

PHARMACOLOGICAL MANAGEMENT OF PATIENTS WITH ANOCA IN BULGARIA: INSIGHTS FROM A SINGLE-CENTER REGISTRY

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ФАРМАКОЛОГИЧНО ЛЕЧЕНИЕ ПРИ ПАЦИЕНТИ С АНОСА В БЪЛГАРИЯ: ДАНИ ОТ ЕДНОЦЕНТРОВ РЕГИСТЪР

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Abstract.

Introduction: Angina with non-obstructive coronary arteries (ANOCA) is frequently encountered in clinical practice but remains poorly understood and inconsistently managed. Despite the absence of significant coronary stenoses, patients often report persistent symptoms and receive extensive pharmacotherapy. Real-world data on medication use and symptom burden in ANOCA populations remain limited. **Material and methods:** We conducted a single-center observational study of 102 patients referred to coronary angiography due to angina, who were subsequently found to have non-obstructive coronary artery disease. Baseline medication use and symptom severity were assessed using the Canadian Cardiovascular Society (CCS) classification and Seattle Angina Questionnaire (SAQ). Associations between treatment and symptoms were analyzed using non-parametric tests. **Results:** The mean age was 61 years; 59% were women. Over 90% of patients were on cardiovascular medications, with 22.6% receiving five or more agents. The most used therapies were β -blockers (59.8%), ACE inhibitors/ARBs (70.6%), and statins (58.8%). Despite this, 54.4% were in CCS class II or higher, and SAQ scores reflected persistent symptoms. No significant associations were found between drug class or medication count and symptom severity. Trimetazidine use was associated with slightly higher CCS class ($p = 0.032$). **Conclusion:** In this ANOCA cohort, pharmacotherapy was intensive but not clearly associated with symptom control. These findings highlight the need for individualized, endotype-guided treatment strategies.

Key words:

ANOCA, angina with non-obstructive coronary arteries, antianginal therapy

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Резюме.

Въведение: Ангина при липса на обструктивна коронарна болест (ANOCA) е често срещан клиничен проблем, който остава слабо разпознат и се характеризира с нееднороден диагностичен и терапевтичен подход. Въпреки липсата на значими стенози, пациентите често съобщават за персистираща симптоматика и са лекувани с интензивна комбинирана фармакотерапия. Данните от реалната клинична практика относно медикаментозното лечение и степента на контрол върху симптомите при тази популация остават ограничени. **Материал и методи:** Проведено е едноцентрово обсервационно проучване сред 102 пациенти, насочени за коронарна ангиография по повод ангинозна симптоматика, при които не са установени обструктивни коронарни лезии. Оценени са изходната медикаментозна терапия и тежестта на симптомите чрез класификацията на Canadian Cardiovascular Society (CCS) и Сиатълския въпросник за ангина (SAQ). Анализирани са връзката между лечението и тежестта на симптоматиката с помощта на непараметрични тестове. **Резултати:** Средната възраст е 61 години; 59% от пациентите са жени. Над 90% от пациентите са на медикаментозна терапия за сърдечно-съдови заболявания, като 22.6% приемат пет или повече медикамента. Най-често използваните медикаменти са β -блокери (59.8%), ACE инхибиторите/ARB (70.6%) и статините (58.8%). Въпреки това 54.4% от пациентите са класифицирани като II или по-висок функ

ционален клас по CCS, а резултатите от SAQ показват персистираща ангинозна симптоматика. Не са установени асоциации между вида или броя на медикаментите и тежестта на симптомите, с изключение на приема на триметазидин, който е асоцииран с по-висок CCS клас ($p = 0.032$). **Заклучение:** При изследваната кохорта бе установено, че фармакотерапията е интензивна, но не показва ясна връзка с контрола на симптомите. Получените резултати подчертават необходимостта от индивидуализиран терапевтичен подход, насочен към съответния ендотип.

Ключови думи:

ANOCA, ангина при липса на обструктивни коронарни лезии, антиангинозна терапия

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INTRODUCTION

Angina with non-obstructive coronary arteries (ANOCA) affects a substantial proportion of patients referred for invasive coronary angiography. Epidemiological data from trials such as WISE and iPOWER suggest that more than 50% of women and nearly one-third of men undergoing coronary angiography fall into the ANOCA category [1-3]. Despite the absence of hemodynamically significant epicardial stenoses, these patients often experience persistent angina, reduced quality of life, frequent hospitalizations, and elevated long-term cardiovascular risk [4, 5].

Patients with ANOCA are often misperceived as having a benign condition, leading to under-recognition and undertreatment. When therapy is initiated, pharmacological management remains largely empirical in most settings, due to the underlying pathophysiological heterogeneity and limited availability of functional coronary testing. Studies such as CorMicA demonstrated that an endotype-guided treatment strategy, based on invasive assessment of microvascular dysfunction and vasospasm, significantly improves symptoms and quality of life compared to standard care [6, 7]. Nevertheless, most patients globally are managed without access to such testing, and data on real-world therapeutic patterns remain scarce.

Trials like WARRIOR and iPOWER have further explored the impact of intensive or targeted medical therapy in ANOCA patients, with mixed results and persistent uncertainty about the optimal regimen for symptom control and prognostic benefit [7, 8]. Clinical guidelines endorse use of beta-blockers, ACE inhibitors, calcium channel blockers (CCB), statins and metabolic modulators, often extrapolated from data in obstructive CAD populations or small observational ANOCA cohorts [3, 5, 10].

In this context, we conducted a single-center observational study to examine pharmacological treatment patterns in patients with angina who were referred for invasive coronary angiography and subsequently found to have non-obstructive coronary arteries. We present contemporary data on medication use and symptom

severity measured by Canadian Cardiovascular Society (CCS) class and Seattle Angina Questionnaire (SAQ) score.

MATERIAL AND METHODS

Study design and setting

This was an observational, single-center study conducted at the Clinic of Interventional Cardiology, University Hospital “St. Marina” – Varna, between February 2023 and April 2025. The study was approved by the Ethics Committee of the Medical University of Varna and all participants provided written informed consent prior to inclusion. This analysis was conducted using the same patient cohort as a parallel study investigating the association between the indexed Time for Contrast to Pass through the Myocardium (iTCPM) and angina severity. While both studies draw on shared data, they address distinct research questions and outcomes.

Study population

A total of 102 patients with typical angina symptoms and non-obstructive coronary arteries (stenosis < 50%) on invasive coronary angiography were prospectively enrolled. Inclusion criteria were age over 18 years, clinical indication for coronary angiography, and provided written informed consent. Patients with prior myocardial infarction, coronary revascularization, valvular heart disease, atrial fibrillation, or elevated cardiac biomarkers were excluded. Functional coronary testing was not performed and patients were managed without endotype stratification.

Data collection

Clinical and demographic data were collected at the time of hospitalization. Cardiovascular risk factors, including age, sex, BMI, hypertension, dyslipidemia, diabetes, and smoking status, were recorded. Medication use was assessed at baseline, including antianginal agents (beta-blockers, CCB, nitrates, trimetazidine, ranolazine) and event prevention therapy (antiplatelet agents, statins, and ACE inhibitors/angiotensin recep-

tor blockers (ARBs)). The total number of concurrently prescribed medications was also noted.

Angina symptom severity was evaluated using the Canadian Cardiovascular Society (CCS) classification and the Seattle Angina Questionnaire (SAQ), translated in Bulgarian.

Transthoracic echocardiography was performed in all patients to assess left ventricular function and valvular pathology. Baseline laboratory data were collected, including lipid profile and renal function.

Statistical analysis

Descriptive statistics were used to summarize clinical characteristics and medication use. Continuous variables were presented as mean \pm standard deviation. Categorical variables were reported as absolute and relative frequencies.

Comparisons of CCS class and SAQ scores were performed between patients grouped by medication usage and total medication burden. The relationship between symptom severity, drug class and the number of medications was analyzed using the Kruskal–Wallis test and Mann–Whitney U test, as appropriate.

Statistical significance was defined as $p < 0.05$. Analyses were performed using Python (v3.10).

RESULTS

Patient characteristics

A total of 102 patients were included in the analysis. The mean age of the cohort was 61 years, and 59% were women. Arterial hypertension and dyslipidemia were the most common cardiovascular risk factors, each present in 94% of participants, followed by

current or past smoking (57%) and type 2 diabetes mellitus (22%). The average body mass index (BMI) was 30.5 kg/m², and the estimated glomerular filtration rate (eGFR) was 87 ml/min/1.73 m². The mean low-density lipoprotein (LDL) cholesterol level was 2.76 mmol/L.

Angina symptom severity, assessed by the CCS classification, showed that 54.4% of patients were in class II or higher. SAQ scores revealed considerable variability, with mean scores as follows: physical limitation – 61.85 \pm 15.08, angina stability – 25.74 \pm 19.09, angina frequency – 74.11 \pm 13.96, treatment satisfaction – 85.40 \pm 12.28, and disease perception – 34.15 \pm 19.14. All five SAQ scales deviated from normality based on the Shapiro–Wilk test (all $p < 0.05$).

Medication use in the ANOCA population

Beta-blockers were the most frequently prescribed antianginal agents (59.8%), followed by CCB (44.1%), trimetazidine (20.6%) and nitrates (16.7%). No patients were receiving ranolazine. Regarding background cardiovascular therapy, 70.6% were on an ACE inhibitor or ARB, 58.8% on statins, 22.5% on acetylsalicylic acid (ASA) and 7.8% were on clopidogrel.

Medication burden

Polypharmacy was common: 8.8% of patients were not taking any cardiovascular medications, while 15.7% were on monotherapy. Dual, triple, and quadruple therapy were reported in 14.7%, 16.7%, and 21.6% of patients, respectively. More than one-fifth (22.6%) were receiving five or more medications simultaneously, indicating a substantial pharmacologic burden in this population. The types and number of medications taken are shown in Figure 1.

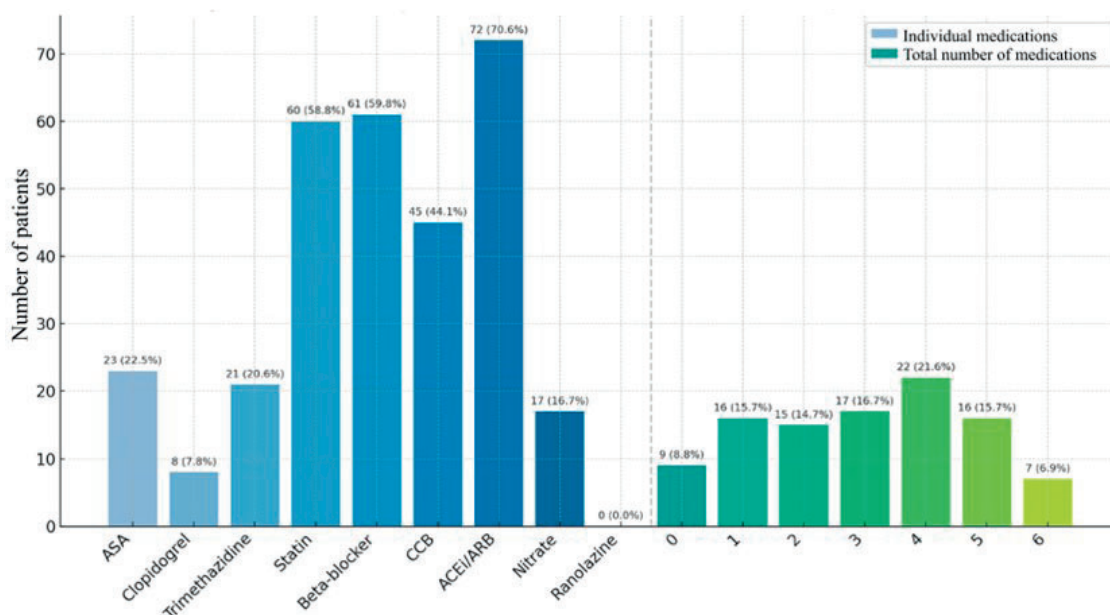


Fig. 1. Baseline distribution of cardiovascular medications in the ANOCA cohort by medication class and total number of agents

Medication use and symptom burden

The relationship between symptom severity and the number of medications was explored using both CCS class and SAQ scores. A non-significant trend toward more intensive pharmacotherapy with higher CCS class was noted: mean medication count ranged from 2.20 (CCS 0–I) to 3.43 (CCS II–III), but the difference did not reach statistical significance (Kruskal–Wallis $H = 5.786$; $p = 0.328$). No statistically significant associations were observed across all five SAQ scale scores (all SAQ scores $p > 0.05$). The results are shown in Table 1 and Table 2.

Table 1. Association between CCS class and total number of medications

CCS Class	Patients (n = 102)	Mean medication count	Standard deviation
0–I	10	2.2	1.87
I	23	2.78	1.98
I–II	13	3.08	1.5
II	24	3.42	1.53
II–III	21	3.43	1.69
III	11	2.45	1.86

Table 2. Association between SAQ scale scores and total number of medications

SAQ Scale	Kruskal–Wallis H	p-value
Physical Limitation	2.7704	0.5970
Angina Stability	4.5338	0.3386
Angina Frequency	1.6987	0.7910
Treatment Satisfaction	3.2515	0.5166
Disease Perception	0.5596	0.9674

To evaluate whether the use of specific medications was associated with differences in angina-related symptom burden, we performed Mann–Whitney U tests comparing both SAQ scores and CCS class between users and non-users of each medication class. No statistically significant differences were observed in any of the five SAQ scales, based on the use of aspirin, clopidogrel, β -blockers, calcium channel blockers, ACE inhibitors/ARBs, statins, nitrates, or trimetazidine (all $p > 0.05$).

Similarly, CCS class did not significantly differ between users and non-users of most medication classes, with the exception of trimetazidine. Patients taking trimetazidine had slightly higher CCS class scores compared to non-users (mean CCS class 2.10 vs. 1.69; $p = 0.032$). For all other medication classes, no statistically significant differences in CCS class were observed (all $p > 0.05$). Full results are provided in Supplementary Tables 1 and 2.

DISCUSSION

This study provides real-world insight into the pharmacological management of patients presenting with angina who were referred for invasive coronary angiography due to persistent symptoms, and subsequently found to have non-obstructive coronary artery disease. Despite the absence of significant stenoses, these patients had a substantial symptom burden and were already receiving extensive antianginal therapy at the time of referral. This highlights a common but often overlooked clinical scenario – the persistence of symptoms despite guideline-based treatment, even in the absence of obstructive disease.

The widespread use of cardiovascular medications in our cohort with over 90% of patients on treatment and nearly one-quarter receiving five or more agents illustrates the intensity of empiric therapy these patients receive before their coronary anatomy is known. The predominance of β -blockers, ACE inhibitors/ARBs, and statins reflects adherence to guideline-based approaches for angina and cardiovascular risk reduction. However, the relatively low use of second-line antianginal agents such as trimetazidine and ranolazine highlights ongoing uncertainty regarding optimal management strategies in this population. These prescribing patterns suggest that while treatment is often escalated in response to persistent symptoms, it is not endotype-guided and may remain insufficiently tailored to the specific pathophysiology of angina.

Despite the high medication burden, symptom control remained suboptimal, as reflected by SAQ scores and CCS class distribution. Importantly, there was no significant association between symptom severity and the number of medications used. These findings suggest that, in the absence of diagnostic clarity regarding the mechanism of angina, empirical treatment alone may be insufficient. The lack of a significant association between medication use and symptom burden may be in part confounded by treatment dynamics, as patients with more severe angina are more likely to receive intensified therapy, potentially improving their symptoms and thus obscuring a direct correlation.

In addition to the lack of correlation between medication burden and symptom relief, our findings further demonstrate that the overall angina burden in this cohort was comparable to that observed in patients with obstructive CAD. Mean SAQ scores for physical limitation (61.9 ± 15.1) and angina frequency (74.1 ± 14.0) were lower than those reported in ISCHEMIA (78.5–80.2 and 80.8–82.1, respectively) and similar to those in ORBITA (71.3–69.1 vs. 63.2–60.0) [11,12]. The CCS class distribution also reflected moderate to severe symptoms, with 43.7% of patients falling into class II or II–III and 10.7% in

class III. Taken together, these findings underscore the clinical relevance of ANOCA and challenge the assumption that non-obstructive disease equates to minimal risk or symptom burden.

Comparison with international ANOCA cohorts reinforces the therapeutic ambiguity and symptomatic burden observed in our population. In studies such as CorMicA, iPOWER, and WARRIOR, patients with non-obstructive coronary disease were prescribed high rates of β -blockers, ACE inhibitors/ARBs, and statins [7-9].

Of note, aspirin use in our study was considerably lower (22.5%) compared to CorMicA (86.8%) and WARRIOR (52.1%), possibly reflecting greater alignment with guidelines discouraging routine antiplatelet therapy for primary prevention. This variation also illustrates the ongoing uncertainty around antiplatelet use in ANOCA, particularly in light of emerging evidence suggesting limited benefit, or even harm in subgroups with vasospastic angina [13].

Calcium channel blockers were prescribed in 44.1% of patients, a higher rate than in iPOWER or WARRIOR, likely reflecting clinical judgment in the context of uncontrolled symptoms and comorbid hypertension. However, the literature suggests that calcium antagonists may be most effective in patients with epicardial vasospasm rather than isolated microvascular dysfunction, highlighting once again the importance of accurate phenotyping [10].

A key limitation of our study is the absence of functional coronary testing to differentiate ANOCA endotypes, meaning that although patients were carefully selected for invasive coronary angiography, it remains possible that in a small proportion the diagnosis may not truly represent ANOCA, reflecting real-world practice where most patients are managed empirically.

CONCLUSION

This study underscores the therapeutic uncertainty and variability that characterizes the management of patients with suspected ANOCA in the absence of clear mechanistic diagnosis. These patients are often treated empirically and many remain symptomatic despite polypharmacy. These findings highlight the need for individualized, endotype-guided treatment strategies.

No conflict of interest was declared

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