Optimal treatment for patients after myocardial infarction: some current concepts and controversies

Grzegorz Gajos

Department of Coronary Heart Disease, Institute of Cardiology, Jagiellonian University, The John Paul II Hospital in Krakow, Kraków, Poland

Abstract: Acute coronary syndromes areone of the most common causes for hospitalizations in developed countries. It is estimated that there are around 1 million patients in Poland after myocardial infarction (MI) requiring medical care. Implementation of optimal treatment in these patients is a significant clinical and social problem. Clinical practice guidelines published by the European Society of Cardiology (ESC) are focused on the crucial tasks such as regular physical activity sufficient to increase exercise capacity, smoking cessation, a Mediterranean diet, intensive control of risk factors for atherosclerosis (hypertension, diabetes, hyperlipidemia), combination pharmacotherapy and in selected cases, coronary revascularization. Of particular importance is that all patients who have had an acute MI should receive optimal treatment with a combination of the drugs that are recommended as class I by the ESC guidelines. Recent registries showed that some of these drugs, including aspirin, clopidogrel, angiotensin-converting enzyme inhibitors, β-blockers and statins, are commonly used in clinical practice in Poland. Recently, it has been highlighted that pharmacological therapy in MI patients should be extended by adding newer agents of the class I recommendations such as omega-3 acid ethyl esters and in selected patients, eplerenone.

Key words: acute coronary syndromes, guidelines, prognosis, secondary prevention

Acute coronary syndromes represent frequent and serious clinical problems, being a significant challenge for health care systems. Acute coronary syndromes are the most common cause of hospitalization of adults in developed countries [1]. Unstable angina, ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) are basic clinical types of acute coronary syndromes. Due to lack of appropriate registries, assessment of acute coronary syndrome morbidity and mortality in Poland is based on the data extrapolated from European and world registries [1]. It is considered that a total number of all acute coronary syndromes in Poland amounts annually to 250,000, at least 150,000 of which are myocardial infarctions (STEMI and NSTEMI) [1]. Patients with previous myocardial infarction should also be included to this number. Based on the British data, a number of patients after myocardial infarction in Polish population may be estimated at 800,000 [2]. Choice of optimal therapy should be made by physicians in almost 1,000,000 Poles after recent and remote myocardial infarction.

Everyday medical practice frequently involves decisions relevant for health and life of patients within limited time. The decisions made are based on knowledge, experience and principles of medical ethics. There exist numerous sources helpful in making appropriate medical decisions. Working out diagnostics and treatment guidelines is becoming still more popular in medicine. To make the guidelines become 'signposts' in clinical practice, they should be worked out strictly according to the properly interpreted data based on reliable, currently published clinical papers. This purpose is met by clinical practice guidelines developed by scientific societies. It should be emphasized that instructions presented in those guidelines are one of the factors considered while making clinical decisions and that their use involves individual assessment of clinical situation.

Main guidelines for the treatment of patients after myocardial infarction were published by the following institutions:

1) European Society of Cardiology (ESC). Including guidelines of 2003 (STEMI) [3], of 2007 (NSTEMI) [4] and also of 2005 (percutaneous coronary interventions) [5]
2) American College of Cardiology/American Heart Association (ACC/AHA) in 2006 and 2007 [6,7]
3) National Institute for Health and Clinical Excellence (NICE) in 2007 [2].

Correspondence to:
Grzegorz Gajos, MD, PhD, Klinika Choroby Wieńcowej, Instytut Kardiologii, Collegium Medicum Uniwersytetu Jagiellońskiego, Szpital im. Jana Pawła II, ul. Prądnicka 80, 31-202 Kraków, Poland, phone/fax: +48-12-633-67-44, e-mail: ggajos@szpitaljp2.krakow.pl
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Given the fact that Polish Society of Cardiology recommended use of the European guidelines in Poland, the principles of treatment of patients after myocardial infarction presented below conform to those instructions.

It should, however, be noted that the guidelines for STEMI treatment were developed in Europe more than 4 years ago. Since then, numerous myocardial infarction treatment reports and recommendations issued by other Societies were published. Therefore, the aim of this article is to present new views and controversies, as well as the resulting clinical implications in the treatment of patients after myocardial infarction (STEMI and NSTEMI).

Guidelines for treatment of patients after myocardial infarction – priorities

1. Each patient should receive recommendations concer ning taking regular physical activity to improve physical fitness. The recommendations shall apply to introduction of exercise, for at least 20–30 minutes a day, until one feels a bit tired. Exercise shall be started gradually, not leading to exhaustion and aiming at improvement of physical fitness. Cardiological rehabilitation shall be recommended and available to all patients after myocardial infarction.

2. All smoking patients should not only be encouraged to stop smoking, but also shall be provided aid in fighting the habit.

3. The patients should receive instructions concerning an appropriate diet. Currently, a Mediterranean-type diet is re commended. It includes more vegetables, fruit, fish, bread and less meat. The diet replaces butter and full-fat cheese with vegetable fat-based products.

4. An essential component of treatment of patients after acute myocardial infarction should be intensive control of at herosclerosis risk factors, especially arterial pressure, diabetes and hyperlipidemia

5. In all patients after acute myocardial infarction, introduction of combined treatment with the following medications should be considered:

- acetylsalicylic acid (aspirin)
- clopidogrel (NSTEMI – 12 months, STEMI – at least 1 month)
- angiotensin-converting enzyme inhibitor
- β-adrenolytic
- statin
- omega-3-acid ethyl esters (STEMI)

6. In patients after acute myocardial infarction with diagnosed left ventricle dysfunction and cardiovascular insufficiency or diabetes, treatment with aldosterone antagonist should be considered [2,4].

7. In every patient after acute myocardial infarction, surgical coronary revascularization should be considered. It requires cardiological consultation, scheduling for appropriate additional tests and taking into account the presence of comorbidities.

Some innovations and controversies

Antiplatelet treatment

Acetylsalicylic acid in 75–100 mg doses is a basis for long--term treatment in patients after myocardial infarction [4]. Within a short time after myocardial infarction, clopidogrel is added (12 months in case of NSTEMI). European guidelines do not specify in detail the duration of combined antiplatelet treatment in patients after STEMI [3,5]. They only conclude that the results of studies concerning duration of clopidogrel therapy in NSTEMI can also be referred to STEMI [5]. However, further clinical studies are necessary [5]. American guidelines are more precise. They recommend a combined 12--month therapy with acetylsalicylic acid and clopidogrel in each patient after acute coronary syndromes [5]. The 2007 European guidelines clearly discourage from temporary discontinuation of double antiplatelet therapy during the first 12 months from STEMI (I-C) [4]. According to the guidelines, temporary discontinuation of such therapy is essential in case of serious or life-threatening bleeding and before surgery, when even small bleeding may have serious consequences (brain or spine surgery) (IIa-C) [4].

Resistance to antiplatelet treatment is a widely discussed clinical issue. There are still more reports that the laboratory-documented resistance leads to increase in the risk of cardiovascular complications, especially after acute coronary syndromes [8,9]. Snoep et al. in a recently published meta-analysis demonstrated that in secondary prevention of coronary heart disease, laboratory-defined resistance to aspirin is associated with a fourfold increase in recurrent cardiovascular events [8]. Nevertheless, current guidelines do not recommend routine assessment of resistance to antiplatelet treatment. Any change of type and dose of antiplatelet treatment, based on the encountered laboratory resistance phenomenon, is also not recommended for everyday clinical practice [4,5]. The exception are patients after percutaneous coronary intervention at risk of of life-threatening stent thrombosis. The 2005 ACC/AHA guidelines on percutaneous coronary interventions suggest consideration of platelet function assessment in such patients. If <50% inhibition of platelet aggregation is found, it could be appropriate to increase the maintenance dose of clopidogrel from 75 mg to 150 mg (class IIb recommendation, level of evidence C) [10]. A substantial problem of measurement of platelet activity is lack of simple and standardized diagnostic methods to be used within a short time and most desirably at the bed side [9].

Treatment with hypolipemic agents

Intensive treatment with hypolipemic agents, being a subject of controversies in stable coronary disease, is strongly recommended after acute coronary syndromes. Its therapeutic aim is to achieve low-density lipoprotein (LDL) cholesterol levels below 100 mg/dl (2.6 mmol/l) (class I recommendation), or

below 70 mg/dl (1.8 mmol/l) (class IIa recommendation) [4]. A recent meta-analysis concerning efficacy of hypolipemic therapy showed that intensive statin therapy after acute coronary syndromes reduces total mortality by 25% (OR 0.75, 95% CI 0.61–0.93) [11]. No such favorable effect was demonstrated in stable coronary disease [11].

In case the HDL cholesterol level falls below 45 mg/dl and/or triglyceride level exceeds 200 mg/dl, it is recommended to add fibrate (class IIa recommendation) to treatment [3,7]. It is particularly favorable in patients with metabolic syndrome or diabetes [12]. It was demonstrated that an increase in HDL level by 5 mg/dl, due to fibrate treatment, results in reduced cardiac mortality by 27% ($p < 0.001$) [13].

Diabetes

After myocardial infarction, diabetic patients particularly benefit from strict glycemia control [12]. It may be achieved both by insulin therapy and also by oral treatment and a diet [12]. According to current guidelines of the Polish Society of Diabetology, insulin therapy is recommended, if a good metabolic control of diabetes cannot be achieved or daily demand for insulin exceeds 30 U [14]. Each patient with abnormalities in carbohydrate balance, after acute coronary syndrome, should be immediately referred to specialist in diabetology [14].

A novelty in the current guidelines of the European Society of Cardiology and the European Society for Diabetes Studies and the European Association for the Study of Diabetes is also to recommend performing early oral glucose tolerance test in all patients after myocardial infarction, in whom abnormalities in carbohydrate metabolism were not diagnosed to date [12]. It results from the fact that the recent studies demonstrated that hyperglycemia after myocardial infarction reflects mainly the previously existing abnormalities of insulin secretion by pancreatic β cells [12]. Therefore, early dysfunction of pancreatic β cells is of pathophysiological significance and may become a future farget for treatment in patients after myocardial infarction.

Hypertension

In accordance with the ESC guidelines on treatment of acute coronary syndromes, arterial pressure in patients after myocardial infarction shall be reduced below 140/90 mmHg (or below 130/80 mmHg in diabetic patients or patients with renal insufficiency). The current guidelines on hypertension treatment also indicate the benefits of achieving blood pressure below 130/80 mmHg, and in patients with left ventricular dysfunction, below 120/80 mmHg [15,16]. In patients after recent myocardial infarction, the guidelines especially recommend the use of β-adrenolytics, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists [15,16].

Omega-3 acids and their ethyl esters

Guidelines of the European Society of Cardiology recommend supplementation with omega-3 polyunsaturated fatty acids administered 1 g/24h in all patients after myocardial infarction [3]. This recommendation was assigned with class I and level of evidence B [3]. For numerous reasons, this class I recommendation is the most uncommonly considered recommendation of the European Society of Cardiology in Poland for secondary prevention in patients after myocardial infarction. Use of omega-3 acids was also included in secondary prevention in the recent guidelines on treatment of patients with stable coronary disease.

Omega-3 polyunsaturated fatty acids (eicosapentaenoic acid – EPA, docosahexaenoic acid – DHA, α-linolenic acid – ALA) show favorable effect on human cardiovascular system. Among others, they result in lowering blood pressure, reduction in triglyceride levels and increase in high-density lipoprotein (HDL) levels. By suppressing the development and progression of atherosclerotic plaques, they have antiatherosclerotic effects. They also have antiarrhythmic effect by increase in polarization of myocardial cell membrane and increase in their sensitivity threshold, especially in ischemic myocardium, where life-threatening ventricular fibrillation is quite common. The effect is reduction in total mortality and risk for sudden deaths by omega-3 acids, what was found particularly in patients with recent myocardial infarction. Considering other properties of omega-3 acids with possible significance for patients after myocardial infarction, antidepressive effect is currently being mentioned [16]. Depression is the acknowledged unfavorable prognostic factor, especially after myocardial infarction [17]. In the recently published meta-analysis of randomized double-blind studies, Lin et al. [18] observed a substantial antidepressive effect of omega-3 polyunsaturated fatty acids.

In the Diet and Reinfarction Trial (DART) study, the patients after myocardial infarction were randomly assigned to a group, where fish consumption was increased (200–400 g of fatty fish per week, correlating with 500–800 mg/24h of omega-3 fatty acids) or to a group with standard fish consumption and 29% reduction in mortality due to all reasons was demonstrated (Fig. 1) [17]. The greatest benefits were seen in the prevention of myocardial infarction complicated by death, therefore, a hypothesis was proposed that omega-3 acids protect the myocardium against unfavorable effects of ischemia [17].

In accordance with the results of DART study and similar ones, the European and American societies of cardiology recommend increase in fish consumption, especially in secondary prevention of coronary disease. The only controversy is maximum acceptable fish consumption, associated with the presence of mercury, dioxins and polychlorinated biphenyls (Fig. 2). In order to achieve the desired supply of 1000 mg/24h EPA/DHA in a patient after myocardial infarction, consumption per week should be as follows:

– 2400 g of canned tuna, or
– 400–1400 g (depending on fishery location) of fresh tune, or

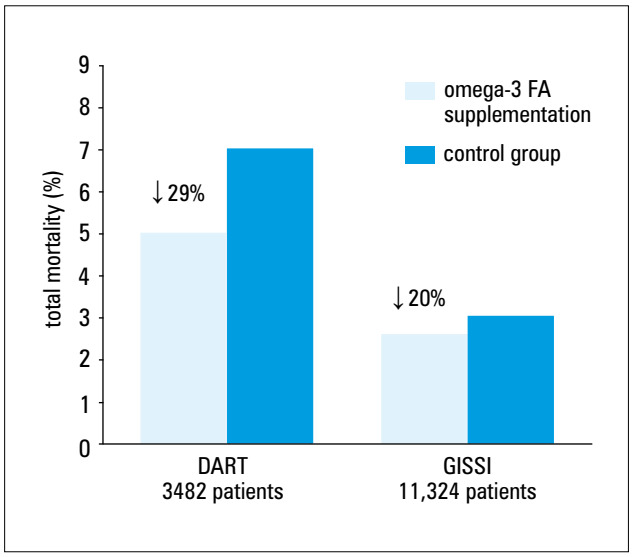

Fig. 1. Impact of omega-3 fatty acids on total mortality in patients after recent myocardial infarction

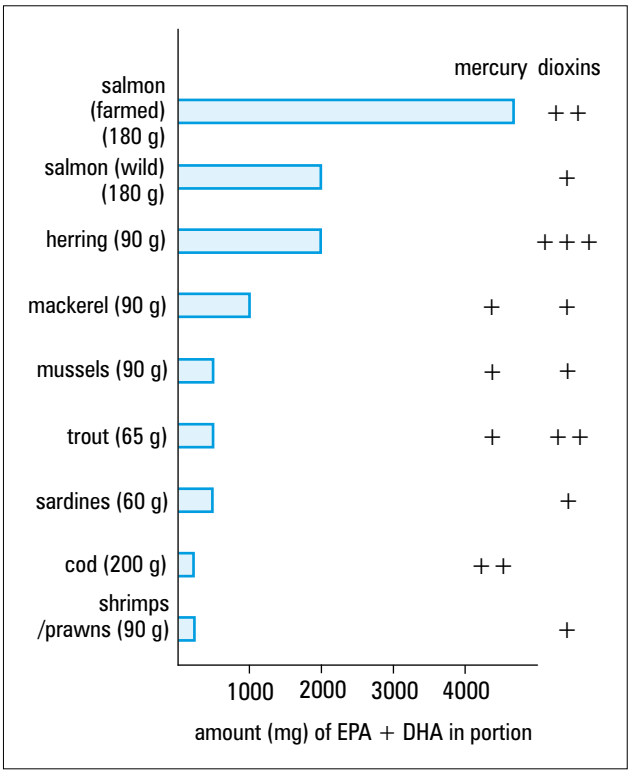

Fig. 2. Content of omega-3 fatty acids and harmful substances in some fish/seafood. Abbreviations: DHA – docosahexaenoic acid, EPA – eicosapentaenoic acid

– 420 g of herring, or
– 400–1700 g of mackerel, or
– 700 g of trout, or
– 500 g of salmon.

It may result in excessive consumption of harmful substances. It strongly depends on fish farming conditions and location of fisheries. Recently, the results of detailed analyses of harmful substance content in some fish species, e.g. in omega-3 acid rich salmon, were published [19]. They may imply that in accordance with recommendations of the US Environmental Protection Agency, due to carcinogenic substance content, salmon from northern Europe shall not be consumed more than once per five months [19]. However, consumption of wild Pacific salmon would be allowed 1–5 times a month [19]. Similar relations could be provided for other fish species.

It should also be noted that apart from fish, there are other natural sources of mono- and polyunsaturated fatty acids (Tab.). Fats and oils with high unsaturated/saturated fatty acid ratio and low omega-6/omega-3 acid ratio are preferred. Attention should be paid to the fact that while omega-3 α-linolenic acid undergoes favorable transformation into EPA and DHA, omega-6 linolic (linolein) acid is metabolized to arachidonic acid and then to eicosanoids and its excess may have an unfavorable effect (Fig. 3). Unfortunately, abilities of human body to transform α-linolenic acid into EPA and DHA are limited.

In such a complex situation, administration of highly purified omega-3 acid ethyl esters may be an alternative in secondary prevention after myocardial infarction. In a study by GISSI, the impact of addition of highly purified omega-3 acid ethyl esters to standard treatment after myocardial infarction was observed in 11,324 patients [20]. After 3.5 years of follow-up, it resulted in a relative decrease in mortality by 21% and sudden cardiac death by 44% [18]. A significant decrease in total mortality by 41% was observed already in the first 3 months of follow-up [21] (Fig. 1). Recently, it was also demonstrated in a double-blind randomized study involving over 18,000 Japanese that even with initially high level of fish consumption and administration of statin to each patient, adding omega-3 acid ethyl esters reduces the occurence of serious coronary events in primary and secondary prevention by 19% [21]. In the aforementioned study, attention can be attracted by a decrease in risk of all types of acute coronary syndromes by approximately 25%.

Considering the significance of an appropriate supply of omega-3 acids after myocardial infarction, British National Institute for Health and Clinical Excellence [2] recently admitted introduction of omega-3 acid ethyl ester (approved for secondary prevention after myocardial infarction) supplementation as one of the priorities in Great Britain for the next 3 years [2]. Detailed analysis performed by NICE showed that introduction of omega-3 acid ethyl ester therapy in only 20% of patients after recent myocardial infarction should allow to protect 2700 British patients against the second myocardial infarction within 3 years from implementation of this priority [2].

Table. Unsaturated fatty acid content in some fats and oils

Fat/Oil	Unsaturated/saturated fatty acid ratio	Content of some fatty acids [%]		
		Monounsaturated	Polyunsaturated	
		Oleic acid C18:1	Linoleic acid (omega-6) C18:2	α-linolenoic acid (omega-3) C18:3
Butter	0.5	29	2	1
Lard	1.2	44	10	–
Train oil	2.9	22	5	–
Peanut oil	4.0	48	32	–
Olive oil	4.6	71	10	1
Walnut oil	5.3	28	51	5
Soybean oil	5.7	24	54	7
Corn oil	6.7	28	58	1
Grapeseed oil	7.3	15	73	–
Sunflower oil	7.3	19	68	1
Flaxseed oil	9.0	21	16	53
Almond oil	9.7	69	17	–
Canola oil (Canadian rapeseed oil)	15.7	62	22	10

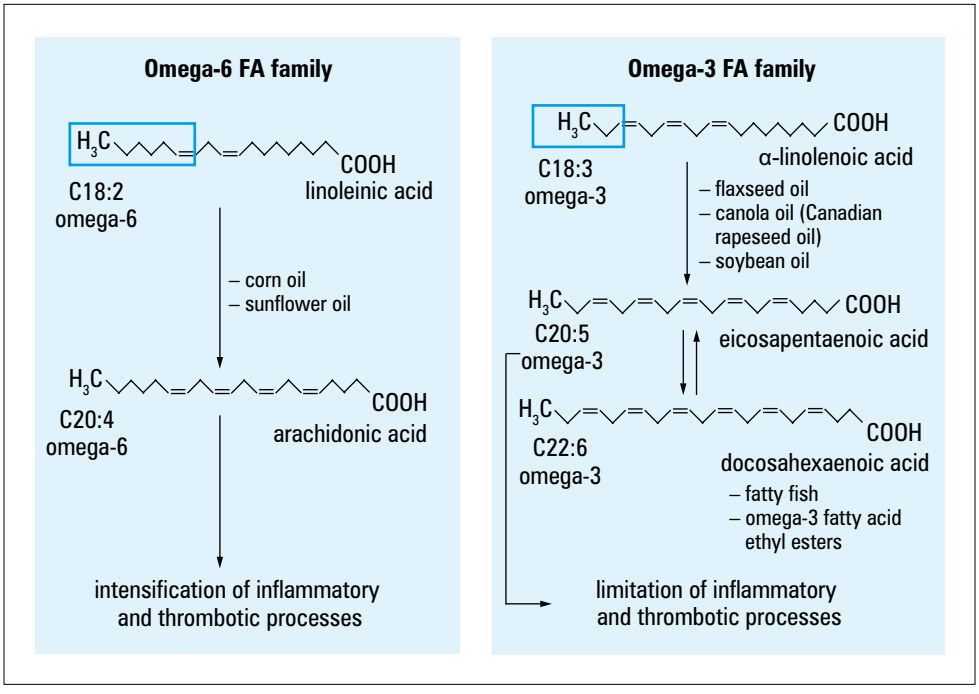

Fig. 3. Different role of omega-3 and omega-6 fatty acids in pathogenesis of atherosclerosis

The guidelines of British National Institute for Health and Clinical Excellence (NICE) unambiguously recommend use of omega-3 acid ethyl esters, which are approved for secondary prevention after myocardial infarction [2]. The recommendations of the European Society of Cardiology concerning omega-3 acids are less precise. It should be emphasized that large randomized trials, like GISSI and JELIS, were carried out using omega-3 acid ethyl esters [20,21].

Obtaining esters from oils or fats by transesterification (alcoholysis) is a significant biochemical transformation, known

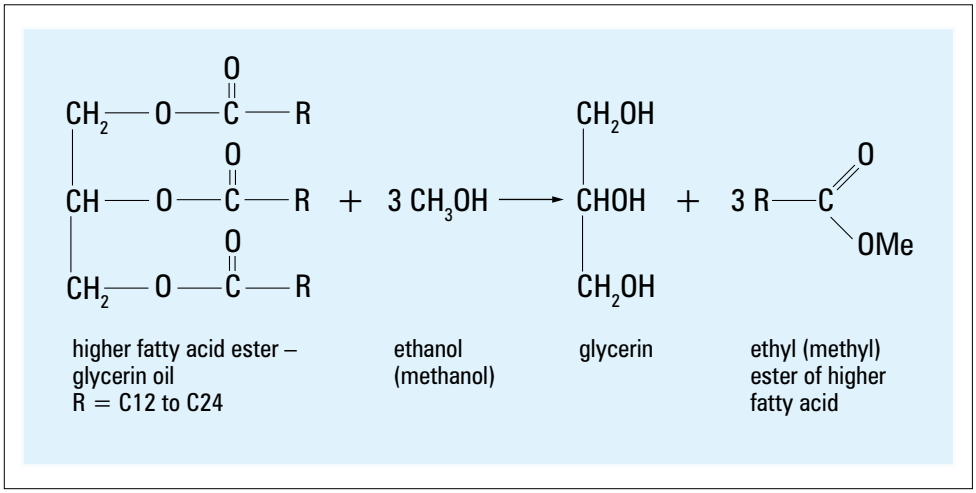

Fig. 4. Obtaining of fatty acid ethyl esters

already since the beginning of the 20th century. The process is widely used for biofuel (biodiesel) production from rapeseed oil. Fish oil undergoes similar biochemical modification at obtaining of omega fatty acid ethyl esters. Generally, ester transformation process consists in reaction of a fatty acid with ethanol or methanol catalyzed by bases (Fig. 4).

It is controversial whether all benefits from using omega-3 acid ethyl esters observed in large clinical trials (GISSI, JELIS), especially in patients after recent myocardial infarction, could be transferred to fish oil available on the market as a dietary supplement.

Aldosterone antagonists

A novelty of recent recommendations on treatment of patients after acute myocardial infarction, demonstrating left ventricular dysfunction and cardiovascular failure or diabetes, is introduction of aldosterone antagonist (class I, level of evidence A) [2,4]. Eplerenone (available in Poland as Inspra) is a new aldosterone antagonist approved for use after recent myocardial infarction [4]. Treatment should be started 3–14 days after myocardial infarction, usually after introduction of angiotensin-converting enzyme inhibitor [2,4]. Significant renal insufficiency, when creatinine levels exceed 2.5 mg/dl (221 μmol/l) in males and 2.0 mg/dl (177 μmol/l) in females, as well as hyperkaliemia (potassium level over 5.0 mmol/l) are contraindications to treatment with aldosterone antagonists [2].

Smoking cessation

Of note, the ability to refrain from smoking is limited and requires permanent supervision and support of a patient. Recent intervention studies show that after one year the percentage of patients maintaining abstinence is as follows: 10.3% in the placebo group, 14.6% in the bupropion group and 23% in the varenicline group (all differences statistically significant) [22]. Varenicline is a new agent, which is a partial agonist of α4β2 nicotinic cholinergic receptor. Furthermore, it also demonstrates weaker effect on other subtypes of α3β4, α3β2, α6 and α7 brain receptors. Binding varenicline to α4β2 receptor only partly stimulates its dopamine excretion, and simultaneously it blocks stimulation of the receptor by nicotine [22,23]. Considering high efficacy and safety of the drug, in July 2007, the British National Institute for Health and Clinical Excellence decided to reimburse total costs of varenicline treatment of patients wishing to give up smoking [23].

Moderate alcohol consumption

A role played by moderate alcohol consumption, particularly red wine, remains controversial, especially in secondary prevention. It was demonstrated by editorial articles on this issue, published in 2007 in leading cardiology magazines, like *European Heart Journal*, *Journal of American College of Cardiology* and *Circulation* [24]. Reliable epidemiological data shows that relation between the amount of consumed alcohol and the total mortality is presented as J-curve [24,25]. It was reported that females consuming 1–2 drinks a day and males consuming 2–4 drinks a day demonstrate lower mortality than teetotalers and persons consuming higher amounts of alcohol [24]. It may be associated with lower incidence of myocardial infarction and cardiovascular failure in those persons [24,25].

The mechanism of protective effect of small amounts of alcohol on cardiovascular system most probably consists in increase in HDL cholesterol level and insulin sensitivity, as well as in antiplatelet and anti-inflammatory effect [24]. It is disputable, whether alcohol itself, or its combination with polyphenols found in red wine, is responsible for these effects [24,25]. Interest is currently raised especially by one of those substances called resveratrol. Experiments showed that it reduces angiotensin II activity, increases the nitric oxide level, and reduces platelet aggregation and LDL oxidation [24]. Agonistic effects of resveratrol on sirtuins was also documented.

Sirtuins, also referred to as SIRT (Silent Information Regulator Two) proteins, are responsible for deacetylation and deactivation of histones, especially factor p53 histone influencing cell ageing [24]. During experiments, its effect resulted among others in life extension of myocytes in the impaired myocardium [24]. We hope that future studies will show whether resveratrol found in red wine (especially *Pinot noir*) is a real longevity factor.

Observational studies on wine consumption in patients after recent myocardial infarction demonstrated that the risk of cardiovascular complications in persons consuming moderate amounts of alcohol mentioned before, in comparison with teetotalers, was significantly lower, i.e. by 59% [25]. A limitation of the study was the number of patients enrolled.

Due to the fact that many questions and doubts concerning real benefits of moderate alcohol consumption still remain unsolved, we shall be careful with recommendations. In recent ESC guidelines on treatment of patients after myocardial infarction, the recommendations read as follows: "Moderate alcohol consumptions may be beneficial in those patients" [4].

Influenza vaccination

Both epidemiological data and randomized clinical trials show that influenza vaccination in cardiovascular patients may reduce frequency of adverse cardiovascular events even by 40–50% [6,26,27]. Only in the United States, influenza is estimated to cause 91,000 deaths a year, by increasing the incidence of myocardial infarction [28].

Based on available clinical data, the ACC and AHA recently recommended influenza vaccination in all cardiovascular patients (class I, level B) [6].

SUMMARY

According to the data presented above, there are several methods influencing prognosis on coronary patients after myocardial infarction. They range from recommendation on changing the lifestyle and pharmacotherapy compliant with guidelines, to the possibility of surgical myocardial revascularization. According to the data from recently published all-Poland register of acute coronary syndromes (PL-ACS), frequency of administration of antiplatelet agents, β-blockers and ACE-inhibitors in patients currently discharged from hospitals after myocardial infarction is rising and ranges from 75 to 85% [28]. Unfortunately, the data does not cover programs of out-of-hospital cardiological rehabilitation and other non-pharmacological treatment methods. It is also evident from the PL-ACS registry that in Poland, frequency of administration of some drugs specified in class I recommendations of the European Society of Cardiology guidelines is quite low [27]. These drugs include ethyl esters of omega-3 polyunsaturated fatty acids, which should be administered to all patients after STEMI. They also include eplerenone, recommended in patients after acute myocardial infarction, in whom left ventricular dysfunction and cardiovascular failure or diabetes are found.

The most effective management in patients after myocardial infarction is multifactor intervention. It should cover not only pharmacotherapy, compliant with current guidelines, but also aggressive treatment of atherosclerosis risk factors, long-term cardiological rehabilitation, as well as appropriate diet and healthy lifestyle. In each patient after myocardial infarction we should consider surgical coronary revascularization.

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