

## Are cardiovascular rehabilitation programs implemented in young patients with acute coronary syndromes following revascularization procedures?

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### Abstract

**Objectives.** The aim of the study was to identify some particularities of young patients with acute coronary syndrome (ACS) related to risk factors, interventional details and differences between sexes. At the same time, the impact of the Anti-Smoking Law in Romania on these characteristics was monitored.

**Methods.** The study included young patients with ACS treated in the Catheterization Laboratory of the Heart Institute in Cluj-Napoca over a period of 4 years. Risk factors, epidemiological, clinical, biological, ultrasound, interventional findings, and in-hospital evolution were analyzed.

**Results.** Of all 789 patients, the majority (73.26%) were men. The predominant risk factors were smoking and those related to inadequate nutrition (dyslipidemia and overweight). Most of the patients had simple lesions, treated with a single stent. During the 4 years, a decrease in the number of non-smoking patients admitted for ACS (from 13.87% to 10.86%) was observed, and in-hospital evolution improved.

**Conclusion.** The main risk factors in young patients with ACS are related to an inadequate lifestyle, particularly smoking. The first beneficiaries of the Anti-Smoking Law in our country are passive smokers. Inclusion of these patients in cardiovascular rehabilitation programs might bring further benefits. More extensive, nationwide studies are required to confirm this fact.

**Key words:** *acute coronary syndrome, young patients, anti-smoking law,*

### Introduction

Although the entire spectrum of acute coronary syndromes (ACS) is characteristic of the elderly population, over the past years there has been an increase in their incidence among young people. This is mainly due to an unhealthy lifestyle: smoking, obesity, inadequate nutrition, sedentary (1). Their incidence in young individuals differs depending on the chosen age limit; up to 10% of the population under 50 years of age (1,2).

The affected young population has a different clinical picture, with fewer comorbidities (arterial hypertension, diabetes mellitus, renal failure), as well as a family history of cardiovascular disease, dyslipidemia, especially familial, and most of the times a smoking status (1-3).

Young men are up to three times more affected, the ratio decreasing with age (4). Young women may develop ACS through different mechanisms: microvascular dysfunction, spontaneous coronary dissection, and the unstable plaques are most frequently caused by erosion and not by rupture (5). Women have more traditional risk factors than men, an atypical presentation, and consequently, they

access medical services at a late stage. Prognosis is often more unfavorable.

The first-line treatment of patients with ACS is percutaneous coronary intervention (PCI). The majority of young people present with an ACS picture which on the 12-lead electrocardiogram does not show persistent ST segment elevation. At the time of angiography, a single unstable lesion is frequently detected (3), which is induced by the rupture of an insignificant soft atherosclerotic plaque that triggers the formation of the platelet thrombus, the main component of the lesion. Hence the particularity of treatment in this case. The association of intense antithrombotic treatment, possibly catheter aspiration, is imperative in the presence of angiographic signs of a considerable thrombus, as well as direct stenting of the lesion in order to avoid distal embolization of the treated vessel. Inclusion of these patients in cardiovascular rehabilitation programs is essential not only for increasing of their effort capacity, but also for a stricter control of cardiovascular risk factors and lifestyle modification.

## Material and methods

The study included young patients with ACS addressed to the catheterization and angiography laboratory of the Heart Institute in Cluj-Napoca in the period 2015-2019 and in whom stenotic coronary lesions of at least 50% were detected, with an indication of revascularization.

The age limit was 50 years for men and 55 years for women. All the medical data from our service was evaluated for the presence of cardiovascular risk factors, electro-cardiographic, echocardiographic, angiographic changes and the treatment used (including interventional treatment).

The analyzed risk factors were: arterial hypertension (HTN), dyslipidemia, obesity (BMI), diabetes mellitus (DM) and smoking.

We did an in-depth analysis of the lipid profile: total cholesterolemia, LDL-cholesterol, HDL-cholesterol and triglycerides levels.

The smoking status was considered non-smoker if the patient did not smoke at all in the last 10 years and former smoker if they had. Active smokers were considered all the patients which were smoking on daily basis at the time of ACS.

From an electrocardiographic and biological point of view, the type of coronary syndrome was assigned to the three categories: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP), and STEMI was classified depending on the location of the infarction territory.

Thus, we comparatively analyzed, over the 4 years, the data collected from the intervention files and the medical records: the first year – before the introduction of the Anti-Smoking Law in Romania (March 2016), the following year (April 2016 – April 2017), the transition year, immediately after the introduction of the law, and the last two years (April 2017 – April 2019).

In this context, we aimed to evidence the possible impact of the mentioned law on the percentage of young smokers, as well as the changes in the analyzed parameters over time.

These patients were not included in cardiovascular rehabilitation programs.

The study was approved by the Hospital Ethics Committee, all participants in the study signing an informed consent.

Microsoft Office Excel and SPSS v.20.0 statistical software was used for data management and analyses.

## Results

### General data

The general characteristics of the patients are synthesized in Table I. Of the 789 patients enrolled, the majority were men (73.26%), with a mean age of  $44.59 \pm 4.84$  years. The mean age of women was  $47.65 \pm 6.15$  years. From a demographic point of view, 60% of the patients came from urban areas; about half of these from Cluj county, and a quarter from the border counties: Alba, Sălaj and Bistrița-Năsăud (in order of prevalence). Regarding the risk factors found, smoking had the highest incidence, almost 90% of the patients being active smokers or former smokers. The great majority of the patients had dyslipidemia (85%) or a high BMI, over  $25 \text{ kg/m}^2$  (80%). About half of the patients were hypertensive (51.96%), and a small proportion were diabetic (16.6%). Among women, there was a lower incidence of the different types of dyslipidemia, overweight and smoking, and a higher incidence of hypertension and diabetes mellitus – Table I. The evolution of smoking status over the years is synthesized in Figure 1. We noticed a trend of a percentage reduction of the non-smokers patients with ACS during the years.

More than half of the enrolled patients (55.70%) presented STEMI: men - 58.82% vs women - 46.92% ( $p=0.002$ ) (Table II). Women had NSTEMI in a significantly higher proportion - 53.08% vs 41.18% ( $p=0.002$ ). With regard to the location of STEMI, 52.16% were in the anterior territory, followed by those located in the inferior territory (32.35%) and those in the lateral territory (15.49%). Of the biological parameters recorded, most of the patients had leukocytosis, a small proportion had anemia (6.5% in men vs 10% in women) and thrombocytosis (5%). A higher percentage of women (16.34 % vs 4.90%) had some degree of renal dysfunction according to the cut-off value of serum creatinine in our institution (serum creatinine was considered to be normal at values of less than 1.2 mg/dl for men and 0.9 mg/dl for women) (Table I).

### Interventional data

The main data related to the performance of the interventional procedures are shown in Table II. The great majority of the patients (86.4%) investigated in our laboratory underwent percutaneous revascularization; a small proportion (4%) underwent surgical revascularization, by aortocoronary bypass, and 9.5% of all patients were medically treated. Conservative treatment was indicated in a significantly higher proportion of

women compared to men - 14.22% vs 7.79%,  $p=0.006$ . These patients could not undergo revascularization because of severe diffuse involvement, or they refused surgery. The predominantly used approach was the radial approach (80%). Approximately half of the patients had a single vessel affected, resolved in the same session; a quarter had two vessels affected, and the rest had 3 or more vessels affected. Also, about 50% had a single lesion, and a quarter had 2 severe lesions on initial angiography. The majority of the lesions were stenotic (64.13%), particularly among women. These also had the left main coronary artery (LM) and the left anterior descendent artery (LAD) affected more frequently supplying a bigger amount of myocardium, while men had more frequent circumflex artery (CX) and right coronary artery (RCA) involvement. In three quarters of the patients, a single stent was used. The use of drug-eluting stents definitely increased over the years, from 65% to 93%. The mean length of the stents used was  $29.85\pm 16.09$  mm, slightly longer in women and the mean diameter was  $3.07\pm 0.40$  mm in women and  $3.24\pm 0.45$  mm in men, the later with a statistical significance ( $p=0.0001$ ). Thrombus aspiration was seldom used (13.43%) only in patients with STEMI, more frequent in men ( $p=0.035$ ).

Table III synthesizes the medication recommended at discharge. It can be seen that most of the patients had cardio-protective medication: aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors, without any differences between sexes. Ticagrelor was more frequently prescribed in men, while clopidogrel was more often prescribed in women. Eighty-three percent of the patients had a favorable evolution during admission, constant over the years. The mean in-hospital death rate was 3.16%.

## DISCUSSIONS

ACS represents the main cause of morbidity and mortality worldwide and its incidence will continue to increase, especially in developing countries (6). In Europe, cardiovascular diseases represent the main causes of death: 40% in men (19% - ischemic heart disease) and 49% in women (19% ischemic heart disease) (7). Cardiovascular diseases are the main cause of mortality in Romania. Of these, acute coronary syndromes (ACS) are responsible for more than half of the deaths. The RO-STEMI (ROmanian ST-Elevation Myocardial Infarction) registry enrolled 15076 STEMI patients with a mean age of

$62.7\pm 12.7$  years from 19 interventional centers and 45 non-interventional centers. Seventy percent were males (8). The main risk factor detected was arterial hypertension, but among young people under 50 years of age, tobacco use was found in more than 70% of the patients (8). Among our cases, in patients under 55 years of age with ACS, the main risk factor detected was smoking, followed by dyslipidemia and body overweight. It should be emphasized that these risk factors are most of the times reversible by using monitoring programs, recommendations and lifestyle changing interventions. Smoking is the most frequent risk factor in young coronary patients. This is responsible for 10% of the deaths of cardiovascular cause according to the latest data provided by the World Health Organization (9). Hence the efforts made at international level to stop this scourge. Among young people, the prevalence of smoking, either active or passive, is the highest. Fournier et al. reported a proportion of 92% smokers among young persons under 40 years of age with acute myocardial infarction (10). Another study conducted by Panagiotakos et al. showed the fact that young smokers have an up to 6 times higher risk to develop myocardial infarction (11). Among our cases, the proportion of smokers was almost 90%, with the predominance of active male smokers. We aimed to monitor their prevalence among patients with ACS presenting to our service, before and after the introduction of the Anti-Smoking Law in Romania in March 2016. After many years of attempts from different medical societies among others, this law was published by the decision-making authorities in our country. Its beneficial effects can already be observed from various polls and estimations, but for a more accurate determination of these effects, a thorough investigation of statistical data from hospitals across the entire country is required. Many studies have shown a reduction in the number of hospitalizations for ACS after the introduction of public anti-smoking laws in the countries concerned. Pell et al. evidenced a 17% reduction of hospitalizations in Scotland in 2006, after the introduction of the anti-smoking law, compared to a reduction of only 4% reported in Great Britain, where there was no such law at that time (12). In Norway, according to the CVNOR registry data, the decrease in the incidence of ACS was mainly due to the decrease in the prevalence of smoking (13). On the other hand, a study in New Zealand reported that despite the public laws applied, the proportion of young

smokers was about 70% (2). Hence it can be concluded that the main beneficiaries of this law are probably passive smokers, most of which are young people who frequently attend public spaces polluted by cigarette smoke. Passive smoking is one of the most common polluting factors in closed spaces. It was estimated that in 2011, globally, 40% of children and 35% of women were regularly exposed to environmental cigarette smoke, as well as more than 50% of the general population in Eastern European countries (14). In our study, we observed a decrease in the prevalence of non-smokers with ACS over the years, which could be explained by the beneficial effects of the law regarding the reduction of passive smoking in public places, frequently attended by young people. In Ireland, the application of a national ban on smoking in public places promptly led to a 12% decrease in ACS hospitalizations, and two years later, a further 13% decrease was seen (15).

Other risk factors with a high prevalence in our study were dyslipidemia and overweight, the latter being predominant among men. Recent data of the EUROASPIRE V study show that in the coronary patients of the 27 countries included in the study, among which Romania, obesity was present in 38%, and low-density lipoprotein (LDL) cholesterol  $\geq 70$  mg/dL was found in 71% (16). The data of the same study demonstrate that most of the patients had increased LDL cholesterol values (17). In our study, hypertriglyceridemia, lower HDL cholesterol values, smoking and overweight were more frequently found in men, with statistical significance. In contrast, arterial hypertension and diabetes mellitus were more frequent in women. In a retrospective analysis using the National Inpatient Sample (NIS), which included young patients under 45 years of age with acute myocardial infarction, young women had a higher prevalence of anemia, chronic lung disease, obesity, peripheral vascular disease, and diabetes. In the case of young men, dyslipidemia, smoking, and alcohol were predominant (18).

Our study shows a slightly increased prevalence of STEMI (55%) among men, STEMI located in the anterior territory being the most frequently found, particularly in women, which corresponds to the involvement of the main arteries (LM and LAD) and to a worse prognosis.

From a technical point of view, PCI procedures have evolved with the optimization of the equipment and materials and the development of new studies that have changed the recommendations (19). The arterial

approach predominantly used in our service was radial, according to the recommendations to reduce local hemorrhagic complications. If in 2014, only 10% of PCIs involved the placement of drug-eluting stents (DES), the following year, these were found in more than half of the procedures, and in the last two years, the percentage of DES was over 90%. The majority of the young patients had a single lesion of one coronary artery, and the proportion of percutaneously revascularized ACS followed an ascending trend from 80% to 90% in the last year. Obviously, the number of thrombaspiration procedures decreased, according to current recommendations (19) being utilized especially in men in accordance with the higher incidence of STEMI between them. A relative estimation of the atherosclerotic load of the coronary tree was intended by quantifying the number of stents and their length per patient. However, there were no detectable differences regarding the stent parameters over the investigated years. Of notice, stent caliber was significantly larger in men than women. A reduction in the rate of percutaneous reinterventions in the young patients was observed over time, possibly in the context of an improvement in the techniques and materials used, of the optimization of treatment, especially with antiplatelet drugs. In this context, a significant decrease in the in-hospital death rate from 4% to 2.5-2.9% was registered. According to the EUROASPIRE V study, the cardio-protective medication prescription rate was: antiplatelets 93%, beta-blockers 81%, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers 75%, and statins 80%. In the current study, except for renin-angiotensin-aldosterone system inhibitors, all medications were recommended in a proportion of over 90% (16). Considering the presence of the above-mentioned cardiovascular risk factors, we emphasize the necessity of cardiovascular rehabilitation programs in these patients due to several advantages. The main benefit is an increase in survival and of the effort capacity of these patients (19). Secondly, sustained physical activity has also proven its advantages on the reduction of cardiovascular risk factors, as it leads to decrease in the values of total cholesterol and LDL-cholesterol, and moreover an increase in the values of HDL-cholesterol (20). Furthermore, it contributes to normalization of blood pressure values in hypertensive patients (21) and to improvement in flow-mediated dilatation (20). Thirdly, performing such programs under surveillance might contribute

to the monitoring of the approach in lifestyle changes used by these patients, which should also be advised to give up smoking (22). Finally, these programs might lead to adherence in the administration of prescribed cardio-protective medication (23). However, rehabilitation programs are globally underused, with a reported percent of only 25-30% among male patients and 11-20% among female patients (24).

### Conclusions

The main risk factors in patients under 55 years of age diagnosed with ACS were modifiable, being represented by smoking, dyslipidemia and overweight, in close relationship with an unhealthy lifestyle. The introduction of the anti-smoking law in Romania is salutary, and this study is the first, to our knowledge, which showed its first positive effects, particularly by reducing the effects of passive smoking in young people. There are small differences regarding the clinical characteristics, drug therapy and revascularization management between men and women, which deserve to be considered in order to particularize diagnosis and treatment depending on sex. Correct treatment of these patients both in terms of intervention and cardio-protective medication can improve their long-term prognosis. Inclusion of these patients in cardiovascular rehabilitation programs might bring further benefits, along with the reduction of cardiovascular risk factors and improving the quality of life.

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Table I. General characteristics of the patients

	Total	Men	Women	P value
Mean age±SD	45.41±5.39	44.596±4.843	47.658±6.159	
Hypertension n (%)	410 (51.96)	285 (49.31)	125 (59.24)	0.013
Diabetes mellitus n (%)	132 (16.6)	85 (14.71)	47 (22.27)	0.012
Hypercholesterolemia n (%)	289 (43.48)	215 (44.06)	74 (41.57)	0.567
LDL-cholesterol ↑n (%)	368 (62.37)	278 (64.2)	90 (57.32)	0.127
Triglycerides ↑ n (%)	334 (52.10)	264 (55.93)	70 (41.18)	0.0009
HDL-cholesterol ↓n (%)	430 (63.70)	332 (73.13)	98 (59.39)	<0.001
Active smokers n (%)	551 (82.98)	422 (86.12)	129 (74.14)	0.0003
Former smokers n (%)	32 (4.82)	25 (5.10)	7 (4.02)	0.568
Non-smokers n (%)	81 (12.20)	43 (8.78)	38 (21.84)	<0.001
BMI> 25 kg/m <sup>2</sup>	385 (79.55)	295 (84.77)	90 (66.18)	0.000005
Blood urea nitrogen↑ n (%)	60 (7.97)	27 (4.9)	33 (16.34)	<0.001
Anemia n (%)	56 (7.47)	36 (6.55)	20 (10)	0.111
Leukocytosis n (%)	500 (67.11)	383 (69.89)	117 (59.39)	0.007
Thrombocytosis n (%)	39 (5.21)	24 (4.36)	15 (7.54)	0.084

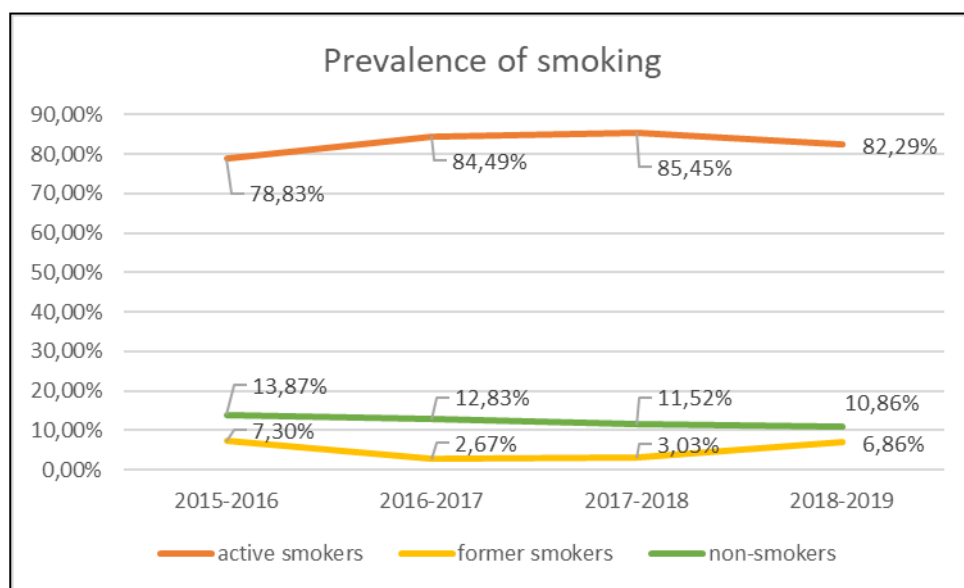


Figure 1. Prevalence of smokers and non-smokers in the period 2015-2019. Patients who quit smoking in the past 10 years, were defined as former smokers

Table II. Types and revascularization treatment of the acute coronary syndromes (ACS) and the variation between men and women.

	Total	Men	Women	P value
<i>Type of ACS n (%)</i>				
STEMI	439 (55.64)	340 (58.82)	99 (46.92)	0.002
ACS without ST segment elevation	350 (44.36)	238 (41.18)	112 (53.08)	0.002
PCI n (%)	682 (86.44)	509 (88.06)	173 (81.99)	0.027
CABG n (%)	32 (4.05)	24 (4.15)	8 (3.79)	0.82
Conservative n (%)	75 (9.51)	45 (7.79)	30 (14.22)	0.006
<i>Acute vessel n (%)</i>				
LM/LAD	403 (51.08)	284 (49.13)	119 (56.4)	0.07
RCA/CX	358 (45.37)	275 (47.58)	83 (39.34)	0.039
<i>No. of vessel n (%)</i>				
1	438 (55.51)	320 (55.36)	118 (55.92)	0.888
2	206 (26.11)	151 (26.12)	55 (26.07)	0.986
≥3	145 (18.38)	107 (18.51)	38 (18.01)	0.871
<i>No. of lesions n (%)</i>				
1	459 (58.17)	340 (58.82)	119 (56.4)	0.54
2	171 (21.67)	119 (20.59)	52 (24.64)	0.22
≥3	159 (20.15)	119 (20.59)	40 (18.96)	0.613
<i>Acute lesion n (%)</i>				
occlusion	283 (35.87)	221 (38.24)	62 (29.38)	0.021
Complete revascularization n (%)	128 (41.96)	94 (42.15)	34 (41.46)	0.914
Aspiration	59	52	7	0.035
Previous revascularization n (%)	93 (11.78)	69 (11.94)	24 (11.37)	0.828
No. of stents/ patient	1.3443	1.1332	1.13744	
No. of DES n (%)	743 (83.11)	550 (84.09)	193 (80.42)	0.593
Stent length (mean±SD)	29.854±16.094	29.284±15.356	31.536±18.002	0.142
Stent diameter (mean±SD)	3.202±0.448	3.248±0.453	3.075±0.409	0.0001

Table III. Medication recommended at discharge

	Total	Men	Women	P value
<i>Treatment at discharge n (%)</i>				
Aspirin n (%)	757 (99.08)	556 (99.11)	201 (99.01)	0.328
Clopidogrel n (%)	316 (41.36)	210 (37.43)	106 (52.22)	0.0002
Ticagrelor n (%)	429 (56.15)	337 (60.07)	92 (45.32)	0.0002
Anticoagulant n (%)	31 (4.06)	23 (4.1)	8 (3.94)	0.921
Statin n (%)	751 (98.30)	551 (98.22)	200 (98.52)	0.593
Beta-blocker n (%)	702 (91.88)	521 (92.87)	181 (89.16)	0.113
ACEI n (%)	615 (80.50)	457 (81.46)	158 (77.83)	0.286
Diuretic n (%)	151 (19.76)	97 (17.29)	54 (26.60)	0.004