased significantly to 18.1% when the

FFR value was between 0.81-0.9; a threefold increase, and as high as 30% when the FFR value remained ≤0.80 (6). Subsequent studies have reproduced Pijls's findings but with a higher proportion of patients achieving FFR values >0.95 (21,22). An important difference in these more recent studies has been the higher use of drug eluting stents. With these cut offs in mind, we see that an optimal result defined as a FFR value of >0.95 was achieved in only 36% of the patients in the Pijls et al. trial, in contrast to only 12% in the current study. Even when we re-define a desirable post-PCI FFR threshold as >0.90 then the proportion rises to 68% in the Pijls study, however it remains disappointingly low at 28% in the current study despite aggressive post dilatation. This notable difference may be explained in part by the considerable additional diffuse atherosclerotic burden as well as stent length. The average stent length is approximately 3 fold longer in our study compared to that seen in Pijls study and that of subsequent studies mentioned above. This suggests that a functionally sub-optimal result as measured by FFR is much more likely to occur if one decides to treat long diffuse coronary artery disease with long drug eluting stents even when these are newer generation DES. In every case, where patients received >50 mm of stent an optimal FFR result >0.95 could not be achieved in any case in this study. Similarly, there were only 2 cases where patients achieved a desirable FFR value of >0.90 but ≤0.95 indicating that the goal of achieving a functionally optimal or even desirable result after PCI in long coronary artery disease was virtually impossible. In support of this, Honda et al. suggested that ultra long (>50 mm) second generation DES implantation should be avoided due to a higher risk of target lesion revascularizition (TLR) (13.5%) at a long-term follow-up (23.2±13.2 months) relative to long (20-50 mm) DES (TLR 7.2%) and short DES (<20 mm) (TLR 6.0%).

In contrast to achieving an optimal or desirable result after PCI, there remains a haemodynamically significant cohort (FFR≤0.80) in all study populations. The proportion of these patients was approximately 6% in Pijls's study rising to 11% in patients with long diffuse coronary disease, as was the case in the current study. Pijls postulated that this persistent ischaemic burden seen in his cohort probably reflected the under appreciated nature of diffuse disease that remains in the unstented segment of the coronary artery. This again is the most likely explanation in our population and in support of these findings, we found that the gradient in the distal vessel (i.e. the residual gradient distal to

the stent) increased significantly as post-PCI FFR values decreased. Furthermore and in contrast to the previous studies (23), the gradient across the actual stented segment itself actually increased as FFR values decreased despite aggressive post dilatation. Notably in the group of patients who remained ischaemic (i.e. FFR≤0.80) the gradient along the entire vessel was significantly higher than in the group of patients who had FFR values >0.80. In the group with residual ischaemia the gradient in the distal vessel itself was the greatest contributor to the total gradient being significantly higher than the gradient across the stent, probably again reflecting the diffuse atherosclerotic burden in the entire vessel. In these patients it may be that despite 2nd generation DES that functionally optimal or even desirable results cannot be achieved, however it may be that adjuvant use of IVUS or OCT imaging could provide an insight into the degree of atherosclerotic burden as well as the causes of this residual in-stent FFR gradient and guide us how to improve functional results. In support of this, focal underexpansion of stents can be seen in as many as 35% of PCI cases when a stent >28 mm is used (24). Further support for this strategy comes from Fearon et al. who show that the absence of a hyperaemic residual pressure gradient is a prerequisite for optimal stent deployment. In this study the FFR gradient was higher in the UL-DES group (0.07±0.03) in comparison to shorter stents (0.04±0.03). This may reflect the altered shear environment within the long stented segment thereby possibly leading to MACE, however it will need a much larger study to prove this theory.

Historically many studies used angiographic assessment for a follow-up. In this study we found following angiographic assessment at 9 months that there was a restenosis rate of 4.7% in keeping with previous studies that have used 2nd generation DES (25). However, in this study we also performed a haemodynamic assessment at 9 months and found a functional restenotic rate of 15.1% equating to a 3-4 fold increase. This suggests that angiographic assessment potentially misses a significant proportion of patients and therefore we should not be surprised if MACE rates are higher particularly in cases where PCI has been performed in long diffuse coronary disease using long 2nd generation DES. Simply believing the angiographic result may not be sufficient in order to avoid MACE, and functional restenosis may be a better predictor of MACE.

While there have been studies using IVUS guidance to optimise stent implantation, thereby increasing minimal luminal diameter, this gain has not been shown

to achieve functionally better results as FFR was not measured. In the AVIO study the increase in MLD did not improve clinical endpoint (26). Honda et al. reported 13,5% TLR rate in a group of patients with stent length >50 mm (UL-DES) vs 6.0% in short stent group (<20 mm) vs 7.2% in 20-50 mm (L-DES) despite IVUS guidance (17). In the recent study Elgendy et al. reported that IVUS-guided percutaneous coronary intervention is superior to angiography-guided percutaneous coronary intervention in reducing the risk of major adverse cardiac events primarily because of reduction in the risk of ischemia-driven target lesion revascularization (27).

Some of the findings of this study may have been explained by the fact that the majority of the cases were diffuse diseases in the LAD. One might speculate that had there been a higher proportion of patients with RCA or LCx disease that more functional optimal results would have been achieved (2).

Our study shows a very significant rate of functional restenosis, however, because of relatively small study group we are underpowered to say what impact this will have on clinical endpoints. We reported a 2-year TVR rate of 8.1%. All TVR occured within the first 12 months and reached the peak in the period of scheduled angiographic and FFR follow-up. There was no target vessel related events during the second year of a follow-up. The reported TVR rate in our study is higher than expected in general population, but it is comparable to the rates reported by Honda et al. with the long DES (7.2% when the total stent length was 20-50 mm and 13.5% with the stents ≥50 mm) (17). In support to the most studies with newer generation DES and in contrast to the studies with the first generation DES and BMS (11,12,28), there was no association between the total stent length and TVR rate at a follow-up. Though, there was a trend towards a higher TVR rates in patients with overlapping DES implanted (9,6% vs 4,5%), suggesting, that the double stent layer at the sites of stent overlap could possibly be related to a risk of DES restenosis. However, this difference was not statistically significant.

In contrast to the studies with the first generation DES, where the rate of the late stent thrombosis was >2% (29), there was no definite stent thrombosis reported in the current study. Considering the mean stent length >50 mm, we can assume, that the total length of newer generation DES implanted does not affect the long term patient safety.

## 5. Conclusions

- Achieving an optimal post-PCI FFR result in patients with long diffuse coronary artery disease is only possible in a limited number of cases equating to 12.2%. An optimal FFR result could not be achieved in any patient who was treated with >50 mm of stent.
- The use of long and ultra-long stents resulted in a high proportion of patients with residual haemodynamically significant ischaemia (10.8% of cases with post-PCI FFR ≤0.80).
- The rate of functional restenosis at 9 months follow-up was shown to be approximately 3 times higher than angiographic restenosis.
- TVR rate at 2 years was 8.1%.

## 6. Practical recommendations

- In the majority of cases diffuse coronary artery disease cannot be functionally effectively treated using long and ultra long drug eluting stents.
- For patients with diffuse coronary artery disease, particularly when the envisaged stent length exceeds 50 mm, other treatment options should be considered (CABG or medical therapy alone).
- Although considering a relatively low TVR rate at 2 years, PCI on long coronary lesions could be used as an option in the high CABG risk patients with diffuse coronary artery disease.

# MIOKARDO REVASKULIARIZACIJOS EFEKTYVUMO ĮVERTINIMAS VYRAUJANT DIFUZINIAM ATEROSKLEROZINIAM ŠIRDIES VAINIKINIŲ ARTERIJŲ PAŽEIDIMUI

Santrauka

## 1. Įvadas

Difuzinės vainikinių arterijų ligos gydymas išlieka viena aktualiausių šiuolaikinės kardiologijos ir kardiochirurgijos problemų. Didėjant sergamumui koronarine širdies liga kartu padaugėjo ir pacientų, besikreipiančių dėl toli pažengusios difuzinės ligos formos. Nepaisant spartaus intervencinės kardiologijos technologijų tobulėjimo, ilgų širdies vainikinių arterijų pažeidimų stentavimo rezultatai nėra geri, o jų įvertinimo priemonės ir kriterijai nėra aiškiai apibrėžti. Klasikinė aortokoronarinių jungčių operacija dažnai taikoma kaip pirmo pasirinkimo revaskuliarizacijos metodas, tačiau esant difuzinei vainikinių arterijų ligai vis dar nėra aišku, kuris gydymo būdas būtų optimalus kiekvienam pacientui, kokios apimties intervenciją pasirinkti ir kaip įvertinti jos efektyvumą. Klinikinėje praktikoje dažniausiai vertinamas angiografinis ir klinikinis perkutaninės koronarinės intervencijos (PKI) rezultatas, tačiau daugeliu atvejų, kai yra difuzinis vainikinių arterijų pažeidimas, angiografijos duomenys neatspindi tikrosios vainikinių arterijų kraujotakos, o pagrindinis visų gydomųjų intervencijų tikslas yra atkurti adekvačią širdies raumens kraujotaką tiek ramybėje, tiek fizinio krūvio metu, o ne anatominę kraujagyslių struktūrą. Nors šiuolaikinei diagnostikai yra taikomi tiek neinvaziniai, tiek invaziniai širdies raumens perfuzijos įvertinimo metodai, tačiau klinikinių tyrimų duomenų apie ilgalaikį funkcinį PKI rezultatą po ilgų vainikinių arterijų pažeidimų stentavimo beveik nėra. Ypač tai pasakytina apie naujesnės kartos vaistais dengtų stentų naudojimo rezultatus.

## 2. Darbo hipotezė, tikslas ir uždaviniai

**Hipotezė:**

Po ilgų vainikinių arterijų susiaurėjimų stentavimo, nepaisant pasiekto gero angiografinio rezultato (liekamoji stenozė < 20 %), funkcinis revaskuliarizacijos efektas išlieka nepakankamas (frakcinis tėkmės rezervas ≤ 0,8).

Vėlyvuoju laikotarpiu po PKI dėl difuzinės neointimos proliferacijos ilgame stentuotame segmente, net ir nesant angiografiškai reikšmingos restenozės, frakcinio tėkmės rezervo tyrimu daliai pacientų nustatoma funkcinė restenozė.

**Tikslas:**

Įvertinti perkutaninės koronarinės intervencijos rezultatą gydant ilgus vainikinių arterijų susiaurėjimus antros ir naujesnės kartos vaistais dengtais stentais, atliekant angiografinį ir funkcinį vainikinių arterijų kraujotakos ištyrimą.

**Uždaviniai:**

Taikant frakcinės tėkmės rezervo tyrimą įvertinti funkcinį ilgų vainikinių arterijų susiaurėjimų stentavimo antros ir naujesnės kartos vaistais dengtais stentais rezultatą iškart po PKI ir po 9 mėnesių.

Išsiaiškinti, kokiai daliai pacientų, stentuojant ilgus vainikinių arterijų susiaurėjimus, galima pasiekti funkciškai optimalų rezultatą (FTR > 0,95).

Palyginti angiografinių ir funkcinių restenozių dažnį praėjus 9 mėnesiams po PKI.

Įvertinti dvejų metų klinikinius ilgų vainikinių arterijų susiaurėjimų stentavimo antros ir naujesnės kartos vaistais dengtais stentais rezultatus bei stentų ilgio įtaką vėlyviesiems kardiovaskuliniams įvykiams.

## 3. Darbo naujumas

Duomenų apie funkcinį (hemodinaminį) revaskuliarizacijos poveikį ligoniams, sergantiems difuzine vainikinių arterijų liga, beveik nėra. Iki šio darbo nebuvo atlikta naujesnės kartos vaistais dengtų stentų tyrimų, kuriuose ligoniams po ilgų vainikinių arterijų susiaurėjimų stentavimo FTR matavimu būtų įvertintas funkcinis stentavimo rezultatas tiek iškart po procedūros, tiek vėlyvuoju laikotarpiu. Šio tyrimo duomenys turėtų padėti parinkti optimalią revaskuliarizacijos taktiką ligoniams, sergantiems difuzine vainikinių arterijų liga.

## 4. Metodika

Šis tyrimas atliktas prospektyviąja metodika, įtraukiant visus pacientus, kuriems numatytu įtraukimo laikotarpiu buvo atlikta širdies vainikinių arterijų angiografija, jeigu jie atitiko toliau aprašytus įtraukimo kriterijus ir raštiškai patvirtino savo sutikimą dalyvauti tyrime. Tyrimui atlikti buvo gautas bioetikos komiteto leidimas.

Į tyrimą buvo traukiami pacientai, sergantys stabilia krūtinės angina arba ūminiu koronariniu sindromu be ST segmento pakilimo elektrokardiogramoje, kuriems vainikinių arterijų angiografijos metu nustatytas ilgas hemodinamikai reikšmingas susiaurėjimas bent vienoje iš didžiųjų vainikinių arterijų. Numatomas stento ilgis, reikalingas padengti visą vainikinės arterijos pažeidimą, turėjo būti $\geq 30$ mm. Hemodinaminis susiaurėjimų reikšmingumas vertintas atliekant frakcinio tėkmės rezervo tyrimą. Reikšmingais klasifikuoti tie vainikinių arterijų susiaurėjimai, už kurių išmatuotas frakcinis tėkmės rezervas buvo $\leq 0{,}8$.

Atlikti tokie frakcinio tėkmės rezervo matavimai:

1. Pradinis FTR ($FTR_{PRE}$) – vainikinės arterijos susiaurėjimo hemodinaminio reikšmingumo įvertinimas prieš PKI procedūrą. Spaudimų vielytės jutiklis pozicionuojamas distalinėje vainikinės arterijos dalyje.
2. FTR po PKI:
    a. $FTR_{POST}$ – frakcinės tėkmės rezervas matuojamas po stento implantavimo spaudimų vielytės jutiklį pozicionuojant toje pačioje kraujagyslės vietoje kaip ir prieš PKI.
    b. FTR gradientas:
        i. FTR gradientas per stentą ($GRAD_{STENT}$) – skirtumas tarp FTR reikšmės, išmatuotos proksimaliau implantuoto stento, ir FTR reikšmės už stento.
        ii. FTR gradientas distaliau stento ($GRAD_{DISTAL}$) – skirtumas tarp FTR reikšmės, išmatuotos iškart už implantuoto stento, ir FTR reikšmės distalinėje vainikinės arterijos dalyje.

iii. Bendras FTR gradientas – skirtumas tarp FTR reikšmės, išmatuotos proksimaliau implantuoto stento, ir FTR reikšmės distalinėje vainikinės arterijos dalyje.

3. Tie patys FTR matavimai atlikti ir per 9 mėnesių kontrolinį FTR tyrimą.

Pamatavus FTR ir nustačius reikšmingą vainikinės arterijos susiaurėjimą, prieš pradedant PKI procedūrą visi pacientai būvo įsotinti antiagregantais (P2Y12 receptorių antagonistais – klopidogreliu arba tikagreloru ir aspirinu). PKI procedūra buvo atliekama tipine metodika. Visiems į tyrimą įtrauktiems pacientams buvo naudojami biolimusu A9 (Biomatrix Flex, Biosensors, Newport Beach, California), everolimusu (Xience Xpedition, Abbott Vascular, IL) arba zotarolimusu (Resolute Integrity, Medtronic Vascular, Santa Rosa, CA) dengti stentai.

Pagal bendrą implantuotų stentų ilgį tolesnės rezultatų analizės tikslais pacientai buvo suskirstyti į dvi grupes: ilgų stentų grupė – bendras stentų ilgis nuo 30 mm iki 49 mm (L-DES) ir labai ilgų stentų grupė – bendras stentų ilgis ≥ 50 mm (UL-DES).

Praėjus 9 mėnesiams po PKI procedūros suplanuota atlikti kontrolinę vainikinių arterijų angiografiją su FTR tyrimu. Klinikinis pacientų įvertinimas (apsilankius pas kardiologą arba telefoniniu skambučiu) numatytas po 12 ir 24 mėnesių.

## 5. Rezultatai

Į tyrimą iš viso įtraukti 74 pacientai. Visiems jiems nustatyti reikšmingi (FTR ≤ 0,8) pažeidimai bent vienoje iš didžiųjų vainikinių arterijų. 71,6 % pacientų diagnozuota stabili krūtinės angina, 28,4 % – ūminis koronarinis sindromas be ST segmento pakilimo. Vidutinis pacientų amžius 67,8 ± 9,9 metai.

Vidutiniškai vienam pacientui implantuota 1,80 ± 0,62 stento. Vidutinis stentuoto segmento ilgis 50,7 ± 14,6 mm (nuo 30 mm iki 98 mm, mediana 49 mm).

Prieš PKI procedūrą vidutinis išmatuotas FTR buvo 0,61 ± 0,11. Vidutinis FTR iškart po procedūros padidėjo iki 0,88 ± 0,06 ($p<0,001$) ir trumpesnių stentų grupėje (L-DES) buvo šiek tiek didesnis, palyginti su ilgesnių stentų grupe (UL-DES), atitinkamai

0,89 ± 0,07 ir 0,87 ± 0,04; p = 0,05. Optimali FTR reikšmė (>0,95) buvo pasiekta tik 9 iš 74 pacientų (12,2 %). 12 iš 74 pacientų (16,2 %) buvo pasiektas geras funkcinis rezultatas (FTR > 0,90, bet ≤ 0,95). 53 iš 74 pacientų nustatyta FTR reikšmė ≤ 0,9, iš jų 8 pacientams (10,8 %) po PKI FTR reikšmė išliko ≤ 0,8. Šiems 8 pacientams revaskuliarizacija buvo funkciškai neveiksminga (vidutinis jų FTR 0,77 ± 0,04, vidutinis stentų ilgis 50 ± 15 mm).

Prieš perkutaninę koronarinę intervenciją FTR reikšmė UL-DES pacientų grupėje buvo mažesnė nei L-DES grupėje (atitinkamai 0,57 ± 0,11 ir 0,64 ± 0,11; p = 0,007). FTR matavimuose po PKI išliko ta pati tendencija (atitinkamai 0,87 ± 0,04 ir 0,89 ± 0,07; p = 0,05). Optimali FTR reikšmė (>0,95) nebuvo pasiekta nė vienam UL-DES grupės pacientui. Visoje tiriamųjų imtyje geras arba optimaus funkcinis rezultatas (FTR reikšmė >0,90) pasiektas 21 iš 74 pacientų (28,4 %), tačiau 19 iš jų priklausė L-DES grupei ir tik 2 buvo iš UL-DES grupės. Šie duomenys parodo, kad pasiekti gerą funkcinį rezultatą implantuojant ilgesnius kaip 50 mm stentus pavyksta tik labai mažai daliai pacientų.

Praėjus 9 mėnesiams po PKI, kontrolinė vainikinių arterijų angiografija buvo atlikta 64 iš 74 pacientų (86,5 %). Funkcinis įvertinimas matuojant frakcinį tėkmės rezervą atliktas 61 iš 74 pacientų (82,4 %). Tik šių 61 pacientų FTR reikšmės praėjus 9 mėnesiams lygintos su reikšmėmis, gautomis iškart po PKI. Pacientų, kuriems nustatytas geras PKI rezultatas (FTR > 0,90) per 9 mėnesius sumažėjo nuo 26,2 % (16 iš 61) iki 23 % (14 iš 61). Pacientų, kuriems po atliktos PKI vis dar nustatoma indukuojama miokardo išemija (FTR ≤ 0,8) padaugėjo nuo 13,3 % (8 iš 61) iki 19,7 % (12 iš 61). Funkcinė restenozė (FTR sumažėjimas ≤ 0,80, atmetus tuos tiriamuosius, kuriems FTR > 0,80 nebuvo pasiektas iškart po PKI) nustatyta 15,1 % pacientų.

Pakartotinių tiriamosios kraujagyslės revaskuliarizacijų dažnis per 9 mėnesių laikotarpį buvo 8,1 % (6 iš 74 pacientų).

Pakartotinių tiriamosios kraujagyslės revaskuliarizacijų dažnis per 24 mėnesių laikotarpį išliko 8,1 % (6 iš 74 pacientų), t. y. per antrus stebėjimo metus pakartotinių tiriamosios kraujagyslės revaskuliarizacijų nebuvo.

## 6. Išvados

Ligoniams, turintiems ilgus vainikinių arterijų pažeidimus, optimalus funkcinis revaskuliarizacijos rezultatas antros ir naujesnės kartos vaistais dengtais stentais pasiektas tik 12,2 % atvejų. Optimalaus funkcinio rezultato nepavyko pasiekti nė vienu atveju, kai stento ilgis buvo ≥ 50 mm.

Iškart po atliktos PKI 10,8 % atvejų išlieka indukuojama išemija gydytos vainikinės arterijos srityje (FTR ≤0,8).

Per 9 mėn. laikotarpį po ilgų vainikinių arterijų pažeidimų PKI funkcinių restenozių dažnis yra daugiau kaip tris kartus didesnis nei angiografinių restenozių ir siekia 15,1 %.

Per dvejų metų laikotarpį po PKI pakartotinių tiriamos vainikinės arterijos revaskuliarizacijų dažnis siekia 8,1 %, visos jos atliktos per pirmus 12 mėnesių.

## 7. Apibendrintos išvados klinikinei praktikai

Esant difuzinei vainikinių arterijų ligai, ilgus vainikinių arterijų pažeidimus stentuojant antros ir naujesnės kartos vaistais dengtais stentais, daugeliu atvejų funkcinis revaskuliarizacijos efektas nėra pakankamas.

Ligoniams, turintiems ilgus vainikinių arterijų pažeidimus, ypač kai numatomas stento ilgis ≥ 50 mm, svarstytina kita gydymo taktika (chirurginė revaskuliarizacija atliekant aortokoronarinių jungčių operaciją arba medikamentinis gydymas).

Įvertinus santykinai nedidelį koronarinių įvykių dažnį per dvejų metų laikotarpį, gydymas PKI būdu taikytinas didelės rizikos pacientams, kuriems negalima atlikti chirurginės revaskuliarizacijos.

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