



Medication adherence in patients with stable coronary artery disease in primary care

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Abstract

Introduction: Lack of research targeting non-adherence to cardiovascular medications in Russia prevents from developing effective interventions to improve adherence. The aim was to study medication adherence in patients with stable coronary artery disease in primary care.

Material and methods: The study was conducted in a primary care setting of Moscow. Demography, medical history, pharmacotherapy data were obtained retrospectively from 386 coronary patients' medical records. Medication adherence was measured by 8-item Morisky Medication Adherence Scale (MMAS-8). A statistical analysis was performed using SPSS Statistics V16.0.

Results and discussion: According to the results from MMAS-8, 188 (48.7%) coronary patients had high medication adherence, 135 (35.0%) – moderate, and 63 (16.3%) – low. By the dichotomous interpretation: 48.7% (n = 188) – were adherent, 51.3% (n = 198) – were non-adherent. These groups were similar in gender distribution, age, and medical history profile ($p > 0.1$ for all variables). Smokers prevailed in the non-adherent group (13.6 vs. 5.3%; $p = 0.009$). Both groups were equally prescribed beta-blockers, antiplatelets, and statins ($p > 0.1$ for all). Use of fixed dose combinations (11.7 vs. 5.6%; $p = 0.048$) and the number of pills taken (mean 5.64 ± 1.52 vs. 5.99 ± 1.62 ; $p = 0.029$) were associated with better adherence. Higher values of total cholesterol (mean 5.2 ± 1.4 vs. 4.7 ± 1.2 mmol/L; $p < 0.001$) and low-density lipoprotein cholesterol (mean 2.9 ± 1.2 vs. 2.4 ± 0.9 mmol/L; $p < 0.001$) were revealed in non-adherents. Subjects with suboptimal adherence visited general practitioners more frequently (median 5 vs. 3 visits; $p = 0.003$).

Conclusion: Medication non-adherence in coronary outpatients exceeded 50%. High adherence was associated with more frequent use of fixed dose combinations and fewer pills taken by patient. Smoking and poorer control of blood lipids prevailed in non-adherents, who also caused higher load on general practitioners.

Keywords

coronary artery disease, medication adherence, Morisky scale, primary care.

Introduction

The famous quote of American surgeon Dr. C. Everett Coop – “Drugs don’t work in patients who don’t take them” (1985) – has become especially relevant over the recent years to highlight an important role of adequate medication adherence in effective pharmacotherapy. Developed countries have already built upscale healthcare systems, so a further increase in pharmacological performance strongly depends on improvement of patient adherence to evidence-supported medications. The global nature of this problem was first raised by The World Health Organization back in 2003 stating that “adherence to long-term therapy for chronic illnesses in developed countries averages 50%. In developing countries, the rates are even lower” (De Geest and Sabate 2003).

According to later studies, medication adherence in patients with coronary artery disease (CAD) is on average 30–70% (Chowdhury et al. 2013; Chen et al. 2015). Such a situation was described as «non-adherence pandemic» (Kolandaivelu et al. 2014). Meanwhile, there is enough evidence that poor adherence is associated with unfavorable clinical outcomes (Du et al. 2015; Lenzi et al. 2017) and higher treatment costs (Bitton et al. 2013) in CAD patients.

In the Russian outpatient care practice, adherence to cardiovascular medications is far from being optimal, and this issue lacks proper scientific attention (Bochkareva et al. 2019). It seems difficult to develop and implement effective interventions to improve adherence without such information. So, the aim of this research was to study medication adherence in patients with stable CAD at the primary care level.

Material and methods

The study was conducted in a large outpatient healthcare facility of Moscow city as part of the Pharmacoepidemiologic Quality Improvement Program of Pharmacotherapy of Stable CAD in Primary Care. The study was approved by the Ethics Committee of this medical institution. At the first stage, 2000 medical records of cardiologic patients treated at the facility were randomly selected. Out of this sample, 805 outpatient records were included into a retrospective analysis in line with the following criteria: age 30 years and older, verified CAD, non-participation in any ongoing clinical trial. The following data were obtained: demographics, medical histories including any documented cardiovascular behavioural risk factors, available results of laboratory tests (lipid profile and glycemic status), pharmacotherapy prescribed to patients by cardiologists, and additional medication maintenance statuses. The information on the number of visits to the cardiologist and general practitioner over the twelve-month period was also collected.

At the second stage, the assessment of medication adherence in coronary patients was conducted. The 8-item Morisky Medication Adherence Scale (MMAS-8) was used

to measure adherence. The patients were interviewed via telephone. Patient self-report tools (questionnaires, scales) are broadly used for exploring adherence to cardiovascular medications because they are inexpensive, simple, and quite accurate (Shi et al. 2010; Culig and Leppée 2014; Nguyen et al. 2014). One of such self-report tools is Morisky scale (4-item or 8-item), which was originally developed and validated in patients with arterial hypertension. The 8-item version has better validation parameters compared with the 4-item scale: internal consistency reliability (described by Cronbach’s alpha) 0.83 vs. 0.61, sensitivity 0.93 vs. 0.81, specificity 0.53 vs. 0.44. It also has strong correlation with validation criteria (Morisky et al. 1986, 2008). Interpretation of MMAS-8 was performed in a standard way. The patients were asked to answer questions 1–7 as “yes” (0 points) or “no” (1 point), except question 5, which was scored the opposite. Question 8 had a five-point Likert response scale and was scored 1 point for the answer “never”. Summing up the points, adherence was assessed as low (less than 6 points), moderate (6–7 points) or high (8 points). The simplified dichotomous interpretation of MMAS-8 (adherent – 8 points, non-adherent – less than 8 points) was also used (Tan et al. 2014).

The data from the medical records and questionnaires were transferred to patients’ case report forms. The study database was constructed in MS Excel. Statistical data processing was performed using IBM SPSS Statistics V16.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean (M), standard deviation (SD), first (Q1), second (median, Q2) and third (Q3) quartiles. Categorical variables were expressed as frequencies and percentages. Significance of the differences between the groups was estimated by standard statistical tests (two-sided). Independent *t*-tests for two independent samples were used for continuous variables distributed approximately according to the normal law; Wilcoxon rank-sum tests were used for continuous variables not distributed approximately according to the normal law. Kolmogorov-Smirnov normality tests were used to check the normality of distribution. Chi-square tests were used for categorical variables. The level of statistical significance was set at $p < 0.05$.

Results and discussion

Data from 386 patients with established stable CAD who gave full and unambiguous replies to all MMAS-8 questions were included into the analysis. According to MMAS-8 scoring, 188 coronary patients had high medication adherence, 135 – moderate, and 63 – low (Fig. 1).

It is notable that in the outpatient cardiovascular registry “PROFILE” the researchers also measured medication adherence ($n = 130$) by MMAS-8 tool. The results revealed that 40.8% of patients had high adherence, 36.9% – moderate, and 22.3% – low (Lukina et al. 2018). But the population was different in some variables, like age and medical history profile from the one described in this study.

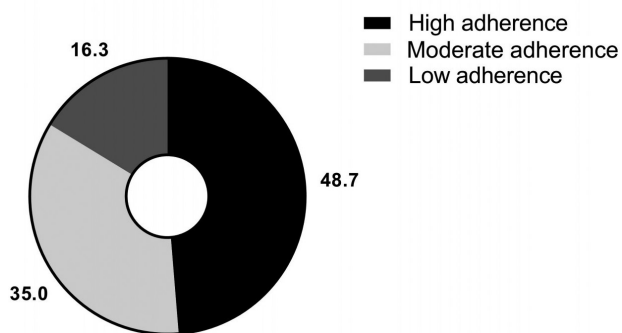


Figure 1. Medication adherence in patients with stable coronary artery disease (n = 386).

The detailed analysis of non-adherent patients’ responses to specific questions MMAS-8 revealed signs of unintentional non-adherence due to forgetfulness (Fig. 2A), which could be expected with regard to the age profile of the study population (mean age 68.9 ± 9.9 years; share of patients ≥ 65 years – 66.8%). However, quite a large number of patients turned out to have intentional non-adherence due to feeling worse (34.2%) or better (31.7%) when taking the prescribed medications (Fig. 2B). Almost one-third of the participants felt hassled about sticking to their treatment regimens. The investigators of the “PROFILE” registry mentioned above reported 23.5% and 23.6% of the patients were prone to breaking the recommended treatment plan when feeling worse or better, respectively (Lukina et al. 2018).

Besides, it seemed interesting to analyze the responses of moderately adherent patients, who were kind of “one step” away from being highly adherent. What prevented them from making this “step”? It turned out the intentional non-adherence was the first to “be blamed” for that (Fig. 3). It is important to pay specific attention

to this finding because it makes the primary direction of possible interventions to improve medication adherence obvious. Analyzing the type of non-adherence is crucial as it should be addressed in different ways, like educational and physician-focused activities to modify intentional non-adherence or behavioral patient-focused strategies to target unintentional non-adherence.

The dichotomous interpretation of MMAS-8 was applied for further analysis. The patients with moderate and low adherence formed the group of non-adherents (51.3%). Such a distribution partly matches available Russian data concerning outpatients with arterial hypertension and CAD, treated at Moscow primary care facilities. According to that data, 61.1% of patients had poor medication adherence (≤ 3 points by 4-item Morisky scale). Yet, the target population was younger, and prevalence of CAD was less than 50% (Fofanova et al. 2017).

The category of patient-related factors of non-adherence is most well studied by now. But there is still no single opinion on this issue. Among possible predictors of poor adherence to cardiovascular medications, the following were mentioned: younger and older age, male sex, low level of income, smoking, forgetfulness due to cognitive disorders, distrust of a healthcare provider, lack of faith in successful treatment outcome, etc. (Warren et al. 2013; Kolandaivelu et al. 2014; Khatib et al. 2019).

First, the groups of adherent and non-adherent patients were compared in respect to the demographic and medical history data (Table 1). The number of male subjects was similar in both groups. No statistically significant differences were identified in prevalence of concomitant conditions, so the groups were comparable in respect to the medical history profiles.

Unfortunately, it appeared to be difficult to analyze prevalence of cardiovascular risk factors in adherent and

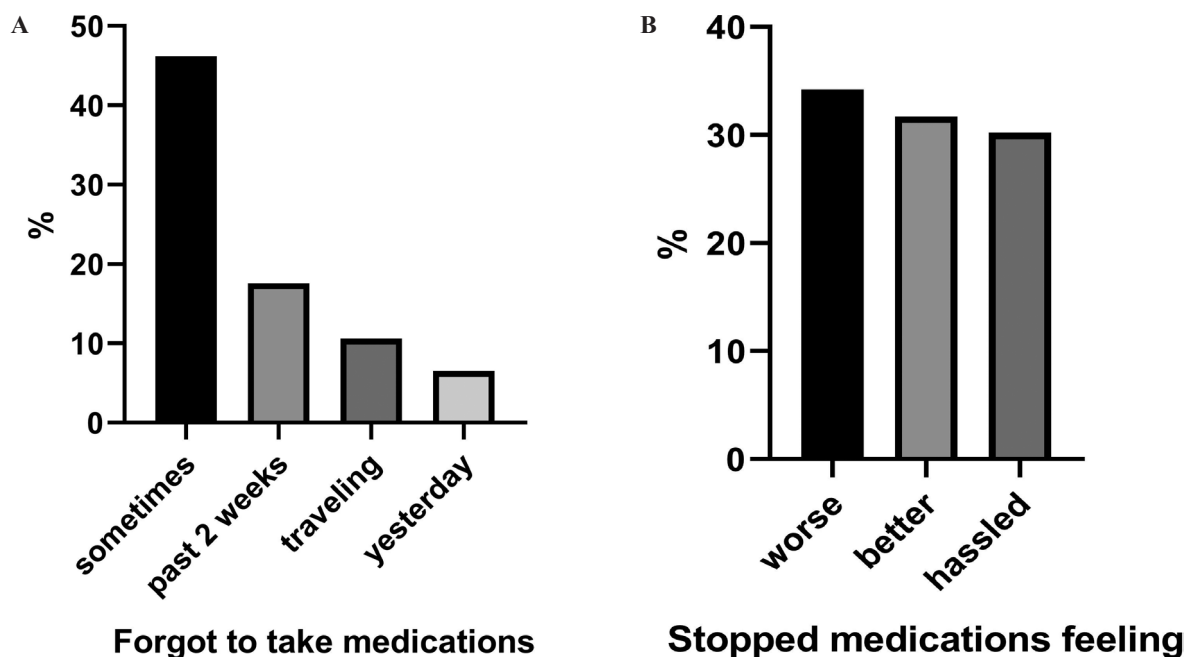


Figure 2. Reasons of unintentional (A) and intentional (B) non-adherence among non-adherent patients (n = 198).

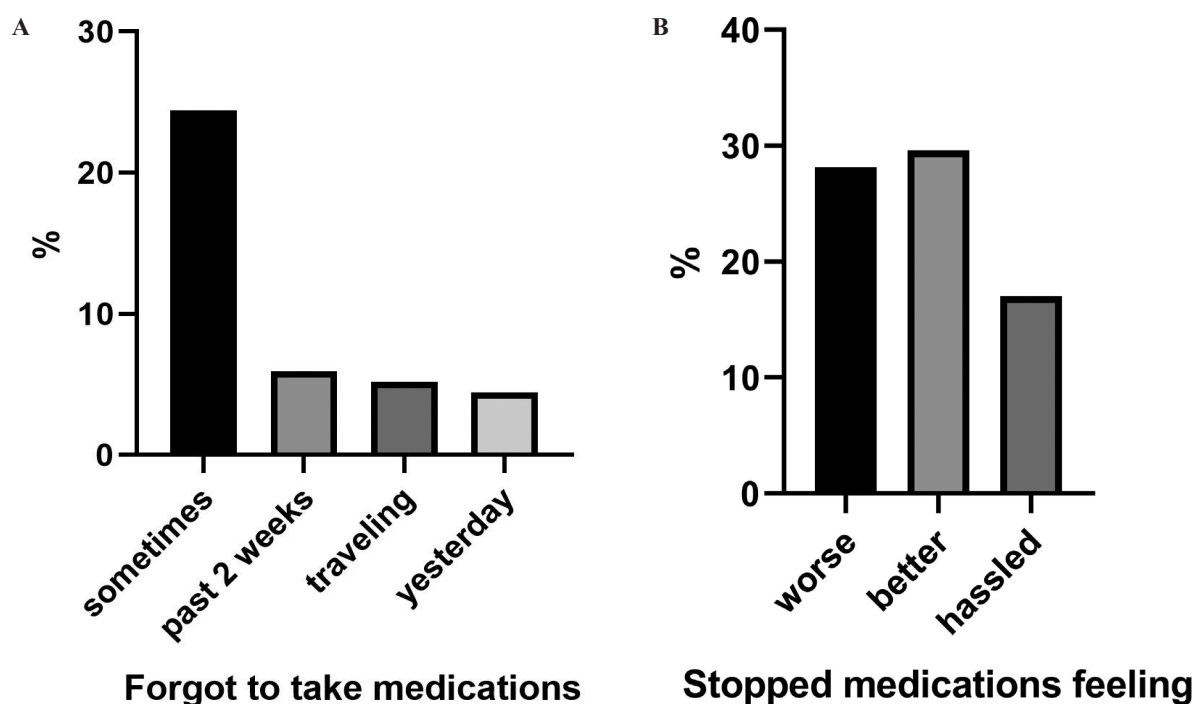


Figure 3. Reasons of unintentional (A) and intentional (B) non-adherence among moderately adherent patients ($n = 135$).

Table 1. Demographics and Medical History Profile of Adherent and Non-adherent Patients with Stable Coronary Artery Disease.

Variable	Adherent (n = 188)	Non-adherent (n = 198)	<i>p</i>
Gender:			
Male, n (%)	66 (35.1)	72 (36.4)	0.797
Female, n (%)	122 (64.9)	126 (63.6)	
Age (years),	69.9 ± 8.9	70.4 ± 9.2	0.909
M ± sd (Q1, Q2, Q3)	(64, 70, 77)	(63, 70, 78)	
Myocardial infarction, n (%)	86 (45.7)	87 (43.9)	0.721
Revascularization, n (%)	80 (42.6)	75 (37.9)	0.349
Stable angina, n (%)	128 (68.1)	142 (71.7)	0.437
Arterial hypertension, n (%)	174 (92.6)	185 (93.4)	0.734
Chronic heart failure, n (%)	168 (89.4)	175 (88.4)	0.760
Atrial fibrillation, n (%)	54 (28.7)	66 (33.3)	0.385
Diabetes, n (%)	44 (23.4)	44 (22.2)	0.782
Dyslipidemia, n (%)	31 (16.5)	37 (18.7)	0.571
Chronic kidney disease, n (%)	40 (21.3)	33 (16.7)	0.248

non-adherent patients due to the low registration rate of such information in medical records. Only a smoking status was an exception. So, 3-time higher prevalence of smoking was identified in the group of non-adherent patients (13.6 vs. 5.3%; $p = 0.009$). The possible explanation here could be the “healthy adherer effect”, which describes the association of better medication adherence with a patient’s healthier lifestyle (Gehi et al. 2007; Ladova et al. 2014).

Another key factor of medication adherence is the quality of prescribed pharmacological treatment (Lukina et al. 2017). Therefore, the next step was to compare the pharmacotherapy patterns of adherent and non-adherent coronary patients in regard with prescription rates of relevant medications (Table 2). The positive aspect was that almost all the patients were recommended drugs to prevent thrombosis. Prescription rates of oral anticoagulants (OACs) correlated with prevalence of atrial fibrillation. The tendency ($p = 0.079$) to higher rates of OACs in non-adherent patients was revealed. It might be explained by high costs

Table 2. Pharmacotherapy Patterns of Adherent and Non-adherent Patients with Stable Coronary Artery Disease.

Variable	Adherent (n = 188)	Non-adherent (n = 198)	<i>p</i>
Beta-blockers, n (%)	144 (76.6)	156 (78.8)	0.605
Calcium channel blockers, n (%)	87 (46.3)	91 (46.0)	0.950
Long-term nitrates, n (%)	18 (9.6)	10 (5.1)	0.087
Antiplatelet agents, n (%)	135 (71.8)	133 (67.2)	0.323
Oral anticoagulants, n (%)	58 (30.9)	78 (39.4)	0.079
Statins, n (%)	159 (84.6)	166 (83.8)	0.843
ACE [†] inhibitors, n (%)	93 (49.5)	82 (41.4)	0.112
ARBs [‡] , n (%)	82 (43.6)	92 (46.5)	0.574
ACE [†] inhibitors or ARBs [‡] , n (%)	175 (93.1)	173 (87.4)	0.060
Fixed dose combinations, n (%)	22 (11.7)	11 (5.6)	0.048
Number of pills taken,	5.64 ± 1.52	5.99 ± 1.62	0.029
M ± SD (Q1, Q2, Q3)	(2, 6, 10)	(2, 6, 12)	

Note: [†]angiotensin-converting enzyme; [‡]angiotensin II receptor blockers.

of these medicines (above 70% of patients were on novel OACs) and a risk of bleeding. Statins were prescribed to 84.2% ($n = 325$) of participants with similar rates in adherents and non-adherents. Renin-angiotensin-aldosterone system (RAAS) inhibitors were recommended to 90.2% ($n = 348$) of the patients. No statistical significance was identified in prescription rates of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) between the groups. However, there was an obvious tendency ($p = 0.060$) to the association of RAAS inhibitors intake with better adherence, possibly, due to a rather favorable safety profile of these medications.

The first line medications – beta-blockers – were justifiably top recommended (77.7%, $n = 300$) among anti-anginal drug therapies. Long-term nitrates were used only in 7.3% ($n = 28$) of cases. And calcium channel blockers were prescribed to 46.1% ($n = 178$) of patients. The patterns of anti-anginal pharmacotherapy were similar in adherent and non-adherent subjects. The only exception was

nitrates having the tendency ($p = 0.087$) to association with better adherence.

The proven strategy to improve a patient's adherence is to prescribe fixed dose combinations (Castellano et al. 2014; Fuller et al. 2017). Unfortunately, such an approach was applied only to 8.5% ($n = 33$) of participants. This must be admitted as a negative sign considering the results of comparison between the groups. The use of fixed dose combinations was associated with higher adherence ($p = 0.048$). Besides, the number of pills taken by a patient was less in the adherent group ($p = 0.029$), which partly confirmed the role of polypharmacy as an important predictor of non-adherence. Furthermore, the study by Khatib et al. (2019) demonstrated that the number of medicines taken by coronary patients ($n = 503$) was an independent predictor of intentional non-adherence (odds ratio 1.18; 95% CI 1.07–1.31).

Thus, the groups of adherent and non-adherent patients with stable CAD turned out to be similar in demographics, medical history profiles and pharmacotherapy patterns, which made it especially interesting to compare the results of cardiovascular risk factors management between these groups. In that regard, the available clinical and laboratory data were analyzed (Table 3). The groups were similar in body mass index. Mean figures of blood pressure also were comparable, although this might be explained by the fact that the patients followed physician recommendations more precisely shortly before the visit to the cardiologist (Feinstein 1990). The studied groups were similar in the glycemic status and some parameters of the lipid profile (triglycerides, high-density lipoprotein cholesterol). However, the levels of total cholesterol and low-density lipoprotein (LDL) cholesterol were higher ($p < 0.001$) in non-adherent patients.

The final task of this research was to calculate the number of visits to the cardiologist and general practitioner over the twelve-month period and define the prevalence of additional medication maintenance in adherent and non-adherent coronary patients (Table 4). So, the participants from the both groups were visiting cardiologists with the same frequency, probably due to comparable severity of their cardiological medical histories. But non-adherent patients needed to visit general practitioners more often ($p = 0.003$), which might be a sign of more frequent complaints and episodes of feeling unwell. The status of additional medication maintenance provided no better adherence. The study by Fofanova et al. (2017) revealed no association either between the additional medication maintenance status and adherence in outpatients with arterial hypertension and CAD.

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Table 3. Modifiable Risk Factors in Adherent and Non-adherent Patients with Stable Coronary Artery Disease.

Variable	Adherent (n = 188)	Non-adherent (n = 198)	p
Body mass index (kg/m ²), M ± SD (Q1, Q2, Q3)	29.6 ± 4.8 (26.2, 29.3, 32.6)	29.3 ± 4.6 (26.3, 29.2, 32.1)	0.788
Systolic blood pressure (mm Hg), M ± SD (Q1, Q2, Q3)	135 ± 18 (120, 130, 141)	134 ± 20 (120, 130, 150)	0.588
Diastolic blood pressure (mm Hg), M ± SD (Q1, Q2, Q3)	79 ± 9 (70, 80, 80)	78 ± 10 (70, 80, 80)	0.380
Total cholesterol (mmol/L), M ± SD (Q1, Q2, Q3)	4.7 ± 1.2 (3.7, 4.5, 5.4)	5.2 ± 1.4 (3.6, 5.0, 5.8)	<0.001
LDL ⁺ cholesterol (mmol/L), M ± SD (Q1, Q2, Q3)	2.4 ± 0.9 (1.8, 2.2, 2.8)	2.9 ± 1.2 (1.9, 2.5, 3.5)	<0.001
Triglycerides (mmol/L), M ± SD (Q1, Q2, Q3)	1.7 ± 0.9 (1.0, 1.4, 2.0)	1.9 ± 1.5 (1.0, 1.4, 2.1)	0.755
HDL ⁺ cholesterol (mmol/L), M ± SD (Q1, Q2, Q3)	1.4 ± 0.3 (1.1, 1.4, 1.6)	1.3 ± 0.3 (1.2, 1.4, 1.5)	0.706
Glycosylated hemoglobin (%), M ± SD (Q1, Q2, Q3)	6.9 ± 1.4 (6.1, 6.6, 7.3)	6.9 ± 1.2 (6.3, 6.6, 7.1)	0.677
Fasting plasma glucose (mmol/L), M ± SD (Q1, Q2, Q3)	6.7 ± 3.1 (4.7, 5.3, 7.5)	6.1 ± 1.5 (5.1, 5.6, 6.6)	0.710

Note: ⁺low-density lipoprotein; ⁺high-density lipoprotein.

Table 4. Use of Primary Care Facility Resources by Adherent and Non-adherent Patients with Stable Coronary Artery Disease.

Variable	Adherent (n = 188)	Non-adherent (n = 198)	p
Visits to cardiologist, median (Q1, Q3)	3.5 (2, 7)	4 (2, 8)	0.376
Visits to general practitioner, median (Q1, Q3)	3 (1, 7.25)	5 (2, 9)	0.003
Share of patients that visited general practitioner, n (%)	146 (77.7)	175 (88.4)	0.005
Share of patients that had additional medication maintenance, n (%)	96 (51.1)	101 (51.0)	0.992

Conclusion

The prevalence of medication non-adherence in patients with stable CAD at a primary care setting was more than 50%. Patient's age and sex, medical history profile and pharmacotherapy pattern were not associated with better or worse adherence. High adherence was related to the use of fixed dose combinations and to fewer cardiovascular medications taken by the patient. Smoking and poorer control of blood lipids (total cholesterol and LDL cholesterol) prevailed in non-adherent patients, who also caused a higher load on general practitioners. An additional medication maintenance status had no influence on medication adherence of coronary patients. Further local research is needed to address this serious problem.

Conflict of interest

The authors have neither funding nor support to report. The authors have no competing interests to declare.

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