

Clinical outcomes of newly diagnosed, stable angina patients managed according to current guidelines. The ARCA (Arca Registry for Chronic Angina) Registry: A prospective, observational, nationwide study

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ARTICLE INFO

Keywords:

Stable angina
Chronic coronary syndromes
Stable ischemic heart disease
Myocardial ischemia
Percutaneous coronary intervention
Appropriateness

ABSTRACT

Background: Clinical outcomes of stable angina patients treated according to guidelines recommendations (medical therapy first, selective revascularization in high risk or unresponsive patients) are not fully known.

Methods and results: Eight hundred thirty-three patients with newly diagnosed, stable angina were enrolled in a prospective, observational, nationwide registry and followed for 1 year. Symptoms and quality of life were evaluated with the CCS angina grading, with a self-assessment scale and with the SAQ-7. A composite end-point of MACEs (all-cause death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina) at 1 year was considered. Upon enrollment, all patients were prescribed guidelines directed medical therapy. After one month of therapy, angina relieved or improved in 47% of the overall population. Patients in CCS class I significantly increased from 28.4% at enrollment to 67.1% at 12 months, and the SAQ-7 score from 58.4 ± 20 to 85.9 ± 14 . The rate of MACEs was low (2.9%) in the overall population. After one month of medical therapy, 40.6% of patients were referred for coronary angiography and revascularization for resistant symptoms (invasive strategy). Among these, 38.2% had normal coronary arteries and 47% actually underwent revascularization. No difference between invasive and medical groups was found at 12 months in symptoms, quality of life and MACEs, except for a greater improvement in self-assessed symptoms in the invasive group. Combined medical and invasive strategies left 28.5% of patients still symptomatic at the end of the study.

Conclusions: The study confirms the efficacy and safety of a tailored approach to stable angina, as recommended by guidelines, with medical therapy first followed by selective revascularization when needed.

1. Introduction

For decades, the approach to myocardial ischemia has been dictated by the assumption that this condition is closely linked to obstructive coronary artery disease (CAD). More recently, ischemic heart disease

(IHD) has been acknowledged to be a complex clinical syndrome, associated with a number of mechanisms, including fixed or dynamic coronary stenosis, coronary vasospasm, microvascular, endothelial and metabolic dysfunction [1,2]. Given the disappointing impact of revascularization on prognosis of stable patients [3], recently confirmed by

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¹ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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<https://doi.org/10.1016/j.ijcard.2022.01.056>

Received 17 January 2022; Received in revised form 24 January 2022; Accepted 26 January 2022

Available online 1 February 2022

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the ISCHEMIA trial results [4], current guidelines recommend to consider invasive coronary angiography (ICA) and revascularization in high-risk patients or when unacceptable angina persists despite optimal medical therapy (OMT) [5]. The latest European Society of Cardiology (ESC) Guidelines on chronic coronary syndromes confirm that OMT is crucial for improving symptoms and preventing adverse cardiovascular events and should be the initial treatment in all angina patients [6]. Myocardial revascularization should be considered on top of medical therapy, without replacing it, in high-risk patients and in those with refractory angina [6]. This recommendation is often disregarded in daily practice and many patients are referred for ICA and revascularization just when the diagnosis of angina pectoris is suspected [7,8].

This common attitude is partially justified by a number of knowledge gaps in the guidelines recommendations and by the limited information on the clinical outcomes of medically managed patients. In particular, it is not well known: how effective is OMT in controlling symptoms; which is the prevalence of obstructive CAD in patients with angina refractory to medical therapy; and which is the rate of major adverse cardiovascular events (MACEs) in newly diagnosed angina patients initially treated with medical therapy.

ARCA Registry is a prospective, observational, nationwide study designed and conducted by the Italian Scientific Society A.R.C.A. (Associazioni Regionali Cardiologi Ambulatoriali) with the purpose to collect information on: severity of symptoms and quality of life in newly diagnosed, stable angina patients treated according to guidelines recommendations; prevalence of refractory angina; prevalence of coronary anatomy suitable for revascularization in patients with refractory angina; MACEs within one year from study inclusion [9].

2. Methods

ARCA Registry is a non-profit, independent study entirely financed by the Obiettivo Cuore Onlus Foundation and conducted by the A.R.C.A. Scientific Society, with the purpose to assess the impact of a guidelines dictated management of stable angina pectoris on symptoms, quality of life and MACEs. The investigators, representative of all Italian regions (see the Appendix), participated in the study on a voluntary, non-profit basis. Two investigator meetings have been held and a series of congresses and webinar offered the opportunity to monitor the study and discuss the interim and final results.

A.R.C.A. cardiologists practice mainly in an outpatient setting. Each investigator was encouraged to enroll patients from his elective activity, in order to select a population as representative as possible of current practice. Patients presenting in emergency conditions have not been considered for the study. Investigators were free to institute and carry on patients' care at their best judgement, to initiate the medical treatment they thought most appropriate and to refer patients for non-invasive investigations and invasive procedures whenever they deemed appropriate. By protocol, however, at least one month of medical therapy trial was recommended before deciding to refer patients for invasive strategy.

Investigators were requested to fill an electronic case report form for data recording. Final data were collected in a web-based, central data base located at the A.R.C.A. Head Quarter.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the National Coordinator (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Area Vasta Nord-Ovest; Pisa, Italy; n. 1441, 25 May 2017).

2.1. Inclusion and exclusion criteria

Patients presenting to a participating A.R.C.A. cardiologist for an elective visit were considered as eligible in the study if they met the following criteria: 1) Stable, newly diagnosed, typical angina [Canadian Cardiovascular Society (CCS) class I, II, III; or CCS class IV, after

stabilization with medical therapy for at least seven days]; or atypical angina associated with myocardial ischemia on a non-invasive stress test. 2) No contraindications to a revascularization procedure [percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG)], if indicated. 3) Informed, written consent for entering the study.

The following exclusion criteria were considered: 1) Acute coronary syndrome ≤ 3 months. 2) Previous PCI or CABG. 3) Contraindications to dual antiplatelet therapy. 4) Heart failure or left ventricular ejection fraction $\leq 35\%$. 5) Dilated or hypertrophic cardiomyopathy. 6) Clinically significant valvular heart disease. 7) Uncontrolled hypertension. 8) Life-threatening hypokinetic and hyperkinetic arrhythmias. 9) Age < 18 years. 10) Pregnancy or intention to pregnancy during the study. 11) Life expectancy < 2 years.

All patients were informed of the nature and aim of the study and of the anonymous management of their demographic data, with the sole exception of the treating cardiologist.

2.2. Design of the study

At visit 1, baseline characteristics, including demographics, risk factors and medical history were collected. A series of comorbidities were also assessed: peripheral artery disease (PAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), malignancies, diabetes. Angina symptoms and quality of life were evaluated by the CCS angina grading [10] and the Seattle Angina Questionnaire shortened version (SAQ-7) [11]. Within the SAQ-7, the summary score, which represents an integration of the patient's physical limitation, angina symptoms and quality of life, has been considered [11]. Patients enrolled were then prescribed OMT, according to the criteria described below.

One month after the inclusion in the study (visit 2), every patient was re-evaluated in order to assess changes in symptoms and functional status. In addition to the CCS angina grading and the SAQ-7, a subjective assessment of symptoms was also obtained, with the following grading system: a) angina relieved (patient asymptomatic); b) angina improved; c) angina unchanged; d) angina worsened. Based on symptoms, clinical profile and results of non-invasive testing (exercise stress test, stress imaging test, coronary computed tomography angiography) after one-month treatment, the investigators could either refer the patient for ICA and possibly revascularization (invasive strategy), or continue with medical therapy (medical strategy). However, patients could be referred for invasive strategy any time throughout the study period, at cardiologist discretion.

Patients were re-evaluated at 4 and 12 months or when even clinically indicated. At each visit, symptoms, functional status and adverse events were assessed by the CCS angina grading, the self-assessment scale, and the SAQ-7. A composite end-point of MACEs (all-cause death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina) at one year was also assessed.

2.3. Optimal medical therapy

Medical management was aimed at event prevention and angina/ischemia relief, through both pharmacological and lifestyle interventions. Investigators were encouraged to educate every patient about lifestyle modification, risk factors control and adherence to drug therapy. According to ESC guidelines [6], every patient was prescribed OMT including at least one drug for angina/ischemia relief plus drugs for events prevention (aspirin or a P2Y₁₂ inhibitor, statins and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). At each visit, patient adherence to therapy was checked. Medication adherence was defined as $\geq 80\%$ of doses taken respect to doses prescribed of overall drug therapy [12].

2.4. Coronary angiography and revascularization

Invasive coronary angiography and revascularization were considered on the basis of the response to OMT. Left and right coronary angiography was performed in multiple projections, preferably by a right radial approach. A diameter stenosis $\geq 50\%$ in the left main or $\geq 75\%$ in the left anterior descending, left circumflex and right coronary artery were considered as haemodynamically significant. The extent of CAD was classified as CAD1, CAD2 and CAD3, depending on the number of major coronary arteries involved. Significant stenoses in other coronary branches (diagonal, septal, marginal, posterior descending and posterolateral branches) were classified as secondary vessels disease. Decisions about revascularization and the best technique (PCI or CABG) were taken by an heart team including a clinical cardiologist, an interventional cardiologist and a cardiac surgeon, based on coronary anatomy and the presumed risk/benefit ratio, respecting the patient's preference.

2.5. Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical variables are expressed as number and percentage. Statistical significance of the difference between continuous variables was assessed by means of the Student *t*-test and ANOVA test. Categorical variables were compared using the chi-square test and the Fisher's exact test. A *p* value < 0.05 was considered as statistically significant. Statistical analysis was performed using the commercially available software Graphpad Prism 8.4.0.

3. Results

From October 2017 to December 2019, 833 patients were enrolled in the Registry from all Italian regions and completed one year of follow-up. Baseline characteristics, risk factors and angina presentation of the study population are reported in Table 1. The mean age of patients was 66.9 ± 10 years; 465 (55.8%) were males. Thirty-two percent of patients had peripheral and/or cerebrovascular disease, 80% hypertension, 58% hypercholesterolemia and 29% were diabetics. Four hundred and eighty eight patients (58.6%) had one or more comorbidities. Of these, 298 (35.8%) had one comorbidity and 190 (22.8%) a multi-comorbidity (≥ 2 comorbidities).

Two percent of patients had persistent/permanent atrial fibrillation and 13.6% had previous history of IHD. Over 75% of patients had typical angina. Less than 25% of the enrolled population had atypical angina with documented ischemia. Atypical angina prevailed in females (112/368 patients: 30.4%), as compared to males (93/465: 20%); $p = 0.0007$.

3.1. Drug therapy

At enrollment, the vast majority of patients was prescribed a renin angiotensin aldosterone system (RAAS) inhibitor (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: 70.8%), aspirin (78%) or a P2Y12 inhibitor (16.3%) and statins (80.2%) with or without ezetimibe (Table 1).

The most prescribed antianginal agents were beta-blockers (532/833 patients; 63.9%). Among beta-blockers, the most used was by far bisoprolol (334/532 patients: 62.8%; mean dosage 3.99 ± 7.1 mg/day), followed by nebivolol (74/532 patients: 13.9%; mean dosage 4.78 ± 0.6 mg/day), atenolol (50/532 patients: 9.4%; mean dosage 62.4 ± 28.9 mg/day), metoprolol (44/532 patients: 8.3%; mean dosage 149.5 ± 129 mg/day) and carvedilol (30/532 patients: 5.6%; mean dosage 19.2 ± 11.9 mg/day). Antianginal metabolic drugs (ranolazine or trimetazidine: 36.8%) were prescribed more often than non-dihydropyridine calcium channel blockers (15.8%) and long acting nitrates (12.2%). Of metabolic drugs, ranolazine was clearly preferred to trimetazidine (94.5% vs 5.5%). Ranolazine was prescribed at the mean dosage of 934 ± 174 mg/day and used as single antianginal drug in 30.7% of the cases

Table 1

Baseline characteristics, risk factors, angina presentation and drugs at study entry.

	Overall (n = 833)	Medical group (n = 495)	Invasive group (n = 338)	p-Value
Clinical characteristics and comorbidities, n (%)				
Previous infarction	48 (5.8)	30 (6.1)	18 (5.3)	0.762
History of IHD	65 (7.8)	42 (8.5)	23 (6.8)	0.430
Atrial fibrillation	17 (2.0)	10 (2.0)	(2.1)	0.475
PAD/CVD	266 (31.9)	163 (32.9)	103 (30.5)	0.495
CKD	54 (6.5)	35 (7.1)	19 (5.6)	0.474
COPD	101 (12.1)	61 (12.3)	40 (11.8)	0.914
Malignancies	40 (4.8)	27 (5.4)	13 (3.8)	0.324
Risk factors, n (%)				
Hypercholesterolaemia	485 (58.2)	274 (55.3)	211 (62.4)	0.045
Diabetes mellitus	243 (29.2)	152 (30.7)	91 (26.9)	0.245
Hypertension	672 (80.7)	405 (81.8)	267 (79.0)	0.326
Family history	188 (22.6)	107 (21.6)	81 (23.9)	0.447
Active or prior smokers	254 (30.5)	140 (28.2)	114 (33.7)	0.107
Obesity	154 (18.5)	100 (20.2)	54 (16.0)	0.145
Angina presentation, n (%)				
Typical angina	628 (75.4)	342 (69.1)	286 (84.6)	<0.0001
- Effort, fixed threshold	298 (35.8)	174 (35.1)	124 (36.7)	0.659
- Effort, variable threshold	168 (20.2)	74 (14.9)	94 (27.8)	<0.0001
- Mixed	133 (15.9)	80 (16.2)	53 (15.7)	0.923
- Rest	29 (3.5)	14 (2.8)	15 (4.4)	0.249
Atypical angina + ischemia	205 (24.6)	153 (30.9)	52 (15.4)	<0.0001
Drugs at study entry, n (%)				
RAAS inhibitors	590 (70.8)	346 (69.9)	244 (72.2)	0.485
Aspirin	650 (78)	380 (76.8)	270 (79.9)	0.307
P2Y12 inhibitors	136 (16.3)	69 (13.9)	67 (19.8)	0.028
Statins	668 (80.2)	395 (79.8)	273 (80.8)	0.790
Ezetimibe	73 (8.8)	42 (8.5)	31 (9.2)	0.803
Beta-blockers	532 (63.9)	301 (60.8)	231 (68.3)	0.027
Calcium channel blockers	132 (15.8)	89 (18.0)	43 (12.7)	0.042
Antianginal metabolics	307 (36.8)	210 (42.4)	97 (28.7)	<0.0001
Long acting nitrates	102 (12.2)	62 (12.5)	40 (11.8)	0.829

CKD: chronic kidney disease. COPD: chronic obstructive pulmonary disease. CVD: cerebrovascular disease.

PAD: peripheral artery disease. RAAS: renin angiotensin aldosterone system.

or in association with other antianginal agents in 69.3% of the cases.

At study entry, 477/833 patients (57.3%) were put on single antianginal therapy, 327/833 (39.3%) on dual therapy and 29/833 (3.4%) on triple therapy.

The adherence to recommended treatment was very high throughout the study: 97% at 1 month, 96% at 4 months and 93% at 12 months.

3.2. Symptoms and quality of life in the overall population throughout the study

At enrollment, 69.8% of patients were in CCS class II-III, 28.4% in

class I and a small minority (less than 2%) in class IV (Table 2 and Fig. 1, panel A). The number of patients in CCS class I progressively and significantly increased up to 67.1% at 12 months, along with a mirror reduction of patients in class II and III. No variation was observed in class IV patients.

After one month of therapy, anginal symptoms were relieved in 7% of patients and improved in another 40%. At 4 months, 71% of patients were either asymptomatic or improved. The number of asymptomatic patients increased progressively and significantly in the following months, up to 37.1% at 12 months. At one year, 71.5% of patients were either asymptomatic or with symptoms improved. Conversely, patients persistently symptomatic (with angina unchanged or worsened) decreased from 53% at 1 month to 28.5% at 12 months (Table 2 and Fig. 1, panel B).

The summary score of the SAQ-7, representative of both physical limitation, angina frequency and quality of life, significantly and progressively increased from 58.4 ± 20 at enrollment to 85.9 ± 14 at the end of follow-up, indicating a progressive improvement of the patient's functional status, consistently with the changes in the CCS angina grading and in the angina self-assessment scale (Table 2).

No significant difference was observed by sex in the severity of symptoms at enrollment. The prevalence of CCS class I was slightly, but not significantly higher in males (142/465: 30.5%) than in females (95/368: 25.8%); $p = 0.1422$. Also the SAQ-7 summary score was similar at inclusion in males (59.3 ± 22) and females (57.3 ± 18); $p = 0.1570$. However, at 12 months females experienced greater persistence of symptoms than males: unchanged or worsened angina 123/243 (33.6%) vs 114/351 (24.5%), $p = 0.0042$; CCS class I 153/243 (63%) vs 198/280 (70.7%), $p = 0.0627$; SAQ-7 score 84.1 ± 14 vs 87.1 ± 14 , $p = 0.0028$, respectively.

Multi-comorbidity at enrollment did not increase the likelihood of angina persistence. Indeed, of 190 patients with multi-comorbidities, 52/237 (21.9%) had persistent angina at the end of the study and 138/594 (23.2%) had angina relieved or improved, $p = 0.715$.

Table 2
Symptoms and quality of life in the overall population during the study.

	Enrollment	1 month	4 months	12 months	p-Value
	n = 833	n = 833	n = 831	n = 831	
Canadian Cardiovascular Society angina grading ^a					
I, n (%)	237 (28.4)	350 (45.2)	400 (62.5)	351 (67.1)	<0.0001
II, n (%)	372 (44.7)	275 (35.5)	199 (31.1)	147 (28.1)	<0.0001
III, n (%)	209 (25.1)	133 (17.1)	33 (5.2)	17 (3.3)	<0.0001
IV, n (%)	15 (1.8)	17 (2.2)	8 (1.2)	8 (1.5)	0.573
Self-assessment angina grading					
Angina relieved (asymptomatics), n (%)		58 (7.0)	191 (22.9)	308 (37.1)	<0.0001
Angina improved, n (%)		333 (40.0)	400 (48.1)	286 (34.4)	<0.0001
Angina unchanged, n (%)		416 (49.9)	221 (26.6)	226 (27.2)	<0.0001
Angina worsened, n (%)		26 (3.1)	19 (2.3)	11 (1.3)	0.0465
Seattle Angina Questionnaire - 7					
Summary score (mean $\pm$ SD)	58.4 $\pm$ 20	67.1 $\pm$ 19	81.1 $\pm$ 15	85.9 $\pm$ 14	<0.0001

^aDuring the study, an increasing number of patients became asymptomatic. The number of patients still symptomatic, (CCS classes I to IV), is: 833 at enrollment, 775 at 1 month, 640 at 4 months and 523 at 12 months.

3.3. Switch to an invasive strategy

Before deciding on medical or invasive strategy, 562 of 833 patients (67.5%) underwent non-invasive testing, most frequently exercise stress test (EST; 346 patients, 41.6%), followed by myocardial perfusion stress imaging (MPI; 160 patients, 19.2%), stress echocardiography (45 patients, 5.4%) and coronary computed tomography angiography (CCTA; 11 patients, 1.3%). Non-invasive testing were performed more frequently in patients referred for invasive strategy (275/338 patients: 81.4%), than in patients maintained on OMT (287/495: 58%). In particular, in advance of referral for ICA and revascularization, 199 patients (58.9%) underwent EST, 57 patients (16.9%) underwent stress MPI, 14 patients (4.1%) underwent stress echo and 5 patients (1.5%) underwent CCTA.

Based on symptoms under medical therapy, clinical profile and results of noninvasive testing, during the study period 338 of 833 patients (40.6%) were referred for ICA and possible revascularization (invasive group), and 495 patients (59.4%) were maintained on OMT (medical group). Most referrals for the invasive treatment occurred between 1 and 2 months and only a minority (15%) after the 4th month.

Among the 338/833 patients referred for ICA, 129 patients (38.2%) were found to have either angiographically normal coronary arteries or non-obstructive CAD, 15 patients (4.4%) secondary vessels disease, 75 patients (22.2%) CAD1, 56 patients (16.5%) CAD2, 54 patients (16%) CAD3 and 9 patients (2.7%) left main disease. The prevalence of normal coronary arteries or non-obstructive CAD was slightly, but not significantly higher in females (57/133: 42.8%) than in males (72/205: 35.1%); $p = 0.1696$.

Among the 209/338 patients with obstructive CAD, 158 (75.6%) underwent revascularization (PCI: 129 patients; CABG: 29 patients). Revascularization by PCI was complete in 100/129 cases (77.5%) and incomplete (i.e. limited to the culprit lesions) in 29/129 cases (22.5%). In 2 cases PCI was unsuccessful due to the failure to cross or dilate the lesion. Revascularization was not performed in 51 patients (24.4%) with obstructive CAD for a number of reasons including coronary anatomy not suitable for revascularization (45%), coronary lesions jeopardizing a limited myocardial amount (45%), or patient refusal (10%).

3.4. Medical versus invasive strategy

Males (205/465: 44.1%) were more likely to be referred for an invasive approach than females (133/368: 36.1%), $p = 0.0230$. Moreover, patients considered for invasive strategy were younger (mean age 65.1 ± 10 years) than those treated with medical strategy (67.9 ± 9 years), $p < 0.0001$. No significant difference between medical and invasive groups was detected in clinical characteristics, comorbidities and risk factors, with the exception of hypercholesterolemia, more frequent in patients treated invasively. Patients presenting with typical angina were more frequently referred for an invasive treatment than those with atypical symptoms (Table 1).

After 1 month of medical therapy, as expected, more patients in CCS class III and IV and with unchanged or worsened angina were referred for an invasive strategy (Table 3; Figs. 2 and 3). Consistently with the CCS angina grading and the self-assessment scale, the SAQ-7 summary score at 1 month was lower, indicating a worse angina related status, in patients referred for the invasive strategy (Table 3; Fig. 4). However, these differences no longer persisted throughout the study period. At 12 months, no difference between invasive and medical groups was observed in CCS angina grading and in SAQ-7 summary score. Moreover, symptoms similarly relieved in nearly 40% of patients in both groups. At the end of the study, however, angina improved in more patients in the invasive group and persisted unchanged in more patients in the medical group (Table 3 and Fig. 3). At 12 months, unchanged or worsened angina significantly prevailed in the medical (163/493, 33%), as compared to the invasive group (74/338, 21.8%), $p = 0.0004$.

Among the 158 revascularized patients, 33 (20.9%) experienced

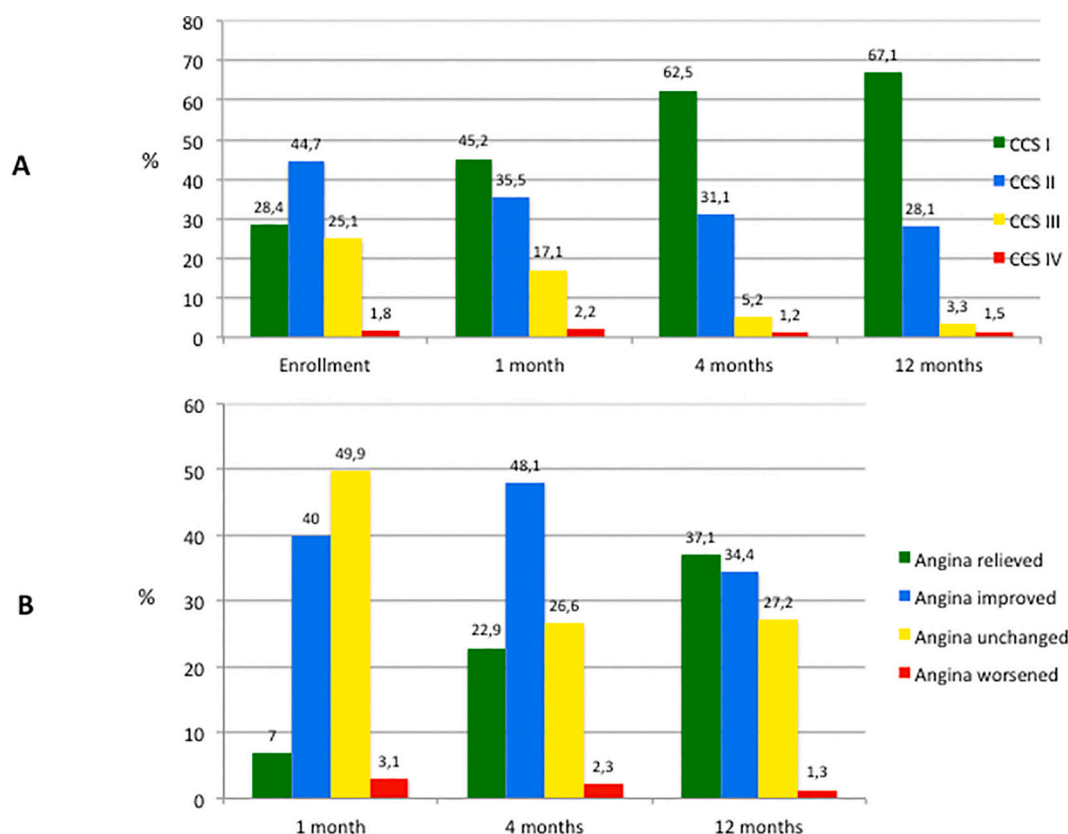


Fig. 1. Time course of symptoms throughout the study in the overall population, evaluated by the CCS angina grading (panel A) and by the self-assessment scale (panel B).

persistence and/or recurrence of symptoms at 1 year, 28/129 post-PCI (21.7%), and 5/29 (17.2%) post-CABG.

3.5. Adverse events

The one-year composite end-point of MACEs was low (2.9%) in the overall population (Table 4). Eleven myocardial infarctions (overall rate 1.3%) and 10 hospitalizations for unstable angina (1.2%) were reported. Only two deaths (one sudden death and one non-cardiac death) occurred, between 1 and 3 months of follow-up. No difference was observed at one year in the composite and in the single components of the end-point between medical and invasive groups (Table 4). In the first month of medical therapy trial, only one adverse event (a myocardial infarction) was reported. In 51/209 patients with obstructive CAD who did not undergo revascularization, three MACEs were observed (two myocardial infarctions and one hospitalization for unstable angina). No significant differences were observed by sex in the composite end-point nor in the single MACEs (composite end-point: 3.2% in males; 2.4% in females; $p = 0.5393$).

4. Discussion

In this Registry, a strategy of OMT first, shifting to an invasive strategy whenever clinically indicated, was effective and safe, improving symptoms and quality of life, without exposing patients to an excess risk of MACEs. The results of the Registry are representative of the Italian nationwide experience of Cardiologists operating in an outpatient setting. Similar registries have been activated in Central Asia, East Europe, and South America to confirm the global validity of this experience.

The study population of ARCA Registry has a moderate to severe anginal burden. At enrollment, 75% of patients had typical angina and

about 70% were in CCS class II-III. The baseline SAQ-7 summary score was 58, indicating a quite poor angina-related health status [11]. At study entry, all patients were recommended lifestyle modification and risk factor control and were prescribed OMT, according to ESC guidelines recommendations, including agents for events prevention (RAAS inhibitors: 70.8%; antiplatelet therapy: 94.3%; statins: 80.2%) and antianginal drugs [6]. Over 40% of patients was put on dual or triple antianginal therapy. The adherence to treatment was stimulated and carefully monitored by investigators throughout the study and remained very high (more than 90%) for up to 12 months.

This Registry is the first study, to our knowledge, providing detailed information on symptoms, quality of life and prognosis in newly diagnosed angina patients treated with OMT and selective revascularization when indicated. After one month of treatment, for the exclusive effect of medical therapy, 7% of patients reported freedom from angina and about 35% at least one CCS class improvement. The rate of patients in CCS class I increased from 28.4% to 45.2% in the first month, and the SAQ-7 summary score improved by 9 points, from 58.4 to 67.1.

The tailored strategy applied in this study, combining OMT with invasive treatment when needed, was associated with a further and progressive amelioration of symptoms and quality of life. At the end of the study, 37.1% of patients were free from angina and 34.4% were significantly improved, 67.1% being in CCS class I. The SAQ-7 summary score progressively rose to 85.9, qualifying the patients as in “excellent conditions” [11]. However, it should be noted that after one year of such tailored management, over a quarter of patients (28.5%) was persistently symptomatic, reporting unchanged or worsened angina. The rate of persistent angina was even higher in females (33.6%) than in males (24.5%).

The results of this Registry also confirm the safety of the guidelines recommended management. The rate of MACEs at one year of follow-up was very low. Of note, only one severe adverse event (a non-fatal

Table 3

Symptoms and quality of life: medical versus invasive group.

	1 month		p-Value	12 months		p-Value
	MED	INV		MED	INV	
	n =	n =		n =	n =	
	495	338		493	338	
Canadian Cardiovascular Society angina grading ^a						
I, n (%)	259 (56.7)	91 (28.6)	<0.0001	205 (64.7)	146 (70.9)	0.1535
II, n (%)	175 (38.3)	100 (31.5)	0.0564	98 (30.9)	49 (23.8)	0.0905
III, n (%)	22 (4.8)	111 (34.9)	<0.0001	9 (2.8)	8 (3.9)	0.6153
IV, n (%)	1 (0.2)	16 (5.0)	<0.0001	5 (1.6)	3 (1.4)	>0.9999
Self-assessment angina scale						
Angina relieved, n (%)	38 (7.7)	20 (5.9)	0.4057	176 (35.7)	132 (39.1)	0.3423
Angina improved, n (%)	254 (51.3)	79 (23.4)	<0.0001	154 (31.2)	132 (39.1)	0.0213
Angina unchanged, n (%)	197 (39.8)	219 (64.8)	<0.0001	155 (31.4)	71 (21.0)	0.0009
Angina worsened, n (%)	6 (1.2)	20 (5.9)	0.0002	8 (1.6)	3 (0.8)	0.5394
Seattle Angina Questionnaire - 7						
Summary score (mean ± SD)	72.6 ± 17	58.3 ± 19	<0.001	85.3 ± 14	86.8 ± 13	0.14

INV: invasive group. MED: medical group.

^a The number of symptomatic patients (CCS classes I to IV) in the medical and invasive groups is, respectively: 457 and 318 at 1 month; 317 and 206 at 12 months.

myocardial infarction) occurred in the first month of medical therapy. The prognosis of ARCA Registry patients is better than that reported in large international registries on stable IHD, such as the CORONOR Study [13] and the REACH Registry [14]. However, patients included in these studies differ from those in ARCA Registry, for a much higher rate of previous myocardial infarction, unstable angina and coronary revascularization in the former, so that respective populations are difficult to compare. The use of medications for event prevention was higher in ARCA Registry than in the REACH Registry (RAAS inhibitors: 71% vs

65–69%; statins: 80% vs 72%; aspirin or other antiplatelets: 94% vs 69%), probably concurring to a better prognosis in our patients [14]. In the CLARIFY Registry, which compared clinical outcomes in 30,977 men and women with stable coronary artery disease, the composite of cardiovascular death, non-fatal myocardial infarction or stroke (1.7% and 1.8% in men and women, respectively) and the rate of fatal and non-fatal myocardial infarction (1.4% and 1.4%) were similar to our population, but one year all-cause death was higher (1.5% and 1.6%) than in our patients [15].

4.1. Symptoms, quality of life and prognosis in medical and invasive patient groups

In this Registry, about 40% of patients were considered for an invasive treatment, due to unsatisfactory results of medical therapy. Of these, slightly less than half (46.7%) actually underwent coronary revascularization, by PCI in over 80% of cases. Hence, the overall rate of revascularization in ARCA Registry was only 19%. The vast majority of patients (81%) was managed medically throughout the study.

Younger patients and patients with typical angina were more likely to be referred for the invasive treatment. As reported in large, non-selected cohorts [15,16], women less frequently underwent the invasive treatment (36.1% vs 44.1%), even though international guidelines do not dictate gender-specific management strategies.

As shown in Figs. 2 to 4, most symptomatic patients, non-responders to medical therapy and those with the worst quality of life, were referred for the invasive treatment. At one year of observation, however, the gap between the two treatment strategies was no longer persistent and no difference was still present in CCS class and in SAQ-7 summary score between medical and invasive patient groups. Interestingly enough, by the self assessment angina scale, patients treated invasively reported a slightly but significantly better condition at one year (angina unchanged or worsened 21.8% vs 33%). This discrepancy with the CCS angina grading and the SAQ-7, confirms that the self-assessment scale is the most subjective among the three methods used in this open-label study for angina evaluation, easily influenced by the knowledge of the treatment [17]. Recently, the ORBITA trial showed that when the efficacy of invasive procedures is assessed in a double-blind, placebo controlled trial, PCI does not improve symptoms and exercise capacity by more than the effect of a placebo procedure [18].

In this Registry, the rate of MACEs did not differ at one year between medical and invasive groups. Of note, three of the 9 MACEs reported in the invasive group occurred in the cohort (24.4%) with obstructive CAD

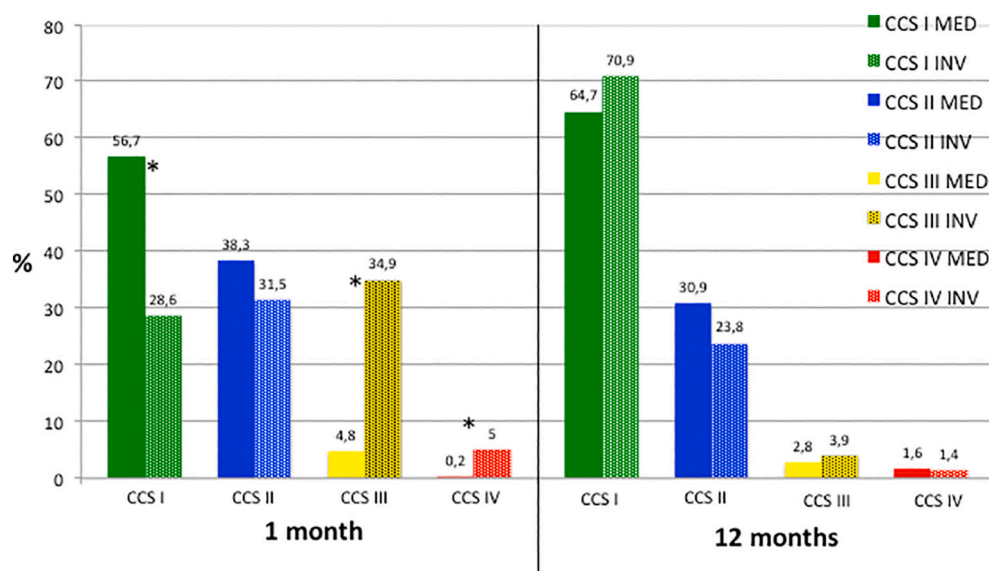


Fig. 2. Symptoms after 1 month of OMT (left side) and at the end of the study (right side), evaluated by the CCS angina grading, in the medical group (solid bar) and in the invasive group (dotted bar). INV: invasive group. MED: medical group. OMT: optimal medical therapy. *: statistically significant differences.

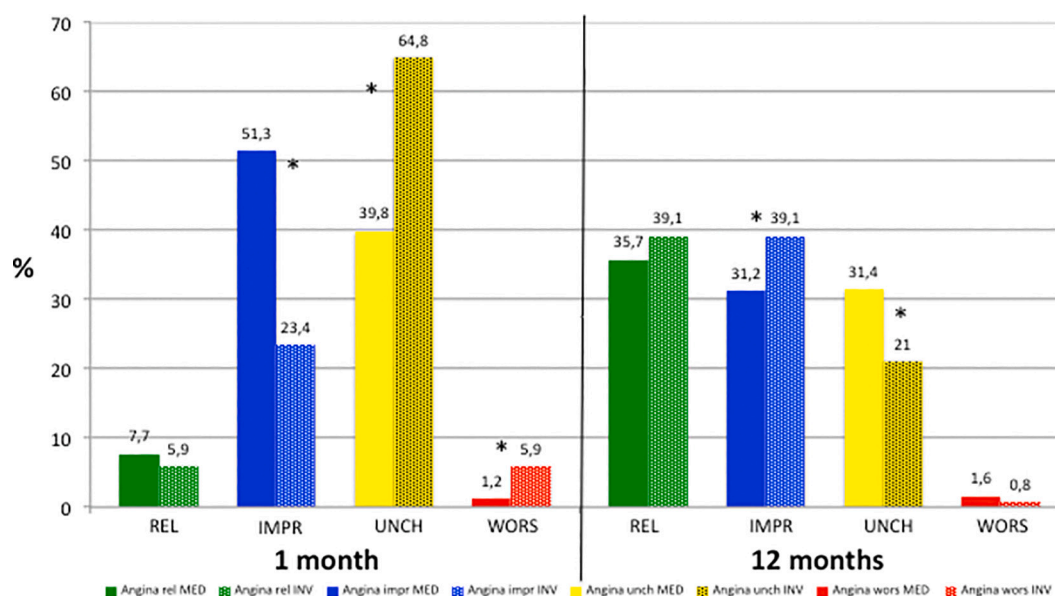


Fig. 3. Symptoms after 1 month of OMT (left side) and at the end of the study (right side), evaluated by the self assessment angina scale, in the medical group (solid bar) and in the invasive group (dotted bar).

REL: patients with angina relieved (asymptomatic). IMPR: patients with angina improved. UNCH: patients with angina unchanged. WORS: patients with angina worsened.

INV: invasive group. MED: medical group. OMT: optimal medical therapy.

*: statistically significant differences.

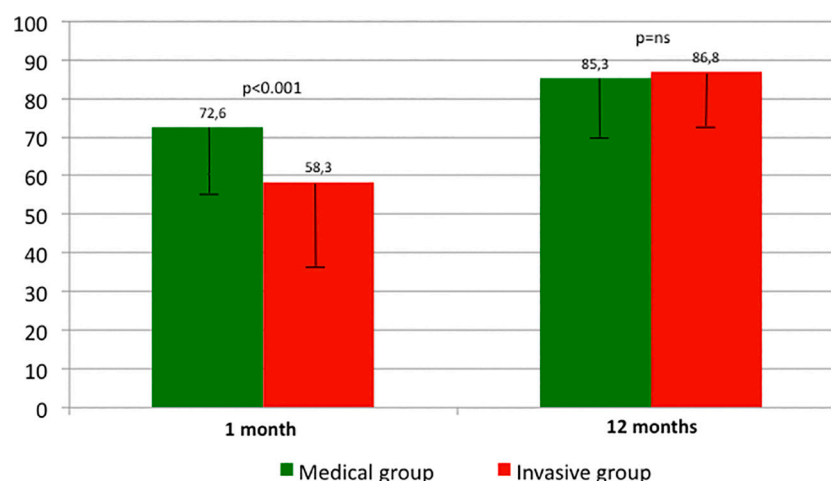


Fig. 4. SAQ-7 summary score after 1 month of OMT and at the end of the study in the medical group (green bar) and invasive group (red bar).

Table 4
MACEs at one year of follow-up.

	Overall n = 833	Medical group n = 495	Invasive group n = 338	p- Value
Composite end-point, n (%) (all-cause death, MI, stroke, hosp for UA)	24 (2.9)	15 (3.0)	9 (2.7)	0.835
All-cause death, n (%)	2 (0.2)	2 (0.4)	0 (0)	0.517
Non-fatal myocardial infarction, n (%)	11 (1.3)	7 (1.4)	4 (1.2)	>0.99
Non-fatal stroke, n (%)	1 (0.1)	0 (0)	1 (0.3)	0.405
Hospitalization for unstable angina, n (%)	10 (1.2)	6 (1.2)	4 (1.2)	>0.99

Hosp: hospitalization. MACEs: major adverse cardiovascular events. MI: non-fatal myocardial infarction. UA: unstable angina.

that did not undergo revascularization. The numbers are too low to draw definitive conclusions. Of course, ARCA Registry is not powered nor was intended for a comparative prognostic evaluation between different treatment strategies. However, our results are consistent with the conclusions of recent trials and meta-analyses on stable IHD [3,4].

4.2. Time course of symptoms in patients treated invasively or non-invasively

After revascularization, angina relief is a time-dependent phenomenon that is maximal early after the revascularization procedure and tends to reduce over time. The rate of angina in revascularized patients rose progressively with time and was no longer different between PCI and OMT patients at 24 months in the BARI 2D trial [19] and at 36 months in the COURAGE trial [20]. The follow-up of our study was limited to one year, too a short interval to assess the long-term time-

course of symptoms. However, it is worth noting that the prevalence of symptoms in medically treated patients behaves in time differently than in revascularized patients. Medically treated patients report a steady, progressive improvement of symptoms, whereas revascularized patients report an early symptomatic benefit followed by a progressive relapse of symptoms. In the very recent Analysis of Evolution and Outcomes of Chronic Stable Angina from the CLARIFY Study [21], angina disappeared at 1 year in 39.6% of medically treated patients, with further annual decreases. This finding, consistent with our observations, and the lack of demonstrated outcome benefit of routine revascularization, encourage to prolong medical therapy even when the early results are below expectations.

4.3. Refractory angina and coronary artery disease

In this Registry, 38.2% of patients who underwent ICA for angina resistant to medical therapy had normal coronary arteries or non-obstructive CAD, suggesting that resistance to medical therapy does not necessarily imply severe underlying atherosclerotic obstructions. This observation is consistent with the hypothesis of a multifactorial pathophysiology of chronic ischemic syndromes, including obstructive coronary stenoses, but also a number of macrovascular, microvascular and non-vascular mechanisms, as suggested by many reports and acknowledged by the 2019 ESC Guidelines on chronic coronary syndromes [1,2,6].

The prevalence of obstructive CAD in patients with symptoms resistant to medical therapy observed in this study, is similar to that reported in much larger series. In 398,978 subjects undergoing ICA for diagnostic purposes, only 40% to 53% of the patients with typical angina had obstructive CAD, a prevalence only slightly higher than that of subjects with no symptoms (32%–43%) or atypical symptoms (18%–27%) [22]. The absence of CAD is not negligible even in patients with acute coronary syndromes (ACS). In randomized controlled trials on ACS, the prevalence of normal coronary arteries or non-obstructive CAD ranges from 8% to 27% in men and from 14% to 31% in women [23]. Finally, the absence of obstructive CAD was documented in 46.3% of patients undergoing elective ICA for chronic angina and enrolled in the recent CorMicA trial [24].

4.4. Residual angina burden

After one year of tailored management, over a third of the patients (37.1%) was free from angina, a further 34.4% had significantly improved and nearly 70% was in CCS class I. However, despite a careful treatment strategy, about a quarter of patients (28.5%) still reported persistent symptoms at one year, with a significantly higher prevalence of unchanged or worsened angina in the medical (33%), as compared with the invasive (21.8%) patient group. The rate of persistent or recurrent angina was slightly lower, but substantial (20.9%), even in patients that actually underwent revascularization.

The prevalence of residual angina in patients treated for stable IHD appears widely variable, but consistently reported in the literature. In the COURAGE trial, 64% of PCI patients and 73% of OMT patients with angina at baseline still presented with symptoms after one year. The rate of symptomatic patients later decreased, but remained substantially high at three years (62% vs 67%, respectively) [20]. In the FAME 2 trial, 6% of patients in the PCI arm and 15% in the OMT arm were still in CCS classes II–IV at 12 months [25]. In the recent ISCHEMIA trial, the probability of being angina-free at one year for patients with a baseline SAQ-7 angina frequency score of 50 (corresponding to one angina episode per week), was about 60% with the invasive strategy and nearly 30% with the conservative strategy. Moreover, the likelihood of angina freedom during the follow-up progressively decreased as the baseline angina status worsened [26]. Finally, the rate of angina after revascularization in our patients is consistent with the prevalence of abnormal exercise stress test results and angina (29%) one year after successful

and uncomplicated PCI in a recent observational study [27].

Several mechanisms could underlie angina persistence in medically or invasively treated patients. Restenosis rate after PCI, usually less than 10%, is not sufficient to justify a much higher rate of residual angina [27]. The adherence to medical treatment was very high (93–97%) in our study, so that poor adherence does not justify persistence of symptoms in nearly a third of patients. Even multi-comorbidity, found in almost a quarter of the population, did not predispose to symptoms persistence. Of course, stable angina is a complex syndrome with multiple pathogenetic mechanisms, that frequently coexist and overlap, even in patients with obstructive CAD [2]. The imperfect knowledge of these mechanisms in individual patients and the lack of adequate therapies for some of them, such as microvascular dysfunction, are of greater importance to explain residual angina burden, that persists even employing the best available therapeutic resources. In the recent CorMicA trial, a strategy of invasive function testing at the time of coronary angiography and tailored medical therapy according to pathophysiological findings, led to a reduction in angina severity and better quality of life [24].

4.5. Sex differences

As commonly reported [6], in this Registry atypical angina prevailed in females (30.4%) than in males (20%), as compared with typical angina presentation (69.6% vs 80%, respectively). No significant differences were observed by sex in the severity of symptoms at enrollment. However, at the end of the study females experienced angina persistence more frequently than males, confirmed by a higher rate of unchanged or worsened symptoms, a lower rate of CCS class I and a lower SAQ 7 score. In agreement with previous registry data [15], no significant differences by sex were found in the incidence of MACEs, even if the sample size, the low events rate and the short observation time do not allow definitive conclusions. Finally, the prevalence of normal coronary arteries or non-obstructive CAD was slightly higher in females (42.8%) than in males (35.1%). This finding, not only confirms a different pathogenesis of angina in the two sexes [6], but could also justify the greater resistance of symptoms in females.

4.6. ARCA Registry and the daily practice of cardiology

The ARCA Registry proves the efficacy and safety of a tailored management of stable angina, where patients are all initially treated medically and selectively referred for ICA and revascularization if and when deemed appropriate. This tailored strategy seems to be even more appropriate after the recent publication of a new analysis of the ISCHEMIA trial, taking into account the effects of treatment on recurrent events, censored in the original analysis, in addition to the first events [28]. In this prespecified re-analysis, an initial invasive strategy did not prevent recurrent or total events more effectively than an initial conservative strategy, despite patients with recurrent events were older, with a higher risk profile and had more multivessel CAD [28].

Worldwide, current cardiology practice is rather inhomogeneous, with countries where elective invasive procedures have markedly declined and countries where the number of procedures are still on the rise. The START Registry described in 2018 the management of stable IHD in Italy [7]. The vast majority of patients (87%) underwent ICA, even though a stress test was performed for diagnosing ischemia in only 34% of patients and OMT was suboptimally prescribed at the rate of 67–70%. In a survey published in the Lancet in 2017, an alarming rate of inappropriateness of both ICA (30%) and PCI (22%) in Italy was reported [29]. PCI is performed inappropriately at the rate of 10–30% worldwide in stable patients and the rate of inappropriateness could be even higher, updating guidelines in the light of the accumulating evidence. In a very recent work, a potential increase in the rate of inappropriateness of elective PCI (from 3.3% to 22.3%), taking into account the ISCHEMIA trial results, has been reported [30].

Despite the weight of evidence going in the opposite direction, too many patients and doctors still believe that elective PCI may improve prognosis, reducing death and myocardial infarction rate [8]. This attitude promotes hundreds thousands of elective PCI around the world in asymptomatic or low symptomatic patients, with an unacceptable risk-benefit and cost-benefit ratio [31].

4.7. Limitations of the study

The study has some limitations. The first limitation is its observational design, suggesting caution when making comparison with randomized controlled trials. However, ARCA Registry was planned not to compare different treatment strategies as a study with controlled design, but to evaluate the outcome in clinical practice of patients treated complying with guidelines recommendations.

The sample size of this registry is limited when fractionated to allow meaningful analysis of subgroups and the length of follow-up too short to assess the long-term impact on the outcomes. The original plan was to enroll a larger population and to follow patients for a longer time. Unfortunately, in the early 2020 the practice of cardiology, in Italy as elsewhere, was disrupted by the COVID pandemic. Encouraged by the consistency of the trends at interim data analyses, we opted to stop the study, in order to assure a patients management consistent with standard practice.

The absence of a standard protocol for drug therapy and for deciding on the invasive strategy could appear a limitation of the study, making the study results not well reproducible. Indeed, the investigators were not given specific criteria for drug choice and for referring patients to invasive procedures. We consistently recommended, in investigators meetings and newsletters, to comply with current ESC Guidelines. The conclusion of this study are representative of current cardiology practice in Italy, one of the countries with the highest rate of invasive procedures in Europe. The results may not necessarily apply to countries with different health organization or limited access to procedures. To test the global validity of the conclusions of this study, a second registry, denominated ARCA International, that will recruit patients in European, Asian and Latin-American countries, is already ongoing.

5. Conclusions

In the management of stable IHD, the gap between evidence and practice is still too large. In particular, an overuse of inappropriate PCI, due to the treatment of asymptomatic/low-risk patients and suboptimal testing of medical therapy before revascularization, is widely reported [29,30].

In ARCA Registry, all patients were treated with a combined strategy of OMT, with ICA considered in less than half of patients persistently symptomatic and revascularization eventually performed in one-fifth of patients. With this cost-saving strategy, the majority of patients experienced a symptomatic benefit, with a significant amelioration in quality of life and with a very low rate of MACEs. These findings could contribute to better appropriateness and value-based care of stable IHD.

In summary:

1. The “tailored” approach to stable angina, medical therapy first and revascularization if and when needed, recommended by current Guidelines, has been tested in this Registry and has proved to be effective and safe.
2. Patients exhibited a progressive amelioration of symptoms and quality of life, without being exposed to an excess risk of MACEs
3. The symptomatic improvement has grown steadily from the time of inclusion in the study to the end of the follow-up, reaching a SAQ-7 score that qualify this population of tailored managed patients as being overall in excellent conditions.
4. Angina refractoriness to medical therapy was not consistently associated with coronary obstructions, confirming that non-obstructive

mechanisms may precipitate myocardial ischemia/angina, as acknowledged by current ESC Guidelines.

5. Persistence of symptoms in about one quarter of patients, and even more in females, strongly support the need for a better understanding of the mechanisms of angina in the individual patient to design a tailored treatment.

Funding

This work received no specific grant from any funding agency in the private, public or commercial sectors.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

The Authors wish to thank Dr. Daniela Consalvi for her helpful secretarial assistance in organizing the study, supporting the relations with investigators and managing the central data base.

Appendix A

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