

CLINICAL UPDATE

# Particularities of Acute Myocardial Infarction in Young Adults

Larisa Anghel<sup>1,2</sup>, Cristina Prisacariu<sup>1,2</sup>, Radu Sascău<sup>1,2</sup>, Liviu Macovei<sup>1,2</sup>, Elena-Cătălina Cristea<sup>1,2</sup>, Georgiana Prisacariu<sup>3</sup>, Cristian Stătescu<sup>1,2</sup>

<sup>1</sup> “Prof. Dr. George I.M. Georgescu” Cardiovascular Diseases Institute, Iași, Romania

<sup>2</sup> “Grigore T. Popa” University of Medicine and Pharmacy, Iași, Romania

<sup>3</sup> “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

## ABSTRACT

Coronary heart disease occurs more often in patients over the age of 45. However, recent data shows a growing incidence of coronary events in younger patients also. Young patients with acute myocardial infarction (AMI) represent a relatively small proportion of subjects suffering from an acute ischemic event. However, they represent a subset that is distinguished from elderly patients by a different profile of risk factors, often atypical clinical presentation, and different prognosis. The prevalence of risk factors such as smoking, dyslipidemia, and a family history of coronary events is higher in this group of patients compared to the general population with AMI. Because of an important negative impact on the patients' psychology, impaired working abilities, and a high socioeconomical burden, myocardial infarction in young patients represents an important cardiovascular pathology. This manuscript aims to present the particularities of AMI occurring at a young age, in comparison with the rest of the population with AMI.

**Keywords:** myocardial infarction, young patients, coronary heart disease, prognosis, mortality

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## CORRESPONDENCE

**Cristina Prisacariu**

“Prof. Dr. George I.M. Georgescu”  
Cardiovascular Diseases Institute  
Blvd. Carol I nr. 50,  
700503 Iași, Romania  
Fax: +40 232 219 270  
E-mail: prisacariu88@yahoo.com

## INTRODUCTION

The main cause of mortality at a global level is coronary heart disease (CHD). Although the rate of cardiovascular deaths is decreasing in highly developed countries, the prevalence of the disease is still high in developing and underdeveloped countries, accounting for about 80% of all deaths attributable to cardiovascular disease.<sup>1</sup> This also includes Eastern Europe, including Romania, where, according to the National Institute of Statistics, in 2016,

60% of deaths occurred in the context of a cardiovascular disorder.<sup>2</sup> Data related to early CHD and acute myocardial infarction (AMI) in the “young” segment of the population is scarce, despite the fact that myocardial infarction can have devastating consequences in the young demographic, mainly because of its higher negative psychological impact, decreased working abilities, as well as higher socioeconomical burden.<sup>3</sup>

In terms of defining the notion of “young” or “young adult”, current data varies from 40 to 55 years, an age

Larisa Anghel: Blv. Carol I nr. 50, 700503 Iași, Romania. Tel: +40 232 211 834, E-mail: larisa\_med86@yahoo.com

Radu Sascău: Blv. Carol I nr. 50, 700503 Iași, Romania. Tel: +40 232 211 834, E-mail: radu.sascau@gmail.com

Liviu Macovei: Blv. Carol I nr. 50, 700503 Iași, Romania. Tel: +40 232 211 834, E-mail: liviughemacovei@yahoo.com

Elena-Cătălina Cristea: Blv. Carol I nr. 50, 700503 Iași, Romania. Tel: +40 232 211 834, E-mail: catalicio02@yahoo.com

Georgiana Prisacariu: Blv. Eroii Sanitari nr. 8, 050474 București, Romania. Tel: +40 21 318 0719, E-mail: prisacariu88@yahoo.com

Cristian Stătescu: Blv. Carol I nr. 50, 700503 Iași, Romania. Tel: +40 232 211 834, E-mail: cstatescu@gmail.com

limit that has grown over time secondary to the process of continuous aging and increasing life expectancy.<sup>4–6</sup> However, in the definition of acute ST-segment elevation myocardial infarction, according to the current ESC Guidelines, the term “young” defines patients under the age of 45 years, while very young people are considered to be under the age of 35.<sup>7,8</sup>

There is only few information published in the literature on AMI in young people. Probably the most comprehensive study on the matter is the Framingham Heart Study, which for a 10-year follow-up period reported an incidence of AMI in young people (defined in this case under 55 years of age) of 51.1/1,000 men and 7.4/1,000 women,<sup>9</sup> compared to older adults, in which the incidence ranged between 8.45% for women and 23.4% for men.<sup>7</sup>

Most young subjects with AMI have been reported to present minimum one recognizable cardiovascular risk factor.<sup>10,11</sup> Hoit *et al.* found that young AMI patients present a higher rate of chronic tobacco use, family history of early coronary heart disease, as well as a higher prevalence of male gender compared to older AMI subjects.<sup>12</sup> Yusuf *et al.* reported cigarette smoking as being the main modifiable cardiovascular risk factor in this AMI age demographic,<sup>13</sup> while other studies reported an incidence of chronic tobacco use in young AMI subjects ranging from 51 to 89%.<sup>12–18</sup> Similarly, Aggarwal *et al.* reported that smoking was significantly more prevalent in young AMI patients compared to an age- and gender-matched cohort that presented with complaints unrelated to the cardiovascular system.<sup>19</sup> Young AMI patients have also been shown to present a two-fold rate of positive family history for premature coronary heart disease compared to their older counterparts, a family history of CHD being present in first-degree relatives under the age of 55–60 years.<sup>3,6,17</sup>

## CAUSES OF MYOCARDIAL INFARCTION IN THE “YOUNG”

There are two causes of AMI in the young population: atherosclerotic and non-atherosclerotic.

### 1. ATHEROSCLEROTIC CAUSES

For a long time, it has been thought that atherosclerosis is a disease of the modern population and that it is closely correlated to patient lifestyle. In fact, the atherosclerotic process begins from early childhood, and early detection can help prevent or delay the development of cardiovascular pathologies. One can say that atherosclerosis starts silently and ends noisily.<sup>20</sup>

An essential role in the onset of the atherosclerotic process is attributed to the vascular endothelium. Endothelial dysfunction increases vascular permeability with lipoprotein accumulation in the intima, adherence of monocytes and platelets, increased endothelial aggregation activity, and decreased vasodilatation properties.<sup>21</sup> Endothelial function can be genetically determined, as it is influenced by insertion/deletion polymorphism of genes that encode the angiotensin-converting enzyme, as well as the polymorphism of the gene encoding the vascular endothelial growth factor that influences the severity of coronary artery disease.<sup>20</sup>

### 2. NON-ATHEROSCLEROTIC CAUSES

Angiographically normal coronary arteries have been found in approximately 20% of young patients with myocardial infarction, unlike those over the age of 45, in whom the prevalence is around 10%. The percentage is even higher for patients under 35 years, being reported as up to 53%.<sup>17,22</sup>

Non-atherosclerotic causes of AMI include: inflammatory disorders (luteal arteritis, Takayasu's disease, Kawasaki's disease), coronary artery trauma, metabolic or proliferative diseases (Fabry's disease, amyloidosis, coronary fibrosis secondary to radiotherapy), lumen stenosis of various causes (Prinzmetal angina, aortic or coronary artery dissection), coronary embolism (infectious endocarditis, mitral valve prolapse, embolism from valvular prostheses or fibroelastoma), congenital coronary anomalies (abnormal coronary artery origin from the pulmonary artery), an altered balance between oxygen demand and supply in the myocardium (aortic stenosis, aortic insufficiency, pulmonary arterial hypertension, thyrotoxicosis), hematological causes (polycythemia vera, thrombocytosis, disseminated intravascular coagulation).<sup>6</sup>

### CLASSICAL CARDIOVASCULAR RISK FACTORS

Young people diagnosed with AMI tend to have a different risk factor profile from that of older patients. In young patients, the cardiovascular risk profile is dominated by smoking, dyslipidemia, and a family history of coronary artery disease at a young age (Table 1).<sup>23,24</sup>

Most young patients with AMI are males; Table 2 summarizes the current literature data on the frequency of risk factors by gender (Table 2).<sup>24</sup>

In most studies, the male : female ratio of the incidence of AMI in young subjects ranges between 5 : 2 and 9 : 1.<sup>11,21,22</sup> A much higher incidence in men than in wom-

**TABLE 1.** Comparison between cardiovascular risk factors<sup>24</sup>

	Patients <45 years	Patients >45 years
Prevalence of myocardial infarction	–	+
Only one cardiovascular risk factor	–	+
Smoking	+	–
Family history	+	–
Dyslipidemia	+	–
Arterial hypertension	–	+
Diabetes mellitus	–	+
Coronary artery disease	+	–

en has also been reported in a 7-year study in America.<sup>12</sup> However, in-hospital mortality was significantly higher for women: 4.5% versus 3%.<sup>25</sup>

Smoking is the most common risk factor identified in younger patients who have had a cardiovascular event, different studies reporting an incidence between 55% and 89%.<sup>3,11,18</sup>

Scientific data often report a higher prevalence of dyslipidemia in patients under 45 years who had suffered an acute coronary event, compared to arterial hypertension that is more common in patients over 45 years of age. The incidence of arterial hypertension was reported at around 23% in a European study,<sup>26</sup> compared with 25% in a study conducted in India.<sup>11</sup>

Diabetes mellitus, an independent risk factor in cardiovascular pathology, is reported in a smaller number of cases in younger patients suffering AMI compared to elderly patients. The prevalence of diabetes ranged from 14.7% in a study in Australia,<sup>3</sup> to 20% in a study performed on an Indian population.<sup>11</sup> Recent data shows that the risk of myocardial infarction is six times higher in young women with diabetes compared to those without diabetes. Also, the risk is four times higher in women with hypertension and three times higher in those with dyslipidemia, compared to women in whom these risk factors are not present.<sup>27,28</sup>

Young people diagnosed with AMI tend to have an increased body mass index, and more often, central obesity.<sup>3</sup> Unfortunately, the global trend shows an increasing number of overweight and obese people, especially in the young, suggesting a possible increase in the incidence of cardiovascular disease in younger populations. A study conducted in India reports a 20% prevalence of obesity and a 46% prevalence of sedentary lifestyle in a group of young patients with AMI hospitalized during a year.<sup>11</sup> The increasing incidence of obesity can be explained by the acceleration of the urbanization process, and by changes in eating habits with low consumption of vegetables and

**TABLE 2.** Different characteristics between young men and women with cardiovascular events<sup>24</sup>

	Men <45 years	Women <45 years
Prevalence	+	–
Smoking	+	–
Dyslipidemia	+	–
Family history	+	–
Arterial hypertension	–	+
Diabetes mellitus	–	+
Associated pathologies	–	+
Coronary vasospasm	+	–
In-hospital mortality	–	+
Long-term mortality	–	+

eating high-fat foods. The urbanization process has also changed the lifestyle of the young population, from physical work to office work, with less hours spent outdoors, with less exercise and more psychological stress.<sup>3</sup> Obese subjects have been shown to present better outcomes and lower rates of complications after coronary revascularization procedures, despite having a high risk for developing coronary artery disease, a phenomenon that has been termed as the “obesity paradox”. The obesity paradox is based on several observations that obese subjects are at a higher risk for CHD, with a concomitant lower risk for developing early and late complications once the cardiovascular disease has been diagnosed, with significantly lower rates of cardiovascular related mortality, myocardial infarction, and their related complications.<sup>29</sup>

## OTHER CARDIOVASCULAR RISK FACTORS

Hyperhomocysteinemia is an independent and important risk factor that directly influences the rapid development of atherosclerosis and subsequent acute coronary and cerebrovascular events. Homocysteine is an amino acid that is formed after the metabolization of methionine and cysteine under the influence of vitamins B6, B12 and folic acid.<sup>28</sup> Disorders of the metabolism of homocysteine lead to increased serum and urine levels of homocysteine. The risk of cardiovascular events is explained by the direct toxic effect of homocysteine on the vascular endothelium, as well as its indirect effect by stimulating the proliferation of vascular smooth muscle cells, platelet activation, and alteration of fibrinolysis. In the blood serum, homocysteine undergoes oxidation with free radical formation that favors the atherogenic process, and the vessels lose their elasticity and dilating ability.<sup>4</sup>

Another independent risk factor for ischemic cardiovascular disease is the level of lipoprotein(a).<sup>28</sup> As a cardiovascular risk factor, it interferes with plasmin generation because it has a plasminogen-like structure; it is deposited in the thickness of the arterial wall, especially in areas with atherosclerotic plaques, together with fibrinogen.<sup>30</sup>

Thrombophilia, including thrombotic events, has been specifically studied in young patients who have had an AMI. In women, AMI was commonly associated with an increased procoagulant activity due to an increase in V and II factor concentrations, while in men it was mainly determined by homozygosity for MTHFR variants with hyperhomocystinemia.<sup>31</sup> Primary or secondary thrombocytosis may represent a cause of myocardial infarction in young people and have been described as precipitating factors for coronary artery occlusion in case of pre-existing atheromatous lesions, although myocardial infarction caused by splenectomy secondary to thrombocytosis has been reported in the absence of coronary changes suggestive of atherothrombotic lesions.<sup>32</sup>

Also, mutations and dysfunctions of factor V Leiden are associated with a high risk of cardiovascular events, being more commonly reported in smokers and in those who use oral contraceptives, because they increase the risk through their procoagulant effect.<sup>33,34</sup>

Connective tissue diseases, through chronic systemic inflammation, and sometimes through long-term therapy, favor coronary atherosclerosis. Although coronary artery disease could complicate the development of connective tissue disease, AMI is a rarely reported entity in these cases, most often through coronary vasculitis and/or atherothrombotic occlusive lesions.

According to several studies, women with systemic lupus erythematosus associate a 50-fold risk of developing myocardial infarction compared to women without the disease, and coronary artery disease occurs in premenopausal subjects.<sup>21</sup>

Antiphospholipid antibody syndrome (APS) is a thrombotic disorder of both the arteries and veins, associated with AMI in approximately 2.8% of affected patients,<sup>31</sup> but in young patients with acute coronary syndromes it was diagnosed in 13–21% of cases.<sup>35</sup> Cardiovascular risk is more evident in pregnant women, being amplified by the association of other cardiovascular risk factors. The mechanism of myocardial ischemia in APS is considered to be acute thrombosis of coronary arteries, which requires therapeutic anticoagulation, in contrast with the atherosclerotic plaque rupture that is effectively treated with antiplatelet and stenting therapies.<sup>35</sup> APS should be considered in young patients with AMI, especially if pre-

vious unprovoked thromboses are present, lower platelet counts, high partial thromboplastin times, and normal coronary arteries or coronary thromboses are identified. Anticoagulation should be provided for life, even after a single first episode; however, the role of coronary stents in these patients is still under investigation and requires further studies.<sup>31</sup>

Contraceptive medication has been reported in 40% of women who have had an AMI.<sup>33</sup> However, studies have shown a favorable effect on venous thrombosis, less on arterial blood pressure. Data related to AMI in this group are contradictory, being influenced by the generation of contraceptives used, the presence or absence of smoking, high blood pressure or prothrombotic status, which may increase by 10 times the risk of myocardial infarction.<sup>36</sup>

Cocaine use has been associated with many cardiovascular complications, including AMI.<sup>7,37</sup> Among patients younger than 30 years admitted with non-traumatic anterior chest pain, cocaine use was identified in 48% of cases.<sup>3,5</sup> Consumption of marijuana and amphetamines is discussed in this setting without being certified.<sup>38</sup>

## CLINICAL PRESENTATION AND MANAGEMENT

Studies show that approximately one third of young AMI subjects will present with ST-segment elevation myocardial infarction (STEMI) and two-thirds will have non-ST elevation myocardial infarction (NSTEMI).<sup>14</sup> While there is a reduced incidence of STEMI in this age demographic, the rate of young AMI patients is increasing.<sup>14</sup> Many young AMI patients present with no medical history of chest pain, previous AMI, or a history of heart failure compared to the older patient demographic.<sup>6,39</sup> A study published by Egiziano *et al.* showed that merely 25% of “young” MI subjects had presented chest pain in the previous 30 days that led up to the acute coronary event, and the rate was even lower for female patients.<sup>12</sup>

Compared to their older counterparts, younger patients with AMI have less extensive coronary artery disease. Zimmerman *et al.* reported angiographically normal coronary arteries in 16% to 21% of patients (males versus females, respectively).<sup>40</sup> Single coronary artery disease that affects the left anterior descending artery is more prevalent among young AMI patients.<sup>15,40</sup> Also, spontaneous coronary artery dissection is more frequent in young patients than their older counterparts. Tweet *et al.* described the occurrence of this pathology in younger AMI subjects, aged around 43 years, most often females.<sup>41</sup>

The therapeutic management of AMI in young patients is not dependent on age and the guidelines suggest

the same treatment regardless of the age demographic.<sup>7</sup> Younger age is an independent favorable prognostic factor for thrombolysis in AMI, and it should be used in situations when primary coronary revascularization cannot be performed.<sup>42</sup> Along with medical treatment, control and modification of cardiovascular risk factors is extremely important in the management of young AMI patients. Chronic tobacco use is the main cardiovascular risk factor that can be targeted in all AMI patients, especially in the young. In a systematic review conducted by Critchley *et al.* on the benefit of smoking cessation in patients with CHD, a 36% reduction in the crude relative risk of death was observed in patients with CHD who had given up smoking (RR 0.64; 95% CI: 0.58–0.71).<sup>43</sup> Smoking cessation has also been shown to reduce recurrent major adverse cardiovascular events.<sup>42,43</sup>

## PROGNOSIS

In-hospital and short-term outcomes are generally favorable in young AMI subjects, with a reported in-hospital and six-month mortality of 0.7% and 3.1%, respectively,<sup>44</sup> compared to their older counterparts whose mortality ranges between 8.3% and 12%.<sup>45</sup> The most powerful independent predictor for mortality is a left ventricular ejection fraction  $\leq 45\%$  (OR 4.4; 95% CI: 1.6–12.4).<sup>1</sup> However, the rate of congestive heart failure following AMI has been significantly reduced due to a mixture of factors including the prophylactic implantation of intracardiac defibrillators.<sup>14</sup> Other factors associated with higher mortality are heart failure, malignant ventricular arrhythmias, angina pectoris, and re-infarction.<sup>1</sup>

There are also several problems associated with a significant reduction of health-related quality of life post MI in “young” MI patients. Depression is one of the most frequent problems occurring after the acute event.<sup>46</sup> Denollet *et al.* had reported a rate of 47% of patients with depressive symptoms after an AMI, in a population aged 54 years.<sup>47</sup> Recurrent angina pectoris may also significantly impair the health-related quality of life post AMI. Therefore, identification and management of depression and recurrent chest pain after AMI in young subjects is of great importance in improving the health-related quality of life of these patients.<sup>48</sup>

## CONCLUSIONS

The prevalence of myocardial infarction in young patients is still high in developing and underdeveloped countries. Young patients with AMI represent a subset of patients that

is distinguished by a different risk factor profile, atypical clinical presentation, and different prognosis compared to elderly patients. Short-term outcomes following an AMI are relatively favorable in this age demographic, but long-term outcomes are relatively poor, especially in subjects with impaired left ventricular ejection fraction.

## CONFLICT OF INTEREST

We declare that there is no conflict of interest.

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