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THERAPEUTIC APPROACH IN ACUTE CORONARY SYNDROME FOCUSING ON ORAL THERAPY*

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SUMMARY – In the light of some new information based on clinical evidence, current therapeutic approach to patients with acute coronary syndrome especially focusing on oral therapy is being considered. The initial stage of treatment does not differ greatly among patients with unstable angina pectoris (UA), non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). It is necessary to simultaneously resolve a series of problems within the first twenty minutes upon admission, i.e. risk assessment, selection of treatment strategy (conservative, invasive), relief of ischemic pain, determination of hemodynamic status and elimination of any undesired complications (hypertension, tachycardia, heart failure), and administration of antithrombotic therapy. Patients suffering from STEMI require reperfusion treatment, and the method of choice is primary percutaneous coronary intervention (PCI) where available. Fibrinolytic reperfusion therapy is limited exclusively to STEMI within the first three hours from the onset of pain. Unlike this, in patients suffering from UA/NSTEMI it is necessary to make risk assessment in the early stage of disease, and thus select the patients that will certainly benefit from invasive treatment through PCI. For pain relief, the patient should be immediately administered nitroglycerin along with oxygen. Beta-blockers that are reasonably used in the initial stage of treatment during the first 24 hours, if not contraindicated, are still underused. Clopidogrel becomes an obligatory drug not only in patients having undergone PCI, but also in those treated conservatively following fibrinolysis.

Key words: *Acute coronary syndrome – drug therapy; Administration oral; Acute coronary syndrome – complications; Coronary disease – drug therapy*

Introduction

The initial therapeutic approach to a patient suffering from acute coronary syndrome (ACS) does not greatly differ, i.e. it is principally identical, regardless of whether unstable angina pectoris (UA), non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI) is concerned. However, it is worth mentioning that fibrinolytic reperfusion therapy is limited only to STEMI within the first three hours from the onset of pain, whereas in patients with NSTEMI it is inefficient and may even be harmful. On drug dosing, attention should be paid to patient age, especially due to the fact that drugs are excreted through kidneys, however, adaptation is not necessary when applying dual antiaggregation therapy with aspirin and clopidogrel.

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When the diagnosis of ACS has been made, an optimal initial approach within the first twenty minutes should include urgent and simultaneous resolution of a number of problems[1,2], i.e. risk assessment, selection of treatment strategy (conservative, invasive), pain relief, determination of patient hemodynamic status and elimination of any undesired complication (hypertension, tachycardia, heart failure, hypotension, cardiogenic shock), and starting antithrombotic therapy.

Initial Assessment

In patients suffering from UA/NSTEMI, it is necessary to make a disease risk assessment in the early stage of the disease, or rather, select the patients that will undoubtedly have a better prognosis with invasive treatment by applying percutaneous coronary intervention (PCI). In high risk patients, the intervention is to be done within 48 hours and in the others this procedure may be delayed until another hospitalization. Since recently, patients with UA/NSTEMI are urgently managed during the first 48 hours of hospital treatment at PCI centers. Clinical testing has identified a number of factors that help us select such patients: ECG changes as depression and extension of changes to ST segment, an increased value of myocardial necrosis markers, hemodynamic instability, and persistent chest pain resistant to therapy. The use of such factors has led to the development of risk score tables such as TIMI, GRACE and PURSUIT, of which we consider TIMI risk score as being especially worth quoting (Table 1)[1,3-8]. Each variable is scored with one point. Low risk is scored 0-2, medium risk 3-4, and high risk 5-7 points. Irrespective of this, two variables indicate urgent PCI although their sum is only two points; these two variables are dynamic changes to ST segment on ECG and increased troponin values.

Elimination of Ischemic Pain

Upon making the diagnosis and ACS risk assessment, ischemic pain relief or elimination should be simultaneously initiated. Besides oxygen, the patient should be immediately administered sublingual nitroglycerine as necessary, even three times consecutively at 5-minute intervals; if the pain is not eased or in the event of hypertensive blood pressure values or heart failure, intravenous (i.v.) administration that may continue for the next 24-48 hours should be undertaken[9-11]. Nitrates may be dangerous if used in patients with right ventricular infarction[12], or in patients with aortic stenosis, and they must be withheld when the systolic pressure values are 100 mm Hg or lower, and in the event of a rise in cardiac frequency exceeding 100/min[13]. The nitrate side effects are headache, orthostatic hypotension (following the second dose, the patient is advised to sit or lie down), and paradoxical bradycardia with hypotension, which are very successfully eliminated by reducing the dose and giving an analgesic if anginal pain recurs, and in the event of bradycardia i.v. atropine as necessary. Nitrate therapy administered over a longer period of time to up to several weeks with no therapeutic benefit (especially in terms of pain elimination) proved to be purposeless and did not reduce mortality as compared with placebo[11].

In the initial stage of disease when applying further therapeutic algorithm, i.v. morphine is the drug of choice, complying with the rule that the systolic pressure values need to exceed 100 mm Hg. One ampule of 1 mL/10 mg diluted in 9 mL 0.9% NaCl should be administered i.v. and repeatedly adminis-

Table 1. Risk score in UA/NSTEMI-TIMI risk score (according to Antman et al.[8]*)*

Variable	Number of points
Age ≥65 years	1
Presence of minimum three cardiovascular risk factors (hypertension, diabetes, smoking and family history of coronary artery disease)	1
Coronary artery stenosis >50% proven on coronary angiogram	1
ST-segment deviation on ECG	1
At least two anginal events in the last 24 hours	1
Elevated cardio-selective markers	1
Administration of aspirin for the last seven days	1

tered fractionally with 2 mL/2 mg at 5-minute intervals until the pain is eased. The effect occurs after 20 minutes. Morphine is contraindicated in cardiogenic shock. All such therapeutic actions require patient bed rest and observation, when possible, followed by continuous monitoring of ECG rhythm to follow up arrhythmias and dynamic ECG changes[1].

Beta Blocking Agents

Agents that are insufficiently used are beta-adrenergic blocking agents (beta-blockers) which, according to some recent guidelines of the European and American Cardiac Societies, are reasonably used in the initial stage of treatment, during the first 24 hours if not contraindicated (Fig. 1). Patients should be hemodynamically stable. Beta-blockers i.v. are recommended for the first 24 hours, especially in patients with persisting anginal pain, hypertension or tachycardia and no signs of cardiac insufficiency. Cardioselective beta-blockers are mostly concerned (metoprolol, atenolol and bisoprolol). In further treatment of stable patients, these agents are administered *per os*, with careful dosing (for example, the initial dose of atenolol is 12.5 mg and of bisoprolol 1.25 mg)[1,14]. Beta-blockers should be administered to all patients with reduced ejection fraction[15]. In such cases, carvedilol proved to be beneficial.

Oral Antithrombotic Therapy

In the initial stage of acute coronary syndrome, therapy of choice is dual antiaggregation medication to prevent progression of thrombosis or embolization with ulcerated plaque. All patients receive aspirin, usually in a dose of 100 mg on a daily basis. The first dosage of 300 mg needs to be chewed, even in patients with gastrointestinal problems. Aspirin is well and quickly absorbed from the stomach and small intestine. Today, agents with lesser effects on mucous membrane are available, therefore rarely showing gastrointestinal side effects. This mode of treatment is combined with clopidogrel administered with either low molecular weight heparin or selective factor X blocker, fondaparinux, or glycoprotein IIb/IIIa inhibitor, all of which increase the tendency to hemorrhagic complications. Of course, patients with STEMI treated with fibrinolytic therapy should not be left unobserved. Gastrointestinal bleeding and very rarely other sites of bleeding (intracranial hemorrhage, ret-

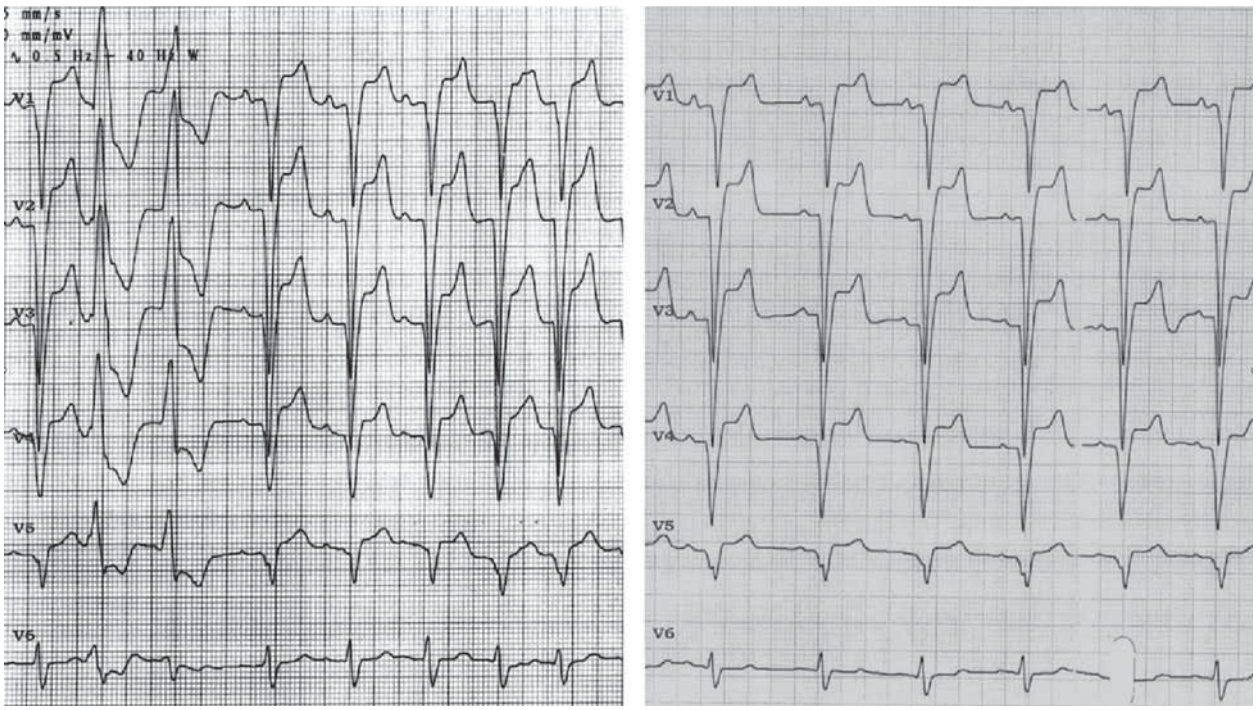

Fig. 1. Effect of beta-adrenergic blockers on heart rate and arrhythmia (left: prior to beta-blocker therapy, 110 beats/min; right: after beta-blocker therapy, 67 beats/min).

roperitoneal hematoma) severely affect ACS patients treated with PCI during which one or more stents have been implanted, since antithrombotic therapy should be discontinued in the event of serious bleeding. In the event of therapy interruption, these patients show an increased tendency of procoagulation effect, i.e. a rebound phenomenon with consequential stent thrombosis[16]. Although it has not yet been systematically investigated whether prophylaxis with proton pump inhibitors (PPI) may reduce the risk of bleeding from digestive tract, in the last few years PPI have been increasingly administered to patients with an increased risk of bleeding[17]. The guidelines issued in 2007 by the American Cardiac Society (ACC/AHA) for unstable angina and NSTEMI expressly recommend prophylactic administration of PPI, however, without specifying the length of treatment. The conclusion is: PPI needs to be prophylactically administered in patients with an increased risk of gastrointestinal bleeding, including the elderly with a history of ulcer disease, previous use of nonsteroidal antirheumatics, liver disease, and thrombocytopenia[1]. The interaction between clopidogrel and PPI is clinically relevant and therefore PPI should only be administered in patients at a high risk of gastrointestinal bleeding[18].

If the patient does not tolerate aspirin, clopidogrel is used as monotherapy. In daily practice, based on a number of positive clinical evidence, clopidogrel is administered immediately following aspirin. It is an agent that is included in the group of thienopyridine derivatives; it blocks adenosine-diphosphate receptors on platelet surface and acts synergistically with aspirin. Such dual antithrombotic therapy prevents platelet adhesion and aggregation. In patients that are not scheduled for early coronarography, clopidogrel is administered in a loading dose of 300 mg orally, followed by the maintenance dose of 75 mg *per* day. If an emergency cardiac procedure is needed, the loading dose of clopidogrel is 600 mg. Such a manner of taking clopidogrel at once contributes to achieving maximum effect as early as within 2-3 hours, unlike 300 mg that starts to take effect only after 12 hours[19,20]. The phenomenon of resistance to clopidogrel has been mentioned recently, however, the increase in the common maintenance dose from 75 to 150 mg (2 tablets) reduces resistance from approximately 30% to only 12% of patients. An urgent, primary PCI in patients with NSTEMI, especially those with a lower or intermediary risk score, as mentioned above, may be delayed. This delay is based on the fact that some patency of the affected coronary artery is maintained in 60%-85% of NSTEMI patients. Regardless of the possibility to perform an immediate or delayed intervention, or only conservative treatment in patients with NSTEMI, in compliance with the 2007 Guidelines of the European Cardiac Society, clopidogrel should be prescribed throughout the next 12 months, unless there is a high risk of bleeding. Such recommendations are based on the findings of the CURE study, which monitored 12,565 patients with NSTEMI infarction for a period of 12 months. The relative risk of mortality with the administration of conservative therapy alone including clopidogrel in comparison with placebo was reduced by 17% at 12 months, and following PCI with clopidogrel in comparison with the group treated only conservatively with placebo by 29%[21]. It is worth mentioning that in patients treated with clopidogrel and scheduled for bypass surgery, clopidogrel should be interrupted and surgery delayed by 5 days, if clinically acceptable.

During the last few years, especially after 2005 when the COMMIT study findings were published, the attitude towards therapy with clopidogrel in STEMI infarction has changed. Since then, in clinical practice clopidogrel has unfortunately still been limited to patients undergoing PCI with stent implantation. The study included 46,000 patients with acute myocardial infarction treated with noninvasive approach, with fibrinolysis performed in some 50% of cases. Study results showed a combination of 75 mg of clopidogrel with aspirin for a period of 28 days (without prior loading dose of clopidogrel) to have reduced mortality at 4 weeks as compared with in the group of patients without clopidogrel by 7% and probability of reinfarction by 9%, while the incidence of cerebral or other fatal bleeding did not increase, i.e. there was no need of blood transfusion even in patients aged over 75 that had been treated with fibrinolytic therapy. The second extension of this study, CLARITY TIMI 28, with invasive monitoring of 3491 patients treated with fibrinolytic therapy followed by clopidogrel therapy showed some interesting findings after 28 days. Coronarography performed 2 to 8 days after the infarction showed the rate of occlusion of target coronary artery, i.e. the artery responsible for infarction, to be

lower by 36% in patients that had been treated with clopidogrel as compared with those not treated with clopidogrel following fibrinolysis[22].

Based on these and some other data, therapeutic administration of clopidogrel has greatly increased and is not limited to patients having undergone PCI with stent implantation anymore.

Other Oral Therapies of Acute Coronary Syndrome

Besides statins, which will be discussed elsewhere, angiotensin-converting enzyme inhibitors (ACE inhibitors) or, in case of patient intolerance (usually due to cough) angiotensin-II receptor blockers (ARB) are drugs that should not be forgotten[23,24]. The favorable effect of ACE inhibitors and ARB in patients with acute myocardial infarction is primarily attributed to their role in slowing down, or rather stopping the post-infarction myocardial remodeling, especially in patients with anterior wall infarction or reduced left ventricular ejection fraction (LVEF) <40% and heart failure. Among numerous studies of the efficacy of ACE inhibitors in acute STEMI, note should be made of three trials performed with the widely available agents lisinopril[11], ramipril[25] and trandolapril[26]. Early administration of ACE inhibitors is recommended, not necessarily within the first 24 hours, in order to avoid follow up hypotension. When reasonably used, these agents are well tolerated and lead to great reduction in mortality within 4-6 weeks of myocardial infarction. The dose should be gradually increased, depending on pressure values and kidney function tests. ACE inhibitors are used in unstable angina and NSTEMI patients with diabetes, heart failure, LVEF <40% and hypertension.

The use of verapamil, a calcium channel blocker, is limited to patients in the early stage of disease with atrial fibrillation and high ventricular rate and without signs of heart failure, if beta-blockers are contraindicated. Amlodipine with no negative inotropic effects may be used in ACS if hypertension is not properly controlled by beta-blockers and ACE inhibitor[27].

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Sažetak

TERAPIJSKI PRISTUP KOD AKUTNOG KORONARNOG SINDROMA USREDOTOČEN NA ORALNU TERAPIJU

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U svjetlu nekih novih podataka zasnovanih na kliničkim dokazima razmatra se terapijski pristup bolesnicima s akutnim koronarnim sindromom koji se osobito oslanja na oralnu terapiju. U početnoj fazi liječenja nema većih razlika u pristupu bolesnicima s nestabilnom pektoralnom anginom, infarktom miokarda bez povišenja ST segmenta (NSTEMI) ili infarktom miokarda s povišenjem ST segmenta (STEMI). Istodobno treba razriješiti niz problema unutar prvih dvadesetak minuta od prijma bolesnika: procjenu rizika, odabir strategije liječenja (konzervativno, invazivno), ublažavanje ishemijske boli, određivanje hemodinamskog statusa i uklanjanje neželjenih komplikacija (hipertenzija, tahikardija, srčano zatajenje), te davanje antitrombotske terapije. Bolesnici koji imaju STEMI zahtijevaju liječenje reperfuzijom, a metoda izbora je primarna perkutana koronarna intervencija (PCI) tamo gdje je dostupna. Fibrinolitička reperfuzijska terapija je ograničena isključivo na STEMI unutar prva tri sata od nastupa boli. Za razliku od toga, kod bolesnika s nestabilnom pektoralnom anginom/NSTEMI treba procijeniti rizik u ranom stadiju bolesti te tako odabrati one bolesnike kod kojih će invazivno liječenje pomoću PCI zasigurno biti korisno. Uz kisik bolesniku treba smjesta dati nitroglicerin radi ublažavanja boli. Primjena beta blokatora je razumna u početnoj fazi liječenja tijekom prva 24 sata, ako nisu kontraindicirani, no oni se još uvijek nedostatno primjenjuju. Klopidogrel postaje obvezatan lijek ne samo u bolesnika podvrgnutih PCI, nego isto tako u bolesnika koji se liječe konzervativno nakon fibrinolize.

Ključne riječi: *Akutni koronarni sindrom – terapija lijekovima; Način davanja – peroralno; Akutni koronarni sindrom – komplikacije; Koronarna bolest – terapija lijekovima*