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## CLINICAL, ANGIOGRAPHIC AND FUNCTIONAL PARAMETERS DETERMINING DECISION TO PERFORM REVASCULARIZATION IN STABLE CORONARY ARTERY DISEASE PATIENTS WITH INTERMEDIATE CORONARY LESIONS

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### Summary

**The aim:** to study the clinical, angiographic and functional parameters, and their relation to the decision on percutaneous coronary intervention (PCI) in stable coronary artery disease (CAD) patients with intermediate coronary stenoses (ICS) at patient and lesion levels.

**Materials and methods.** The cross-sectional study enrolled 123 patients (62±9 years; 73,2 % males) with stable CAD and angiographically ICS (50-90 %). Stable angina CCS class II (CCSII) was diagnosed in 70 (56,9 %) patients, class III (CCSIII) – 29 (23,6 %); 24 (19,5 %) patients were free from angina (Afree). Fractional flow reserve (FFR) was assessed in 74 (60,2 %) patients (min per patient). The hemodynamically significant lesion was considered if  $FFR \leq 0,80$  a.u. The decision to perform PCI was undertaken in 93 (76 %) patients. In addition, the functional data from 128 lesions were analyzed.

**Results.** The CCSIII group was characterized by less frequent previous PCI (21 % vs. 46 % in the pooled group [CCSII + Afree];  $p=0,018$ ); the predominance of cases with (max) severe [70-90 %] coronary stenosis (96 % vs. 78 % in CCSII and 54 % in Afree;  $p_{trend} < 0,001$ ); the lower (min) FFR ([median, quartiles] 0,70 (0,64-0,74) vs. 0,87 (0,81-0,90) in Afree;  $p < 0,002$ ); and the decision to perform PCI in the vast majority of cases (93 % vs. 79 % in CCSII and 46 % in Afree;  $p_{trend} < 0,001$ ). The Afree/CCSII/CCSIII groups demonstrated a trend towards a decrease in frequency of cases with (max) [60-69 %] stenosis (38 %, 13 % and none, respectively;  $p_{trend} < 0,001$ ), and a tendency towards the cases with (max) [80-90 %] stenosis to be more prevalent (29 %, 39 % and 55 %, respectively;  $p_{trend} = 0,051$ ). The frequency of cases with (max) stenosis [70-79 %] was comparable in the studied groups (Afree/CCSII/CCSIII: 25 %/39 %/41 %, respectively [ $p_{trend} = 0,240$ ]). At lesion-level, all [80-90 %] lesions ( $n=28$ ) appeared to be hemodynamically significant. In turn, the [60-69 %] lesions ( $n=24$ ) included 5 (21 %) significant ones. Finally, the [70-79 %] lesions ( $n=44$ ) included 28 (64 %) significant and 16 (36 %) non-significant ones.

**Conclusions.** Among the stable CAD patients with angiographically ICS, those with CCSIII were characterized by less frequent previous PCI, significant decrease in FFR and the decision to perform index PCI in the vast majority of cases. There is a need for more precise diagnosis and assessment of myocardial ischemia in patients with an intermediate pre-test obstructive CAD probability, including the cases of previously performed PCI.

**Key words:** coronary artery disease, myocardial revascularization, coronary angiography, fractional flow reserve

### INTRODUCTION

Current international guidelines comprehensively cover the principles of invasive management of patients

with stable coronary artery disease (SCAD), emphasizing the primary role of its clinical presentation while decision-making regarding myocardial revascularization, particularly via percutaneous coronary intervention (PCI) [1-5].

However, the real-world practice is facing a challenge of different SCAD patients' profiles, being inconclusive in terms of PCI appropriateness. For instance, the angina pectoris could be quite often manifested at the background of «non-critical» coronary lesions, detected by means of invasive coronary angiography (ICA) [6-8]. In case of the absence of clear anatomical criteria suggesting the potential increase of survival after revascularization, the decision-making is primarily based on SCAD clinical severity and/or the myocardial ischemia burden assessment, balancing the need to improve patients' quality of life and/or survival [1-5].

The existing evidence suggests inconsistency between the current guidelines and routine clinical practice regarding the sequence of diagnostic steps in patients with suspicion on SCAD. Such discrepancies could be, at least partially, related to the limited availability of guideline-directed non-invasive tools for ischemia burden assessment, and, on the contrary, a wide abundance of ICA facilities [9-11]. As a consequence of the prevailed anatomical diagnostic strategy, one should mention the relatively frequent detection of intermediate (by the degree of luminal stenosis) coronary lesions. Importantly, available evidence is inconclusive with respect to the appropriateness of PCI in such relatively «non-severe» patient profiles [6-8, 12].

The final decision-making regarding myocardial revascularization in SCAD is predominantly based on thorough analysis of patient profile, including clinical, anamnestic and angiographic data [1-6, 8, 12]. Moreover, the set of patient characteristics could be supplemented by the functional parameters of epicardial coronary flow, e.g. the data on fractional flow reserve (FFR). FFR, representing a hemodynamic sequel of coronary stenosis, is widely accepted as an additional factor impacting the decision to perform PCI in SCAD patients, considering the fact, that the lesions with similar anatomical significance could be substantially different in terms of their functional compromise [13, 14]. However, the availability of routine functional assessment of coronary flow is still limited [13-15].

Thus, there is an obvious need to analyze the real-world SCAD patient profiles, with respect to the evaluation of clinical, angiographic and functional data relationships, and to specify the factors indicating a necessity of PCI, particularly in cases where the anatomical criteria are not definitely conclusive for the revascularization appropriateness.

### THE AIM

We aimed to study the clinical, angiographic and functional parameters, and their relation to the decision on PCI in SCAD patients with intermediate coronary stenoses at patient and lesion levels.

### MATERIALS AND METHODS

The cross-sectional single-center study consecutively enrolled and analyzed the data from 123 patients with SCAD and ICA-derived intermediate coronary lesions (luminal narrowing with a diameter stenosis 50-90 % [3]) during the period Jun-Dec 2019. The enrolled sample included 74 (60,2 %) patients with concomitant FFR assessment.

The study did not include patients with acute coronary syndrome; myocardial infarction (MI) within the last month; acute heart failure; severe comorbidities; severe valvular heart disease requiring surgical treatment; previous cardiac surgery, left main coronary artery disease; coronary lesions with stenoses <50 % and >90 %; multivessel disease, suitable for surgical revascularization; and without informed consent.

We enrolled 90 (73,2 %) males and 33 (26,8 %) females aged 39 to 82 years; mean age  $62 \pm 9$  years. Body mass index (BMI) was (hereinafter – median (Me); interquartile range [IQR]) 29,1 (26,5-31,8) kg/m<sup>2</sup>; 49 (39,8 %) patients were obese.

The essential hypertension (HTN) was diagnosed in 117 (95,1 %) patients; stable angina pectoris – 99 (80,5 %) (including 70 (70,7 %) and 29 (29,3 %) patients with Canadian Cardiovascular Society (CCS) classes II and III [1], respectively); previous MI – 56 (45,5 %); and chronic heart failure (HF) stage B – in 39 (31,7 %), and stage C – in 84 (68,3 %) cases [16]. Percutaneous coronary intervention (PCI) has been already performed in 49 (39,8 %) cases.

Twenty (16,3 %) patients suffered previously from stroke or transient ischemic attack (TIA). Atrial fibrillation (AF) was registered in 23 (18,7 %) patients, and atrial flutter – in 5 (4,1 %) cases.

Diabetes mellitus type 2 (DM) was present in 30 (24,4 %) patients, peripheral arterial disease (PAD) – 16 (13,0 %), and chronic kidney disease (CKD) – 18 (24,6 %). Two (1,6 %) patients had either chronic obstructive pulmonary disease (COPD) or bronchial asthma, respectively.

All the patients received guideline-directed pharmacotherapy [1, 16].

Laboratory tests were performed in all the patients according to the standardized procedures.

The transthoracic echocardiography was performed according to the standard protocol. Left ventricular (LV) myocardial mass was calculated by the ASE-modified cube formula, and indexed by body surface area [17]. LV hypertrophy (LVH) was identified in 41 (33,3 %) patients (mild – 17, moderate – 9, and severe – 15 cases). The mean LV ejection fraction in the total sample was 58 % (53-61 %).

ICA was performed by the use of the Optima IGS 330 angiography system (GE Hualun Medical Systems Co., Ltd., China) according to the standard practice. The stenosis of the epicardial coronary artery was considered in case of a lesion with a visually assessed diameter stenosis of at least 50 % in a vessel larger than 2 mm in diameter [3]. We analyzed the stenotic lesions in three major subepicardial coronary arteries, namely left anterior descendent (LAD), circumflex (Cx) and right coronary artery (RCA), as well as their branches, considering the SYNTAX score coronary anatomy [3]. In case major coronary artery was unaffected, the lesion(s) of its branch(es) was (were) taken into account.

The stenotic lesions related to LAD territory were observed in 94 (76,4 %) patients, Cx – 55 (44,7 %), and RCA – 52 (42,3 %). Proximal lesion of LAD was visualized in 46 (37,4 %) patients.

Regarding the number of the affected major arteries territories, 66 (53,6 %) patients presented with single vessel disease, 36 (29,3 %) – 2-vessel, and 21 (17,1 %) – 3-vessel disease.

In case of  $\geq 2$  stenotic lesions in the territory of major coronary artery, the maximal value among these lesions was analyzed. The coronary stenosis severity in the range 50-69 % was referred as «moderate» stenosis», and 70-90 % – «severe» stenosis [18]. Totally, 27 (21,9 %) patients presented with (maximal) moderate, and 96 (78,1 %) – severe coronary stenosis (at least, in a single major artery basin).

The extent and severity of coronary artery disease (CAD) was assessed with SYNTAX score [3]. The average SYNTAX score among the enrolled patients was 7 (4-12) points, varying from 1 to 31 points. The vast majority of the enrolled patients ( $n=121$  [98,4 %]) presented with mild CAD complexity (SYNTAX score  $\leq 22$  [3]), and 2 (1,6 %) patients – moderate CAD (SYNTAX score 23-32 [3]).

The FFR measurement was performed according to the standard practice [19, 20]. For the purpose of data analysis at patient level, we used the single patient's available FFR value, or the minimal one among the several ( $\geq 2$ ) available values per patient (FFRmin). Accordingly, in case of a single available FFR value, it was also considered as «FFRmin». The FFR  $\leq 0,80$  arbitrary units (a.u.) was considered as a hemodynamically significant [19, 20]. According to this cut-off value, 48 (65 %) patients presented with at least one hemodynamically significant lesion (FFRmin  $\leq 0,80$  a.u.) (including 2 patients with «borderline» FFRmin = 0,80 a.u.), and 26 (35 %) patients were free from such lesions (FFRmin  $> 0,80$  a.u.).

Aiming at the assessment of relationships between the studied parameters at patient level, we subdivided

the enrolled sample of patients according to the CCS classification [1], particularly the groups without angina ( $n=24$  [19,5 %]), and with angina CCS II ( $n=70$  [56,9 %]) and CCS III classes ( $n=29$  [23,6 %]).

For the purpose of data analysis at lesion level, we studied the available data from 238 coronary lesions, being localized in the LAD ( $n=111$  [46,6 %]), Cx ( $n=62$  [26,1 %]) and RCA ( $n=65$  [27,3 %]) territories. According to stenosis degree, the studied lesions were distributed as follows: 50-59 % – 58 (24,4 %); 60-69 % – 36 (15,1 %); 70-79 % – 88 (37,0 %); and 80-90 % – 56 (23,5 %). The data on functional significance were obtained from 128 (53,8 %) lesions: FFR  $> 0,80$  a.u. – 65 (50,8 %), and FFR  $\leq 0,80$  a.u. – 63 (49,2 %; including 7 lesions with «borderline» FFR).

A decision on index PCI was positive in 93 (75,6 %) patients (including 9 cases, where PCI was recommended, but had not been performed until the end of index hospitalization). Accordingly, an index PCI was judged not to be performed in 30 (24,4 %) patients.

We used the certain statistical software programs for the data analysis, namely Statistica v. 14.0.0.15 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), MedCalc v. 22.001 (MedCalc Software Ltd., Belgium), MedStat v.5.0 [21] and EZR 1.61. Quantitative variables were presented as Me (IQR), and qualitative ones – as absolute and relative (%) frequency (with the standard error of proportion ( $\pm \Delta\%$ ) and 95 % confidence interval (CI), as required). To compare the quantitative variables, we used Kruskal-Wallis H test with the following *post hoc* Mann-Whitney U-test (considering the Bonferroni correction). To compare the qualitative variables, we used the  $\chi^2$  test with *post hoc* Marascuilo-Liakh-Gurianov (MLG) procedure [21],  $\chi^2$  test for trend and Fisher's exact test (for «2x2» tables). The relationship between the quantitative variables was determined by the use of Spearman's rank coefficient of correlation ( $\rho$ ). A 2-tailed  $p < 0,05$  was considered statistically significant (considering the Bonferroni correction).

## RESULTS

At the patient level, the studied groups were comparable by the majority of clinical parameters (Table I). Besides, females were more frequent in the pooled group with stable angina [CCS II + III classes], as compared to patients without angina: 31/99 (31 %) vs. 2/24 (8 %), respectively ( $p=0,022$ ). Moreover, patients with angina CCS III class presented with less frequent history of PCI, in comparison to the pooled group [no angina + angina CCS II class]: 6/29 (21 %) vs. 43/94 (46 %), respectively ( $p=0,018$ ).

Table 1

**Baseline clinical characteristics of patients without and with stable angina of CCS classes II and III**

Parameters		No angina N=24	Angina CCS II class N=70	Angina CCS III class N=29	p
Age, years		61 (56-68)	66 (60-70)	63 (59-70)	0,116
Gender, n (%)	Males	22 (92)	48 (69)	20 (69)	0,074
	Females	2 (8)	22 (31)	9 (31)	
BMI, kg/m <sup>2</sup>		28,5 (24,3-31,4)	29,1 (26,5-32,7)	28,9 (27,6-31,6)	0,510
Obesity, n (%)		10 (42)	29 (41)	10 (35)	0,797
HTN, n (%)		22 (92)	67 (96)	28 (97)	0,671
History of MI, n (%)		15 (63)	29 (41)	12 (41)	0,177
History of PCI, n (%)		12 (50)	31 (44)	6 (21)	0,049
HF stage, n (%)	B	7 (29)	27 (39)	5 (17)	0,111
	C	17 (71)	43 (61)	24 (83)	
AF, n (%)		5 (21)	13 (19)	5 (17)	0,945
History of stroke/TIA, n (%)		2 (8)	13 (19)	5 (17)	0,496
DM, n (%)		5 (21)	18 (26)	7 (24)	0,890
PAD, n (%)		3 (12)	7 (10)	6 (21)	0,354
CKD, n (%)		4 (17)	9 (13)	5 (17)	0,813
COPD, n (%)		0	0	1 (3)	0,195

All three groups of patients were comparable by the studied laboratory parameters. Additionally, severe LVH was registered in 24 % (7 of 29 cases; 95 % CI [10-42 %]) of patients with angina CCS class III, being numerically (but non-significantly) more frequent than in the CCS class II group (8/70 (11 %); 95 % CI [5-20 %]; p=0,462),

and (significantly) more prevalent as compared to patients without angina (0/24; 95 % CI [0-8 %]; p=0,041).

The studied groups were also comparable by the total number of affected major vessel territories and overall CAD complexity (Table II).

Table 2

**Baseline ICA characteristics of patients without and with stable angina of CCS classes II and III**

Parameters		No angina N=24	Angina CCS II class N=70	Angina CCS III class N=29	p
CAD complexity (vessels), n (%)	1-vessel	15 (62)	37 (53)	14 (48)	0,847
	2-vessel	5 (21)	21 (30)	10 (35)	
	3-vessel	4 (17)	12 (17)	5 (17)	
SYNTAX score, points		5 (3-14)	8 (5-13)	6 (5-11)	0,112
Coronary stenosis (maximal) severity, n (%)	Moderate (50-69 %)	11 (46)	15 (22)	1 (4)	p <sub>1-3</sub> =0,002 p <sub>2-3</sub> =0,089
	Severe (70-90 %)	13 (54)	55 (78)	28 (96)	
In-stent restenosis, n (%)		3 (12)	7 (10)	5 (17)	0,604

At the same time, we revealed the opposite trends in the frequency of moderate and severe coronary lesions, at least of a single major vessel territory (decrease and increase, respectively), while enhancing the severity of angina pectoris (Table II; p<sub>trend</sub> <0,001).

Moreover, the cases of moderate lesions, namely with 60-69 % stenosis, were the most prevalent among patients without angina, and registered in 13 % of those with angina CCS class II (Fig. 1). In addition, the increase

of angina severity was associated with the numerical, but non-significant rise in the frequency of patients with at least one lesion of ≥80 % stenosis. However, the prevalence of (maximal) 70-79 % coronary stenosis cases did not demonstrate a significant trend along with the enhancing of angina severity. Finally, the angina CCS class III was almost entirely represented by the patients with severe coronary stenosis, with the cases of (maximal) stenosis ≥80 % being registered in more than a half of those patients (Fig. 1).

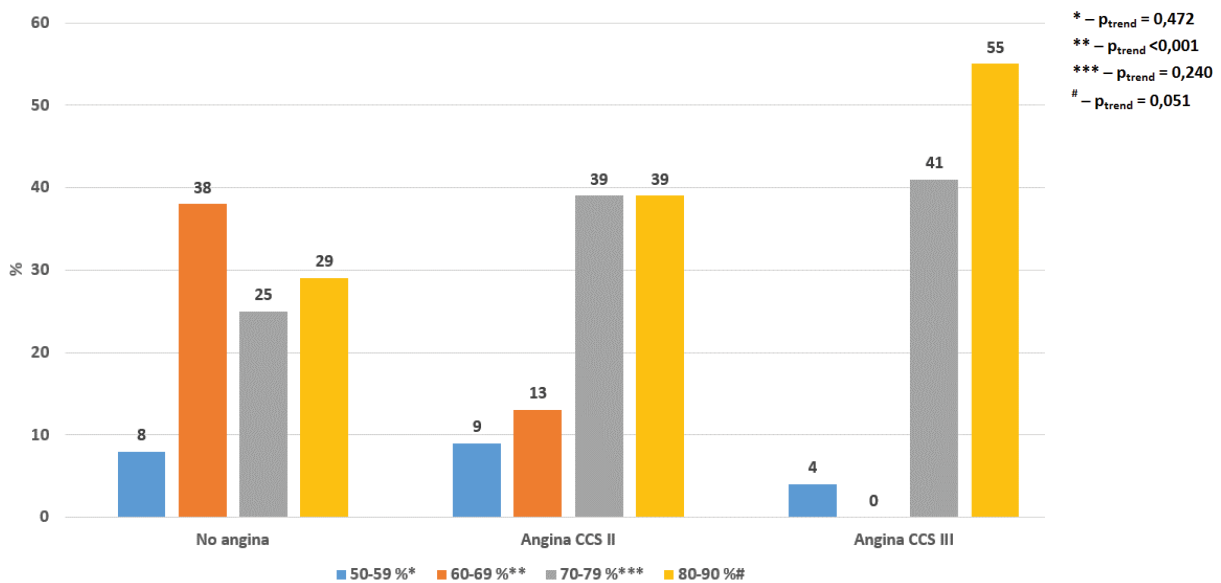
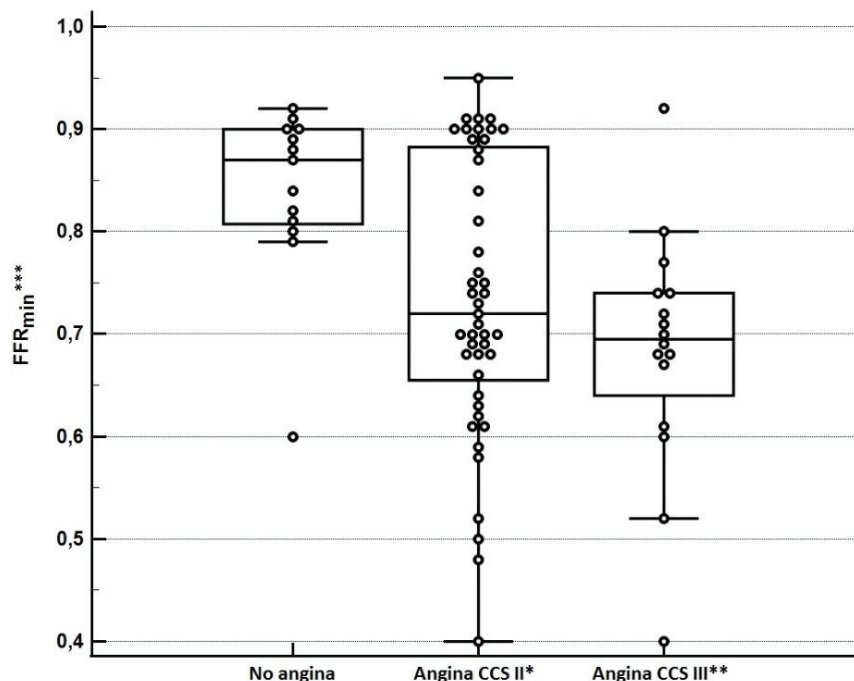


Fig. 1. The frequency (%) of maximal coronary stenosis patterns in patients without (N=24) and with angina CCS II (N=70) and III (N=29) classes

The analysis of functional data from 74 patients with concomitant FFR assessment revealed that the angina CCS class III group was characterized by the lower  $FFR_{min}$  (0,70 (0,64-0,74) a.u.;  $FFR_{min} \leq 0,80$  a.u.: 15 of total 16 cases), as compared to patients without angina (0,87 (0,81-0,90) a.u.;  $FFR_{min} > 0,80$  a.u.: 10 of total 13 cases) (Fig. 2). At the same time,  $FFR_{min}$  in patients with angina CCS class II (0,72 (0,66-0,88) a.u.)

was lower than that in patients without angina, but did not differ significantly from the corresponding average value in the angina CCS class III group (Fig. 2). It is noteworthy that the angina CCS class II group appeared to be represented by two distinct subgroups («clusters») of patients regarding  $FFR_{min}$  value ( $FFR_{min} > 0,80$  and  $\leq 0,80$  a.u.: 15 and 30 cases, respectively, of total 45) (Fig. 2).

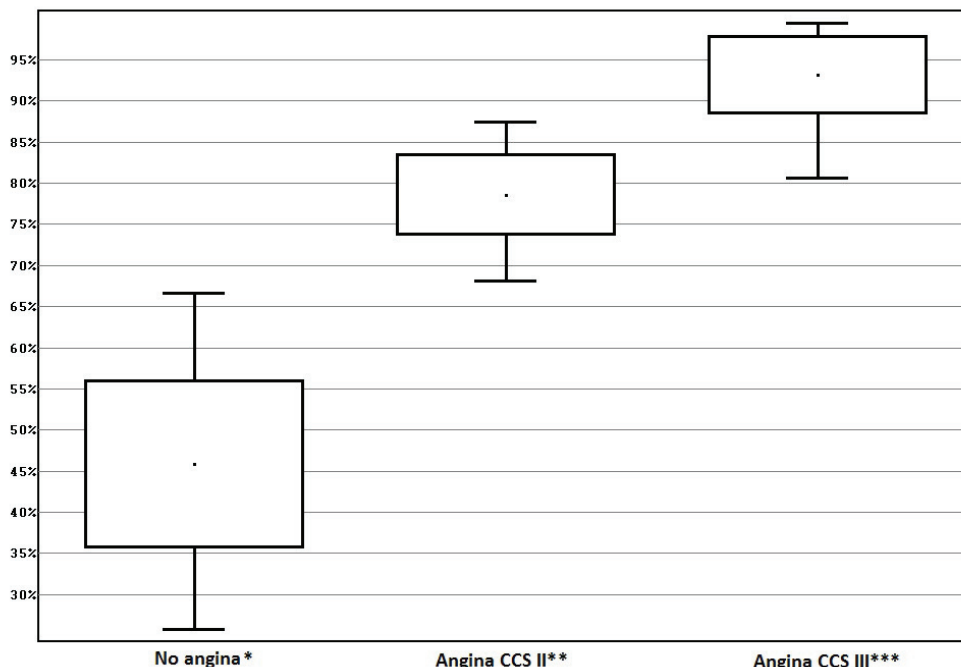


\* –  $p < 0,044$  (vs. no angina)  
 \*\* –  $p = 0,002$  (vs. no angina)  
 \*\*\* –  $FFR_{min} \leq 0,80 / > 0,80$  a.u. (cases): no angina – 3/10; angina CCS II – 30/15; angina CCS III – 15/1 ( $p_{trend} < 0,001$ )

Fig. 2.  $FFR_{min}$  in patients without (N=13) and with stable angina of CCS classes II (N=45) and III (N=16) (box-and-whisker and dot plots [all the data])

The decision to perform PCI was more frequent in patients with both angina CCS classes III (the vast majority of cases) and II, as compared to the patients without angina.

Of note, a PCI was judged not to be performed in slightly more than a half (54 %) of patients without angina, and in 21 % of patients with angina CCS class II (Fig. 3).



\* – Positive/negative decision: N=11 (45,8 % [95 % CI 25,8-66,6 %])/N=13 (54,2 % [95 % CI 33,4-74,2 %]); p = 0,028 (vs. no angina)  
 \*\* – Positive/negative decision: N=55 (78,6 % [95 % CI 68,1-87,5 %])/N=15 (21,4 % [95 % CI 12,5-31,9 %]); p < 0,001 (vs. no angina)  
 \*\*\* – Positive/negative decision: N=27 (93,1 % [95 % CI 80,6-99,4 %])/N=2 (6,9 % [95 % CI 0,6-19,4 %])

The trend:  $p_{trend} < 0,001$

Fig. 3. The positive decision on PCI (%±Δ%; 95 % CI) in patients without (n=24) and with angina CCS II (n=70) and III (n=29) classes

At the lesion-level, we revealed the degree of coronary stenosis to be strongly inversely correlated with FFR value ( $\rho = -0,795$ ;  $p < 0,001$  [n=128]), thus demonstrating a clear trend towards the progression of lesions' functional compromise along with the increase of their anatomical significance (Fig. 4). Noteworthy, the vast majority of moderate coronary lesions (stenosis 50-69 %) were hemodynamically non-significant. On the contrary, all the most advanced lesions (stenosis 80-90 %) appeared to be functionally compromised. In turn, the (60-69 %) lesions (n=24) were predominantly non-significant (19 of 24 [79 %]), but included 5 (21 %) significant ones. Finally, we observed a close to moderate negative correlation between FFR and the level of coronary stenosis ( $\rho = -0,483$ ;  $p < 0,001$  [n=44]) in the subsample of less compromised severe lesions (70-79 %) (n=44), being characterized by the presence of two relatively distinct opposite «clusters» with respect to their functional significance (28 (64 %) significant and 16 (36 %) non-significant lesions) (Fig. 4).

The lesion-level analysis (among all available lesions) demonstrated a clear trend towards more frequent decisions to perform PCI along increase of the coronary

lesion severity (Fig. 5). However, the alternative decisions were made in the particular proportion of patients with moderate (60-69 %) and more advanced (70-79 %) maximal coronary stenosis, namely regarding the PCI to be (25 %) or not to be performed (26 %), respectively (Fig. 5).

The decision not to perform PCI was undertaken in all 65 (100 %) cases of functionally non-significant (FFR >0,80 a.u.) lesions. At the same time, the PCI was considered to be performed in the vast majority of cases with functionally significant (FFR ≤0,8 a.u.) lesions (55 of 63 [87 %]).

The lesion-level study (among 128 (53,8 %) lesions with available functional data) revealed the predomination of decisions to perform PCI in the case of stenosis 80-90 %, or not to perform it in the case of moderate coronary lesions (Fig. 6). At the same time, the functional assessment of the (70-79 %) lesions favored the alternative decisions either to perform or not to perform PCI in 57 % and 43 % of cases, respectively (Fig. 6), reflecting the abovementioned functional «clustering» of this group (Fig. 4).

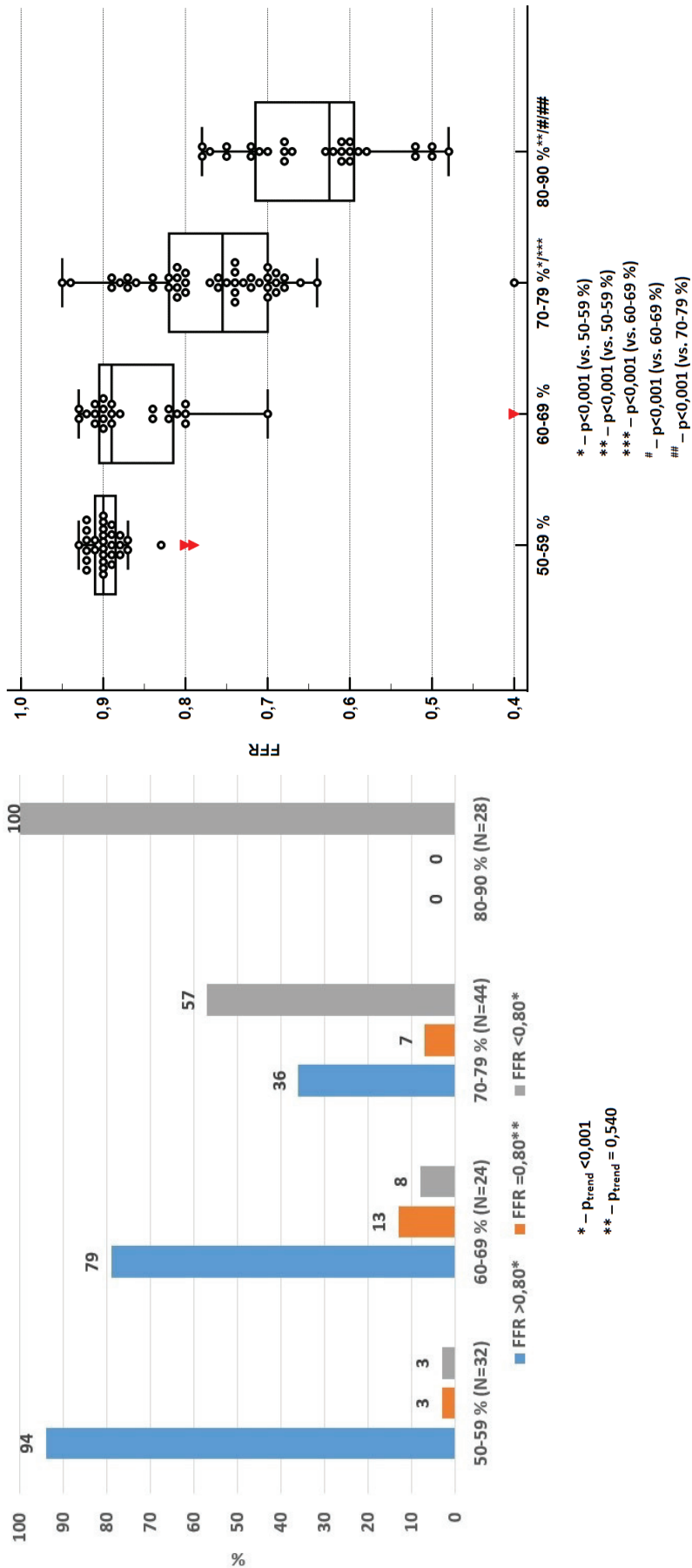
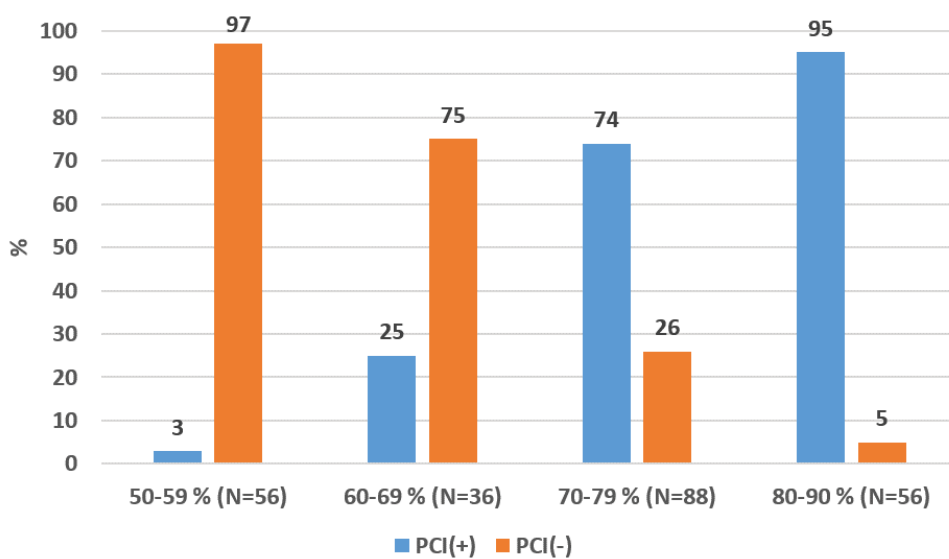


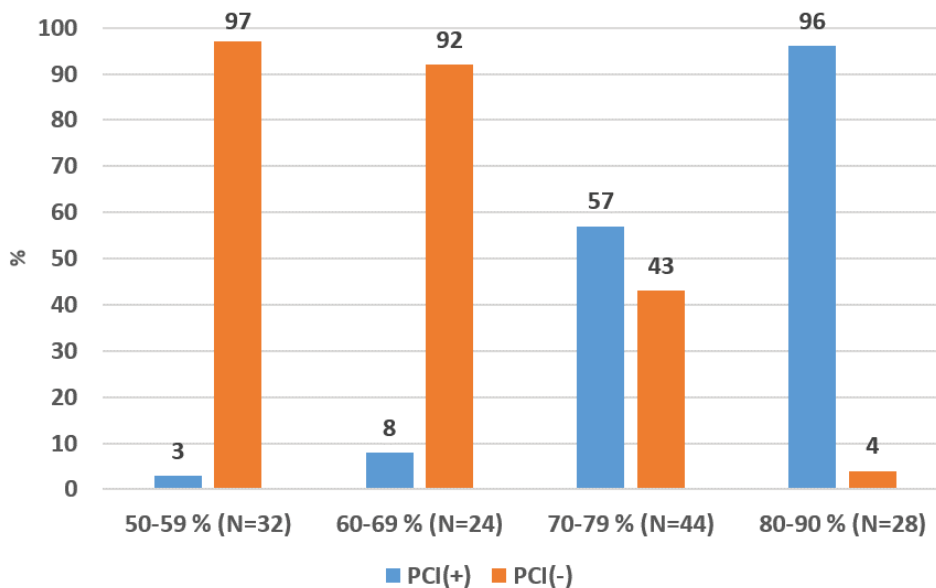
Fig. 4. (A) The hemodynamic patterns (%) of the coronary lesions with different degree of stenosis. (B) FFR in the groups of coronary lesions with different degree of stenosis (box-and-whisker and dot plots [all the data])



*p(%)	50-59%	60-69%	70-79%
60-69%	0,048	-	-
70-79%	<0,001	<0,001	-
80-90%	<0,001	<0,001	0,015

\* – The significance of difference (p[%]) between the studied groups  
 The trend:  $p_{trend} < 0,001$   
 PCI(+) – positive decision on PCI  
 PCI(-) – negative decision on PCI

Fig. 5. The decision regarding PCI (%) in the groups of coronary lesions with different degree of stenosis (all available lesions; n=236)



*p(%)	50-59%	60-69%	70-79%
60-69%	0,996	-	-
70-79%	<0,001	<0,001	-
80-90%	<0,001	<0,001	0,002

\* – The significance of difference (p[%]) between the studied groups  
 The trend:  $p_{trend} < 0,001$   
 PCI(+) – positive decision on PCI  
 PCI(-) – negative decision on PCI

Fig. 6. The decision to perform PCI (%) in the groups of coronary lesions with different degree of stenosis (the lesions with available functional data; n=128)



## DISCUSSION

According to the current guidelines, selection of SCAD patients for PCI should be based on comprehensive evaluation of clinical data, pre-procedural risk stratification, and the results of non-invasive anatomical and functional assessment [1-5]. However, the routine clinical practice is strongly influenced by a number of subjective and objective factors which is difficult to take into account in the revascularization guidelines [6, 7]. Hence, the results of randomized clinical trials (RCTs) should be supplemented by the real-world data, including those obtained from the high-volume centers specialized in invasive coronary procedures [9-11]. Such real-world studies are aimed at the analysis of factors, impacting the local practice of invasive procedures in SCAD patients and selection for PCI [8-12].

The appropriateness of myocardial revascularization in SCAD patients is mostly driven by the need to relieve the symptoms and/or to increase the patients' survival in particular anatomic lesions. In particular, the latter issue is related to the highly specific patient profiles, being selected by the presence of strictly pre-defined criteria of anatomic eligibility for PCI, left ventricular function, or by the results of myocardial ischemia burden assessment [1-5]. However, one should admit the substantially restricted availability of the facilities allowing for the imaging and quantitative assessment of myocardial ischemia in real-world settings [9-11, 15, 22]. In turn, the beneficial effect of revascularization upon SCAD symptoms could be mostly achieved in cases of typical and severe angina pectoris (or its equivalents), significantly worsening the quality of life, and, at the same time, being a basis for the ICA [1-7]. This aspect is fully matched with the decision to perform PCI in the vast majority of patients with angina CCS class III.

Nevertheless, there is a substantial proportion of patients with an intermediate pre-test probability of CAD, requiring a «clarifying» non-invasive diagnostic stage, namely anatomical (coronary computed tomography angiography) and/or functional (stress echocardiography, stress cardiac magnetic resonance imaging, single-photon emission computed tomography and positron emission tomography) tests, with the purpose to justify the need for ICA [1-5, 23, 24]. Such debatable patient profiles include the cases of angina CCS class II or doubtful cardiac pain, but with additional reasons for CAD evaluation to be performed. Considering that such patients predominated in the study sample, and due to the pre-specified exclusion criteria, one could explain the prevailed mild CAD complexity according to the SYNTAX score.

There are certain discrepancies in the current guidelines regarding the degree of «intermediate» stenotic lesions, at which FFR assessment is recommended when deciding on PCI [3, 4]. In particular, European experts indicate a rather wide range of lesions (stenosis 50-90 %), being positioned as «intermediate» [3], and which, in fact, became one of the inclusion criteria in the current study. However, in the ACC/AHA/SCAI guidelines, this

range covers only the lesions with 50-70 % stenoses [4]. Moreover, the data from earlier performed large-scale studies indicate a frequent mismatch between the severity of coronary stenoses and their functional significance [1].

According to the present study results, the «marginal» degrees of the «intermediate» stenoses spectrum (50-59 % and 80-90 %) were mainly homogeneous regarding their functional significance, leading, respectively, to the decision to perform PCI or not to do it. At the same time, both more advanced moderate (60-69 %) and less advanced severe stenoses (70-79 %), in particular proportion of cases, demonstrated borderline/significant (21 %) or borderline/non-significant (43 %) hemodynamic properties, respectively, which could impact on the alternative multidisciplinary decisions on PCI appropriateness.

There is a need to clarify the range of «intermediate» lesions, that should be prioritized in terms of evaluating their hemodynamic sequelae. It seems reasonable to «narrow» and «extend», respectively, the European [3] and American [4] approaches to the assessment of functional significance of «intermediate» coronary lesions, considering the likely heterogeneity of both moderate and severe stenoses in terms of their hemodynamic consequences, being demonstrated also in the present study (mainly in the range of 70-79 %). At the same time, the potential analysis of larger lesion-level data would allow to outline the expected functional «clustering» of various degrees of coronary stenosis, in particular of the lesions in the range of 60-69 %. In addition, one should account for the diagnostic performance of non-invasive coronary functional tests, being suitable for patients with intermediate pre-test probability of CAD [1-5, 13-15, 25, 26].

The obtained results reflect the real practice of decision-making regarding the PCI appropriateness in SCAD patients with angiographically intermediate (50-90 %) coronary lesions in a high-volume specialized center. In particular, a positive decision on PCI is justified in SCAD patients in the case of a typical and advanced angina pectoris (namely its CCS class III) [1-7]. The profile of those patients was also characterized by the presence of severe coronary lesions and, importantly, the prevailed cases of  $FFR_{min} \leq 0,80$  a.u. (with the lowest average  $FFR_{min}$ ). Besides, considering the existing evidence [19, 20], the lower average  $FFR_{min}$  was consistent with more frequent severe LVH observed in those patients.

At the same time, there is a need to clarify the factors leading to the choice of invasive procedures among the patients with less burdensome symptoms (regarded as angina CCS class II), and without typical angina attacks. These patients had either severe (mostly in case of angina CCS class II) or moderate (predominantly in patients without angina) coronary lesions, and demonstrated the broader spectrum of their worst functional significance (by  $FFR_{min}$ ). It should be noted that the presently observed hemodynamic «clustering» of patients with angina CCS

class II was, at least partially, related to the largest number of such cases in the enrolled sample.

The revealed anatomical and functional characteristics of patients without angina and with angina CCS class II determined the need for additional «non-invasive» examination of patients with doubtful or non-severe angina pectoris before decision on ICA. This is particularly important in patients after previous PCI, being currently observed more often in the groups without angina or with its CCS class II. In this setting one should benefit from assessment of intermediate coronary lesions functional significance, being applied either at non-invasive diagnostic step or at the moment of ICA [1-5, 23-28]. At the same time, as already mentioned, the decision to skip the non-invasive stage and proceed immediately to invasive procedures in patients with angina CCS class III is determined primarily by the presence of burdensome symptoms significantly limiting the quality of life.

The obtained results should be interpreted with several limitations, inherent to its retrospective, single-center design and modest sample size. The FFR data were available only in slightly more than half lesions. Furthermore, the different functional consequences of the (60-69 %) coronary stenoses might be more prominent in case of larger sample size and more extensive hemodynamic assessment. In addition, the strict patient selection should be considered, related not only to the enrollment of the cases with angiographically intermediate (50-90 %) coronary lesions, but also to the exclusion of patients being definitely suitable for surgical revascularization. Obviously, such a spectrum of exclusion criteria has led to the enrollment of patients with predominantly mild CAD complexity by the SYNTAX score. At the same time, similar methodological approaches to patient selection were, at least partially, implemented in a number of previously conducted large RCTs [6-8, 12], where the obtained results consequently delineated the broad spectrum of issues related to the appropriateness of ICA and myocardial revascularization among such relatively «non-severe» SCAD patients.

### CONCLUSIONS

Among the SCAD patients with angiographically intermediate (50-90 %) coronary stenosis, those with angina CCS class III were characterized by less frequent

previous PCI, significant decrease in FFR and the decision to perform an index PCI in the vast majority of cases. There is a need for more precise diagnosis and assessment of myocardial ischemia in patients with an intermediate pre-test obstructive CAD probability, including the cases of previously performed revascularization procedures.

### PROSPECTS FOR FUTURE RESEARCH

It is reasonable to perform a long-term prospective observation of the patients with intermediate coronary stenoses and stable angina CCS class II, including the changes in health-related quality of life, depending on the functional significance of the lesions and the decision to perform PCI.

### COMPLIANCE WITH ETHICAL REQUIREMENTS

The present study was conducted in accordance with the basic principles of the European Convention of Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulations. The study protocol was approved by the local ethics committee. The written informed consent was obtained from all the patients.

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The authors declare no conflict of interest related to this paper.

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*Резюме***КЛІНІЧНІ, АНГІОГРАФІЧНІ ТА ФУНКЦІОНАЛЬНІ ПАРАМЕТРИ, ЩО ВПЛИВАЮТЬ НА РІШЕННЯ ПРО РЕВАСКУЛЯРИЗАЦІЮ У ПАЦІЄНТІВ ЗІ СТАБІЛЬНОЮ ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ ТА ПРОМІЖНИМИ УРАЖЕННЯМИ КОРОНАРНИХ АРТЕРІЙ****Микола В. Стан<sup>1,2</sup>, Кирило О. Міхалєв<sup>3</sup>, Олег Й. Жарінов<sup>1,2</sup>, Андрій В. Хохлов<sup>2</sup>, Борис М. Тодуров<sup>1,2</sup>**

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**Мета:** дослідити клінічні, ангіографічні та функціональні характеристики пацієнтів зі стабільною ішемічною хворобою серця (ІХС) та проміжними ураженнями коронарних артерій, та визначити їхній зв'язок з ухваленням рішення про проведення перкутанних коронарних втручань (ПКВ) (аналіз у вибірці пацієнтів та у масиві уражень).

**Матеріали та методи.** У крос-секційному дослідженні включили 123 пацієнти (62±9 років; чоловіки – 73,2 %) зі стабільною ІХС та ангіографічно проміжними коронарними ураженнями (стеноз 50-90 %). Стабільна стенокардія напруження II функціонального класу (ФК) за класифікацією CCS (CCSII) була діагностована у 70 (56,9 %) пацієнтів, III ФК (CCSIII) – 29 (23,6 %); 24 (19,5 %) пацієнти – без стенокардії (БС). Фракційний резерв кровотоку («fractional flow reserve» [FFR]) визначили у 74 (60,2 %) пацієнтів (з оцінюванням min значення у пацієнта). Гемодинамічно значущим вважали ураження при  $FFR \leq 0,80$  у.о. Рішення про проведення ПКВ було ухвалено у 93 (76 %) пацієнтів. Додатково оцінили функціональні дані у масиві 128 коронарних уражень.

**Результати.** Група CCSIII характеризувалася більш рідкісними випадками раніше проведених ПКВ (21 % проти 46 % в об'єднаній групі [CCSII + БС];  $p=0,018$ ); домінуванням випадків (max) тяжкого (70-90 %) коронарного стенозу (96 % проти 78 % [CCSII] та 54 % [БС];  $p_{\text{trend}} < 0,001$ ); нижчим (min) значенням FFR ([медіана, квартилі] 0,70 (0,64-0,74) проти 0,87 (0,81-0,90) [БС];  $p < 0,002$ ); а також ухваленням рішення про проведення ПКВ у переважній більшості випадків (93 % проти 79 % [CCSII] та 46 % [БС];  $p_{\text{trend}} < 0,001$ ). Групи БС/CCSII/CCSIII демонстрували тренд щодо зниження частоти виявлення випадків (max) коронарного стенозу [60-69 %] (38 %, 13 % та жодного випадку, відповідно;  $p_{\text{trend}} < 0,001$ ), а також тенденцію щодо частішого виявлення випадків (max) коронарного стенозу [80-90 %] (29 %, 39 % та 55 %, відповідно;  $p_{\text{trend}} = 0,051$ ). Частота виявлення випадків (max) коронарного стенозу [70-79 %] була зіставною у групах порівняння (БС/CCSII/CCSIII: 25 %/39 %/41 %, відповідно [ $p_{\text{trend}} = 0,240$ ]). При аналізі у масиві коронарних уражень виявлено, що всі найтяжчі стенози [80-90 %] ( $n=28$ ) були гемодинамічно значущими. Своєю чергою, група стенозів [60-69 %] ( $n=24$ ) включала 5 (21 %) значущих уражень. Нарешті, група стенозів [70-79 %] ( $n=44$ ) включала 28 (64 %) значущих та 16 (36 %) незначущих уражень.

**Висновки.** При стабільній ІХС з ангіографічно проміжними ураженнями коронарних артерій, у пацієнтів зі стенокардією III ФК, поряд з менш частим проведенням ПКВ в анамнезі, відмічали значуще зниження FFR та схвалювали рішення про індексне ПКВ у переважній більшості випадків. Існує потреба у здійсненні ретельнішого діагностичного пошуку та оцінювання обсягу ішемії міокарда у пацієнтів з проміжною претестовою ймовірністю стенозуючих уражень коронарного русла, включаючи випадки раніше проведених ПКВ.

**Ключові слова:** ішемічна хвороба серця, реваскуляризація міокарда, коронароангіографія, фракційний резерв кровотоку