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Tailored treatment of specific diagnosis improves symptoms and quality of life in patients with myocardial Ischemia and Non-obstructive Coronary Arteries

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Ischemia and non-obstructive coronary arteries (INOCA) represents a challenging clinical scenario affecting a considerable proportion of patients undergoing coronary angiography. INOCA manifests with various pathomechanisms, including abnormalities in coronary microvessels and vasomotor disorders. INOCA patients experience substantial symptoms and heightened risk of adverse cardiac events. Guidelines outline diagnostic and treatment strategies, emphasizing tailored approaches for improved outcomes. This study aimed to evaluate symptoms and quality of life changes in INOCA patients following tailored treatment based on comprehensive diagnostic assessment of the coronary circulation. This is a single-center prospective registry of symptomatic adult patients diagnosed with INOCA. Comprehensive invasive physiological diagnostics including assessment of coronary microcirculation function and coronary artery reactivity were conducted. Clinical outcomes, angina severity (Canadian Cardiovascular Scale), and quality of life (SF-36 questionnaire) were assessed at baseline and after 12 months of tailored anti-angina treatment based on pathophysiological background. A total of 150 patients were enrolled. At baseline 8% of patients had angina CCS I, 70% CCS II and 22% CCS III. After 12 months 46% had no angina symptoms, 22% had angina CCS I, 26% CCS II and 6% CCS III. Following tailored treatment, angina severity significantly decreased ($p < 0.001$). The quality of life (SF-36 questionnaire) was significantly better after 12 months compared to baseline (66 [45; 103] vs. 91 [69; 115] points; $P < 0.001$). In this observational study, a proposed care pathway for patients with INOCA was presented. Despite the observational nature of the study, both symptoms and quality of life improved, underscoring the need for future prospective randomized controlled trials. Further research, including adequately powered sample sizes of patients is warranted to evaluate the influence of pathophysiology-tailored treatment of INOCA on long-term major cardiovascular events.

Keywords Angina, Coronary microcirculation, Coronary microcirculatory disease, INOCA, Physiological assessment, Quality of life, Vasospastic angina, Abnormal vasodilation, Abnormal vasoconstriction

Up to 70% of patients undergoing coronary angiography due to angina do not have significant lesions in the epicardial coronary arteries[1,2]. Confirmation of myocardial ischemia in non-invasive stress tests in this group leads to a working diagnosis of ischemia and non-obstructive coronary arteries (INOCA). This clinical situation is more frequently observed in female patients, estimated at approximately 65%[3]. Various pathomechanisms are responsible for ischemia in these patients[1]. Abnormal coronary flow reserve (CFR) and/or microcirculatory resistance index (IMR) may result from changes in the structure of coronary microvessels[4]. Vasomotor disorders can lead to microcirculatory or epicardial vasospastic angina[5,6]. It is noteworthy that different pathomechanisms may overlap and coexist[7,8]. Patients with INOCA experience significant symptoms, a decreased quality of life,

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more frequent rehospitalizations, unnecessary repeated coronary angiography, and, interestingly, higher risk of myocardial infarction and mortality[9,10]. The diagnosis of epicardial vasospastic angina is associated with a higher rate of major adverse cardiac events (MACE), including acute coronary syndromes, severe ventricular tachyarrhythmias, and death[11,12]. The management of INOCA patients, diagnostic pathways, and recommended treatment methods have been published in the European Cardiology Society (ESC) guidelines on chronic coronary syndromes and in an EAPCI Expert Consensus Document on Ischemia with Non-Obstructive Coronary Arteries[1]. Recent study results have demonstrated that tailored treatment based on specific, detailed diagnoses may lead to an improvement in the symptoms and quality of life of INOCA patients[13].

The aim of this study was to evaluate the influence of pathophysiology-tailored anti-angina treatment of patients with INOCA on clinical symptoms and quality of life at a 12-month follow-up.

Methods

Coronary Microcirculatory Disease and Inflammation in Patients with Chronic Coronary Syndrome And No Significant Coronary Artery Stenosis Study (MOSAIC-COR) was conducted as a prospective, observational registry of consecutive, adult patients with INOCA. A total of 150 symptomatic patients with chronic coronary syndrome and confirmed myocardial ischemia by non-invasive stress tests (myocardial perfusion imaging using single-photon emission computed tomography [SPECT] and exertion treadmill test [ETT]) were prospectively enrolled. INOCA was defined in accordance with ESC guidelines for chronic coronary syndromes without significant coronary artery stenosis (less than 40% diameter stenosis in epicardial arteries or Fractional Flow Reserve [FFR] > 0.8 and Resting Full-cycle Ratio [RFR] > 0.89)[14–16]. Patients with prior coronary revascularization, a life expectancy of less than 1 year, severe valvular pathology, or chronic heart failure with reduced ejection fraction were excluded from the study. The research protocol adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Medical Chamber in Krakow (application number 304/KBL/OIL/2019). The study is registered on ClinicalTrials.gov (Identifier NCT05313919), and all patients provided written informed consent.

Coronary angiography was preceded by the intracoronary administration of 200–500ug of nitroglycerin. Angiography was recorded approximately 60 s after nitroglycerin administration to ensure that maximum vasodilation had been achieved. For patients with non-obstructive coronary artery disease observed during angiography, complex functional coronary assessment and tests of coronary artery reactivity were performed. Physiological measurements were conducted using the PressureWire X (Abbott Vascular, Santa Clara, US) introduced into the distal part of the epicardial artery. Resting Full-cycle Ratio (RFR) was measured through three consecutive measurements. Stable hyperemia was induced by a constant intravenous infusion of adenosine at 140 μg/kg/min for a minimum of 120 s[17]. Fractional Flow Reserve (FFR) was measured under hyperemic conditions. Using the thermodilution method and Coroflow software (Coroventis, Uppsala, Sweden), the Index of Microcirculatory Resistance (IMR) and Coronary Flow Reserve (CFR) were determined[18,19]. Coronary artery reactivity was assessed through a provocative test with acetylcholine administered to the coronary artery in incremental doses according to the standardized protocol[20]. Clinical symptoms, epicardial spasms observed in angiography, and ischemic changes in the 12-lead ECG were evaluated throughout the examination[20]. A positive result in the provocative test led to the intracoronary injection of 100ug nitroglycerin to alleviate induced ischemia. During the invasive diagnostics, comprehensive patient monitoring was conducted, including symptom assessment, 12-lead ECG recording, direct blood pressure measurement, and oxygen saturation measurement to ensure procedure safety. The study adhered to the STROBE criteria for an observational cohort study[21,22]. The study was partially financed with an unrestricted scientific grant from Abbott Medical.

We categorized patients into four subgroups based on the ESC guidelines for the management of chronic coronary syndromes published in 2024:

1. Adenosine-mediated impaired vasodilation (AMIV) – characterized by negative result of artery reactivity test and an abnormal functional assessment, including increased IMR (≥ 25) or decreased CFR (< 2.0).
2. Abnormal vasoconstriction (AV) - identified by normal result of both IMR and CFR along with the presence of epicardial vasospasm (presence of symptoms and ischemic ECG changes as well as identified significant spasm [> 90% diameter] in coronary epicardial artery during provocative reactivity testing (epicardial subtype) or without significant spasm in coronary epicardial artery (microvascular subtype).
3. Mixed subtypes – overlapping of Adenosine-mediated impaired vasodilation and Abnormal vasoconstriction.
4. No coronary disorder – diagnosed when both the coronary reactivity test and coronary functional assessment yield normal results.

Moreover, endothelial dysfunction was defined as at least 20% reduction of vessel diameter in response to the acetylcholine intracoronary bolus.

Demographic and laboratory data

We gathered and confirmed demographic details, medical history, laboratory test outcomes, echocardiographic data, and medication records through face-to-face interviews and medical documents. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in square meters). Standard laboratory tests were assessed using an automated biochemistry analyzer.

Echocardiography

A trained physician conducted a two-dimensional transthoracic echocardiogram both at the beginning and before hospital discharge. All measurements were carried out following the recommendations of the American Society of Echocardiography and the European Association of Echocardiography[23].

Treatment

All patients were advised to make lifestyle modifications, including smoking cessation. Patients in the adenosine-mediated impaired vasodilation group were primarily treated with beta-blockers, with an emphasis on nebivolol. For patients diagnosed with abnormal vasoconstriction, treatment was based on non-dihydropyridine calcium channel blockers (non-DHP CCB), dihydropyridine calcium channel blockers (DHP CCB), and long-acting nitrates. Significant emphasis was placed on vasospastic pathology when treating patients with mixed subtypes. Statins and angiotensin-converting enzyme inhibitors, especially zofenopril, were considered for all patients.

Clinical outcome

The severity of angina was assessed using the Canadian Cardiovascular Scale (CCS). Patients' quality of life was evaluated using the SF-36 questionnaire[24]. All-cause death, myocardial infarction, stroke, coronary revascularization (PCI or CABG) and hospital readmission due to cardiovascular disease were defined as major adverse cardiac and cerebrovascular event (MACCE). Data was gathered at baseline and after 12 months.

Statistical analysis

Quantitative variables were presented as numbers and percentages. For qualitative variables with a normal distribution, mean values with standard deviations were provided, while for variables without a normal distribution, the median with standard deviation was used. Normal distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Chi-squared tests were employed to compare qualitative variables. A significance level of $P < 0.05$ was established as the threshold for statistical significance. Statistical analysis was conducted using SPSS Statistics version 26 (New York, US) and R-Studio, version 8.9 (Boston, US) packages.

Results

A total of 150 patients were enrolled, with 32% being male. Approximately 90% of them suffered from arterial hypertension and dyslipidemia. Other risk factors of cardiovascular diseases such as a history of smoking or diabetes, were observed in one-third part of the entire group. Moreover, 25% of patients had a diagnosis of hypothyroidism, and 5% had a diagnosis of chronic kidney disease. Table 1 shows general characteristics of the study group. 91.4% of patients has confirmed endothelial dysfunction.

	Overall
	***N* = 150**
Age, years	66 [59; 71]
Sex male, N (%)	48 (32)
BMI, kg/m^2	28.4 [25.3;32.4]
Medical history	
Arterial hypertension, N (%)	135 (90)
Dyslipidemia, N (%)	140 (93)
Diabetes, N (%)	46 (31)
Smoking, ever N (%)	47 (31)
Overweight/obesity, N (%)	114 (76)
Hypothyroidism, N (%)	38 (25)
Chronic kidney disease, N(%)	8 (5)
Laboratory results	
HGB, [g/dl]	13.6 [12.9; 14.4]
WBC, [10^3/ul]	7.4 [6.3; 8.4]
PLT, [10^3/ul]	238 [206; 272]
hsCRP, [mg/L]	1.30 [0.79; 2.75]
LDL, [mmol/L]	2.46 [1.88; 3.36]
eGFR, [ml/min/1.73 m^2]	79 [67; 89]
HbA1c, [%]	6.0 [5.6; 6.4]

Table 1. Baseline clinical data. Quantitative variables are presented as number (percentage), while qualitative variables as median (interquartile range). BMI – body mass index; eGFR – estimated glomelural filtration rate; HbA1c – glycated hemoglobine; HGB - hemoglobine; LDL – low density lipoprotein; PLT – platelets; WBC – white blood count.

91.4% of patients has confirmed endothelial dysfunction

At the time of enrollment, 70% of patients were classified as having angina class II according to the Canadian Cardiovascular Scale (CCS), 22% were class III, and 8% were class I. After 12 months of tailored treatment 46% of patients were free of angina, 22% had angina class I, 26% class II and 6% class III. After 12 months of tailored treatment, a significant reduction of angina severity was observed ($P < 0.001$). The composition of angina severity assessed at baseline and in the 12-month follow-up is presented in Fig. 1.

In the entire study group, the quality of life, as assessed by the SF-36 questionnaire, was significantly better after 12 months compared to baseline (66 [45; 103] vs. 91 [69; 115] points; $P < 0.001$) (Fig. 2).

At baseline, 72% of patients were treated with beta blockers, compared to 30% after treatment modification ($P < 0.001$). A significant increase in the use of non-dihydropyridine calcium channel blockers and nitrates were observed (6% vs. 65%, $P < 0.001$; 1.3% vs. 9.4%, $P = 0.003$, respectively). Moreover, significantly more patients were treated with zofenopril as a tailored treatment compared to baseline (25% vs. 2%; $P < 0.001$) (Table 2.)

In AMIV group, the general use of beta blockers and ACEIs was similar at baseline and during observation. However, a significant increase in the use of nebivolol and zofenopril was observed (22% vs. 71%, $P = 0.017$; 0% vs. 36%, $P = 0.04$, respectively).

In AV group fewer patients were treated with beta blockers (75% vs. 14%, $P < 0.001$), DHP-CCB (56% vs. 7%, $P = 0.02$) and ARB (25% vs. 18%, $P = 0.049$). Conversely, patients were more frequently treated with non-DHP CCB (7% vs. 88%, $P < 0.001$), statins (81% vs. 91%, $P = 0.018$) and zofenopril (5% vs. 25%, $P = 0.009$).

No significant treatment modifications were registered in non coronary disorder group.

In mixed AMIV + AV (epicardial subtype) group beta blockers were used less frequently (55% vs. 6%, $P < 0.001$). A more common use of non-DHP CCB (10% vs. 77%, $P < 0.001$), statins (68% vs. 94%, $P = 0.02$) and zofenopril (0% vs. 26%, $P = 0.005$) was observed.

In mixed AMIV + AV (microvascular subtype) group, a significant reduction in treatment with beta blockers was noted (77% vs. 32%, $P < 0.001$). Conversely, non-DHP CCB and zofenopril were used more frequently (7% vs. 61%, $P < 0.001$; 0% vs. 32%, $P < 0.001$, respectively).

Complete medical treatment data for the subgroups are presented in Fig. 3; Table 3.

During a 12-month observation period, one patient died from a non-cardiovascular cause, and fourteen patients were readmitted to the hospital for cardiovascular causes. There were no cases of myocardial infarction, stroke or coronary revascularization (PCI or CABG) recorded.

Discussion

The main findings of our observational analysis suggest that tailored treatment following comprehensive invasive diagnostics in the INOCA population appears to alleviate the severity of angina and may improve quality of life over a 12-month observation period. However, confirmation of these conclusions requires prospective, randomized controlled trials. The diagnosis of INOCA is associated with significant symptomatology and decreased quality of life[25,26]. Recent analyses have underscored the importance of comprehensive, invasive diagnostics in patient with angina and no obstructive coronary arteries[27]. It has been demonstrated that implementing tailored treatment according to specific diagnoses reduced angina severity in the INOCA population[28]. In CorMicA study researchers noted a significant reduction in angina assessed with Seattle Angina Questionnaire (SAQ) in both 6-month and 12-month observations[13,29]. An improvement of angina level according to the classic CCS classification was reported in patients diagnosed with CMD after a tailored treatment[30]. Strong evidence confirms a poor quality of life in INOCA patients[3,28]. This observation is more pronounced in the female population compared to males[31]. An association between quality of life measured using 36-Item Short-Form Health Survey (SF-36) and vascular endothelial function assessed with flow-mediated dilation in brachial artery has been reported[32]. To our best knowledge there is a lack of data on the improvement of quality of life described with SF-36 after tailored treatment in INOCA patients.

Moreover, it has been shown that patients with nonobstructive CAD have a higher risk of myocardial infarction and all-cause mortality compared to patients with no apparent CAD[9,33]. The association between coronary microcirculatory disease and poor long-term prognosis has been confirmed in patients with intermediate coronary artery stenosis[34]. Patients diagnosed with a vasospastic angina characterize worse long-term outcomes with a higher risk of acute coronary syndrome, severe ventricular arrhythmias and sudden cardiac death occurrence[35–37]. Noteworthy, the coincidence of vasospastic angina and increased microvascular resistance is associated with a poor prognosis[38]. There is scarce evidence on the improvement of long-term outcomes and reduction of MACE occurrence after tailored treatment in INOCA patients. Ongoing trials such as WARRIOR and PRIZE are expected to provide data on improved long-term prognosis in this group[39,40].

Calcium channel blocker and long-acting nitrates form the basis of treatment for vasospastic angina, while beta-blockers, especially nebivolol, are recommended for microvascular angina, with lifestyle modifications and management of cardiovascular risk factors on top of that as recommended by An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group[1]. New treatment strategies are being assessed to improve management of INOCA patients. Several antianginal agents, for instance trimetazidine, nicorandil, and ivabradine have been described as potentially efficient for the treatment of CMD[41,42]. Ranolazine has shown promising results for treatment of CMD, however further analyses are necessary[43,44].

A coronary sinus reducer is a novel antianginal therapy. Currently published data indicate its effectiveness in reducing angina symptoms in patients with CAD[45]. Interestingly, it has shown promising results in the treatment of patients diagnosed with CMD[46]. Several trials, such as COSIMA, Remedy Pilot and Mayo Study, are being conducted to evaluate efficacy of a coronary sinus reducer in INOCA patients.

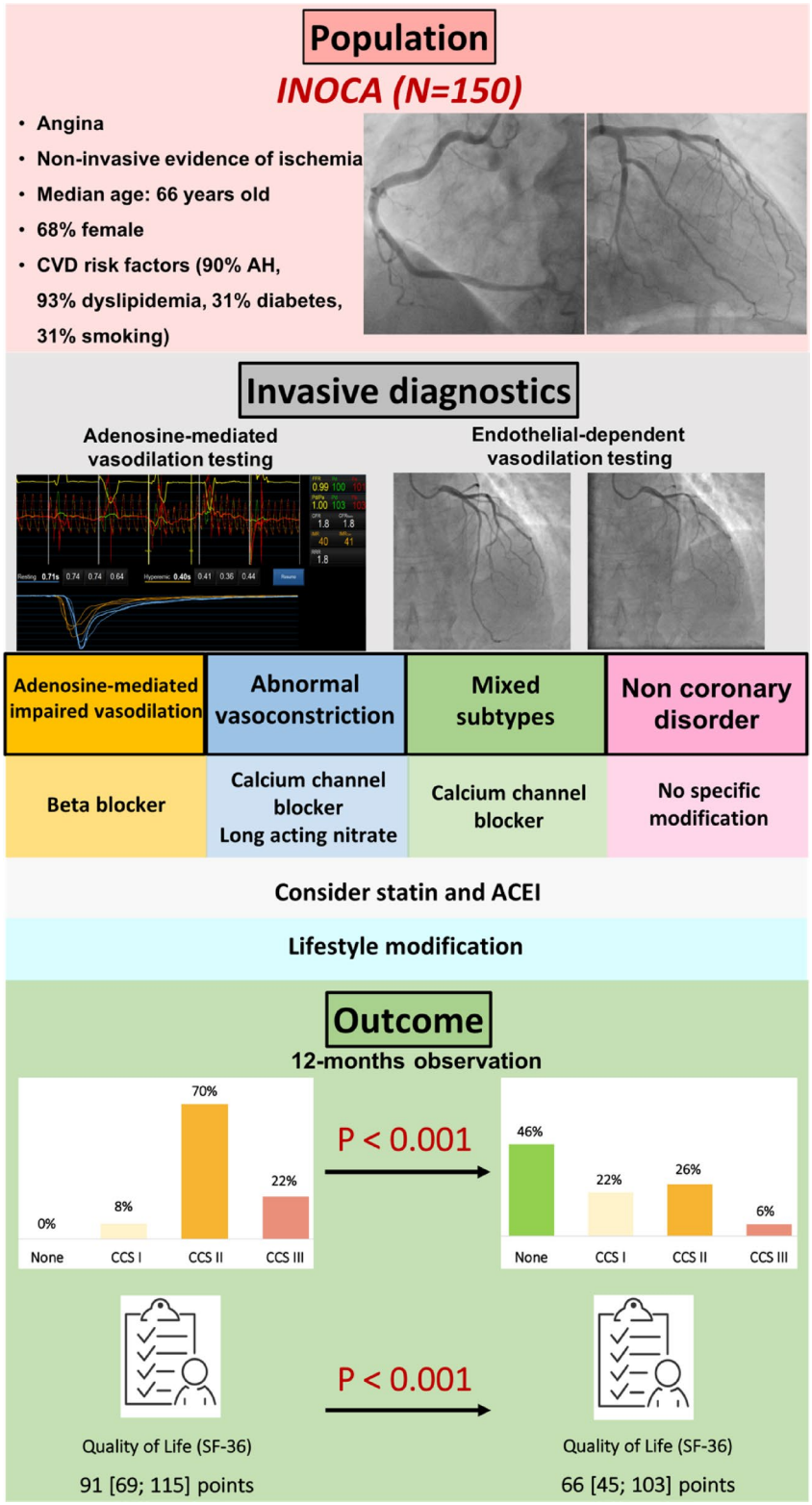

Fig. 1. Central illustration. Change of angina severity and quality of life at baseline and after 12 months observation. ACEI – angiotensin-converting enzyme inhibitor; CCS – angina severity according to Canadian Cardiovascular Scale; SF-36 - 36-Item Short Form Survey.

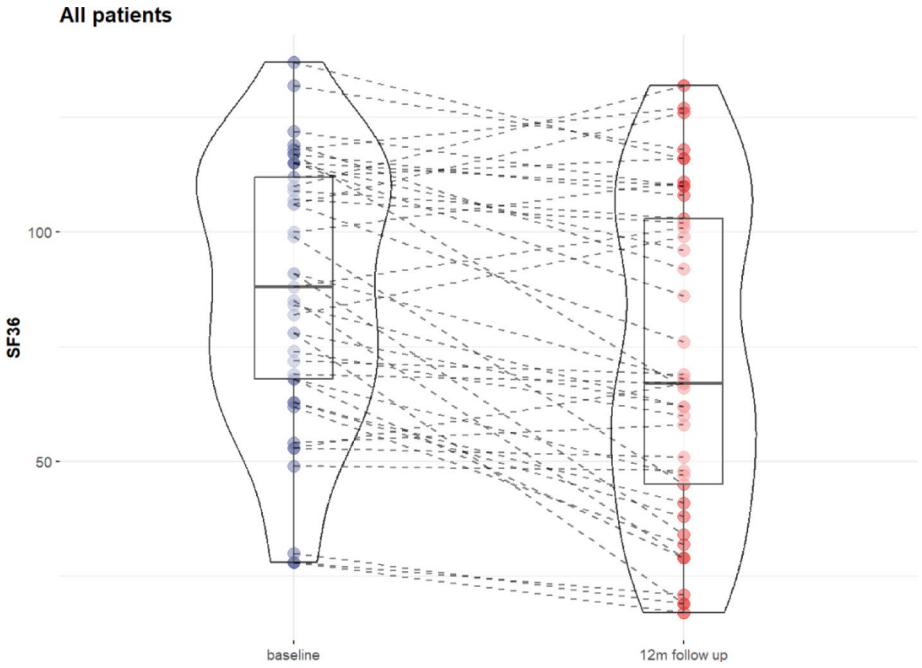

Fig. 2. Comparison of quality of life measured using SF-36 questionnaire at baseline and after 12 months observation. SF-36 - 36-Item Short Form Survey; 12m -12 months.

	Initial treatment	Treatment of specific diagnosis	*P* value
Beta blocker	108 (72)	45 (30)	< **0.001**
Nebivolol	23 (15)	26 (17)	0.75
Other beta blocker	85 (57)	19 (13)	< **0.001**
DHP CCB	54 (36)	46 (31)	0.42
Non-DHP CCB	9 (6)	97 (65)	< **0.001**
Nitrate	2 (1.3)	14 (9.4)	**0.003**
ACEI	62 (42)	82 (55)	0.095
Zofenopril	3 (2)	37 (25)	< **0.001**
Other ACEI	59 (39)	45 (30)	0.12
ARB	42 (28)	28 (19)	0.094
Statin	116 (78)	138 (93)	0.17

Table 2. Comparison of initial and tailored treatment in the study population. Quantitative variables are presented as number (percentage). ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; DHP CCB – dihydropyridine calcium channel blocker; Non-DHP CCB – non-dihydropyridine calcium channel blocker. Significant values are in [bold].

Thoracic sympathectomy is considered a potentially effective method of treatment in patients with refractory VSA[47]. Further research is needed to assess the efficacy of this method and its impact on long-term outcome in patients with VSA.

Study limitations.

First, this study was conducted using a single-center protocol. Second, it is an observational, cohort study without randomisation enabling comparison between the intervention and control groups. Nevertheless, there is scarce of data in the literature conforming the effectiveness of tailored treatment in INOCA patients, and the findings of this study are convergent with those of the CorMicA trial. Third, a single questionnaire was used to assess the quality of life. Fourth, the observation period lasted for 12 months. It would be beneficial to gather a larger sample and extend the observation period, particularly to evaluate the occurrence of MACCE.

Conclusions

In this observational study, a proposed care pathway for patients with INOCA was presented. Despite the observational nature of the study, both symptoms and quality of life improved, underscoring the need for future prospective randomized controlled trials. Further research, including adequately powered sample sizes of

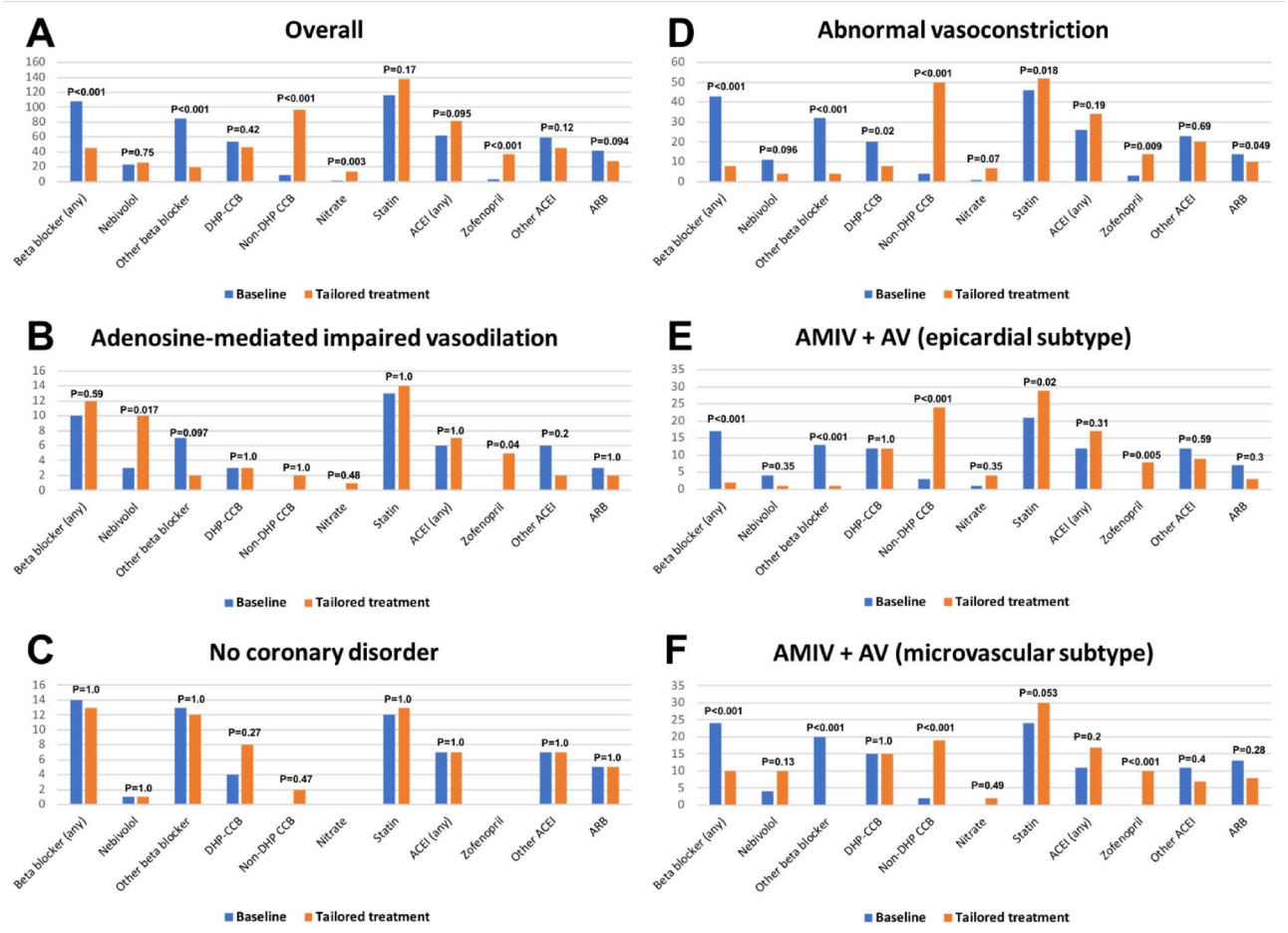

Fig. 3. Comparison of initial and tailored treatment in the study group and its subgroups. ACEI – angiotensin converting enzyme inhibitor; AMIV+AV - AMIV – adenosine-mediated impaired vasodilation and abnormal vasoconstriction (mixed subtype); ARB – angiotensin receptor blocker; DHP CCB – dihydropyridine calcium channel blocker; Non-DHP CCB – non-dihydropyridine calcium channel blocker.

patients is warranted to evaluate the influence of pathophysiology-tailored treatment of INOCA on long-term major cardiovascular events.

	AMIV			AV			No coronary disorder			AMIV + AV (epicardial subtype)			AMIV + AV (microvascular subtype)		
	N = 14			*N* = 57			*N* = 17b			*N* = 31			*N* = 31		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
Beta blocker (any)	10 (71%)	12 (86%)	0,59	43 (75%)	8 (14%)	**< 0.001**	14 (82%)	13 (76%)	1	17 (55%)	2 (6%)	**< 0.001**	24 (77%)	10 (32%)	**< 0.001**
Nebivolol	3 (21%)	10 (71%)	**0,017**	11 (19%)	4 (7%)	0,096	1 (5%)	1 (5%)	1	4 (13%)	1 (3%)	0,35	4 (13%)	10 (32%)	0,13
Other beta blocker	7 (50%)	2 (14%)	0,097	32 (56%)	4 (7%)	**< 0.001**	13 (76%)	12 (70%)	1	13 (42%)	1 (3%)	**< 0.001**	20 (65%)	0 (0%)	**< 0.001**
DHP-CCB	3 (21%)	3 (21%)	1	20 (35%)	8 (14%)	**0,02**	4 (24%)	8 (47%)	0,27	12 (39%)	12 (39%)	1	15 (48%)	15 (48%)	1
Non-DHP CCB	0 (0%)	2 (14%)	0,48	4 (7%)	50 (88%)	**< 0.001**	0 (0%)	2 (12%)	0,47	3 (10%)	24 (77%)	**< 0.001**	2 (7%)	19 (61%)	**< 0.001**
Nitrate	0 (0%)	1 (7%)	1	1 (2%)	7 (12%)	0,07	0 (0%)	0 (0%)	NA	1 (3%)	4 (13%)	0,35	0 (0%)	2 (7%)	0,49
Statin	13 (93%)	14 (100%)	1	46 (81%)	52 (91%)	**0,018**	12 (70%)	13 (76%)	1	21 (68%)	29 (94%)	**0,02**	24 (77%)	30 (97%)	0,053
ACEI (any)	6 (43%)	7 (50%)	1	26 (46%)	34 (60%)	0,19	7 (41%)	7 (41%)	1	12 (39%)	17 (55%)	0,31	11 (35%)	17 (55%)	0,20
Zofenopril	0 (0%)	5 (36%)	**0,04**	3 (5%)	14 (25%)	**0,009**	0 (0%)	0 (0%)	NA	0 (0%)	8 (26%)	**0,005**	0 (0%)	10 (32%)	**< 0.001**
Other ACEI	6 (43%)	2 (14%)	0,20	23 (40%)	20 (35%)	0,69	7 (41%)	7 (41%)	1	12 (39%)	9 (29%)	0,59	11 (35%)	7 (23%)	0,40
ARB	3 (21%)	2 (14%)	1	14 (25%)	10 (18%)	**0,049**	5 (29%)	5 (29%)	1	7 (23%)	3 (10%)	0,30	13 (42%)	8 (26%)	0,28

Table 3. Comparison of initial and tailored treatment in the subgroups. Quantitative variables are presented as number (percentage). ACEI – angiotensin converting enzyme inhibitor; AMIV – adenosine-mediated impaired vasodilation; ARB – angiotensin receptor blocker; AV – abnormal vasoconstriction; DHP CCB – dihydropyridine calcium channel blocker; Non-DHP CCB – non-dihydropyridine calcium channel blocker. Significant values are in [bold].

Data availability

The dataset collected and analyzed in this study is available from the corresponding author on reasonable request.

Received: 9 January 2025; Accepted: 13 May 2025
Published online: 30 May 2025

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Author contributions

P.S. contributed to design, acquisition, analysis, interpretation and drafted manuscript. B.G. contributed to conception, design and acquisition. Ł.N. contributed to acquisition, analysis and interpretation, drafted manuscript. P.K. contributed to acquisition, analysis, interpretation, drafted manuscript. A.B. contributed to acquisition, analysis. M.D. contributed to acquisition, analysis. M.S. contributed to acquisition, analysis. K.Ż. contributed to conception, design, interpretation. J.L. contributed to conception, design, acquisition, interpretation and drafted manuscript.All authors approved the final version to be published.

Funding

This article was supported by the science fund of the St. John Paul II Hospital, Cracow, Poland (SN/07/2025 to PS).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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