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Trends in secondary prevention after myocardial infarction – emerging approaches

Trendi v sekundarni preventivi po srčnem infarktu – umestitev novosti

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Abstract

The secondary prevention after myocardial infarction is aimed to reduce the risk for recurrent cardiovascular events, other complications, and thereby mortality. Despite the emerging guideline-directed pharmacological therapies, certain residual cardiovascular risk still remains. Recent studies focused on reducing this residual risk by adding mainly antithrombotic, lipid–lowering, or anti-inflammatory drugs (without exhibiting significant side effects) to the existent therapy. In the field of antithrombotic treatment, the prolongation of dual therapy with aspirin and ticagrelor or aspirin and low-dose rivaroxaban beyond one year after acute coronary syndrome proved to be efficient. There are also many novelties in the treatment of dyslipidemias where maximum possible lowering of LDL cholesterol is emphasized. In this regard, cardiovascular prognosis was improved by ezetimibe and PCSK9 inhibitors. Anti-inflammatory drugs represent the third option of effective anti-atherosclerotic treatment, though they have not yet entered the clinical platform. Moreover, for patients after myocardial infarction with concomitant diabetes, there are new possibilities in ameliorating their cardiovascular prognosis by using glucagon-like polypeptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors. Overall, besides a healthy lifestyle it is reasonable to optimize pharmacological treatment by including new therapeutic options for all patients meeting the criteria. That may lead to further reduction of residual cardiovascular risk and consequently to a better quality of life after myocardial infarction.

Izvleček

Cilj sekundarne preventive po srčnem infarktu je zmanjšati tveganje za ponovne srčno-žilne dogodke, druge zaplete in umrljivost. Kljub medikamentni terapiji, ki so jo skozi čas priporočale smernice, je vedno ostajalo in še ostaja prisotno določeno preostalo srčno-žilno tveganje. Namen novejših raziskav je bil z dodatkom predvsem protitrombotičnih, hipolipemičnih ali protivnetnih zdravil brez pojavljanja pomembnih neželenih učinkov znižati to prisotno tveganje. V sklopu protitrombotičnega zdravljenja se je tako eno leto po akutnem koronarnem sindromu kot dodatek aspirinu izkazalo učinkovito podaljšano zdravljenje s tikagrelorjem ali z nizkimi odmerki rivaroksabana. Veliko novosti je tudi na področju

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hipolipemičnega zdravljenja, ki kot najbolj koristno zagovarja čim večje znižanje holesterola LDL. Raziskave kažejo, da so za doseganje ciljev učinkoviti ezetimib in zaviralci PCSK9. Tretja možnost učinkovitega proti-aterosklerotičnega zdravljenja so protivnetna zdravila, ki pa se še niso prebila v klinično prakso. Pri bolnikih po srčnem infarktu s sočasno sladkorno boleznijo dodaten ukrep v izboljšanju srčno-žilne napovedi izida omogoča uporaba agonistov receptorjev GLP-1 (angl. glucagon-like polypeptide-1) in zaviralcev SGLT2 (*angl.* sodium-glucose co-transporter 2). Če bolniki izpolnjujejo merila za uvedbo novih terapevtskih možnosti, je poleg zdravega življenjskega sloga smiselno čim bolj optimizirati medikamentno zdravljenje, saj lahko ob tem pričakujemo nadaljnje znižanje preostalega srčno-žilnega tveganja in s tem izboljšanje kakovosti življenja po srčnem infarktu.

1 Introduction

Secondary prevention after a myocardial infarction has been the subject of research for decades. In recent years, there have been many new findings in this area, confirming that additional pharmacological treatment can further reduce cardiovascular risk. The basis of secondary prevention is definitely a protective lifestyle, which includes sufficient physical activity, proper nutrition, achieving target body weight and smoking cessation (1). The scope of this article is limited to drug treatment for secondary prevention. The paper summarizes and compares the latest research in the field of secondary drug prevention after myocardial infarction, places them in a broader context and tries to provide guidelines that should be implemented in future clinical practice. It is related to the recommendations issued in 2020 by the European Society of Cardiology (ESC) for the treatment of patients after non-ST-elevation myocardial infarction (NSTEMI) (2) and 2017 recommendations for the treatment of patients with ST-elevation myocardial infarction (STEMI) (3). At the same time, it includes European recommendations for the treatment of hyperlipidaemias, diabetes in cardiovascular patients and recommendations for dual antiplatelet therapy (4-6). This paper also touches on the recommendations for the treatment of patients with chronic coronary syndrome, which, in addition to various clinical entities, also includes patients after a myocardial infarction (7). The classes of recommendations listed in the paper are: *I – treatment is beneficial, useful, effective (is recommended); IIa – Weight of evidence/opinion is in favour of usefulness/efficacy (should be considered); IIb – Usefulness/efficacy is less well established by evidence/opinion (may be considered); III – treatment is not effective and may be harmful (is not recommended). The following levels of evidence are listed: A – data derived from multiple randomized clinical trials or meta-analyses: B – data derived from a single randomized clinical trial or large non-randomized studies; C – consensus of opinion of the experts and/or small studies, retrospective studies, registries.*

2 Antiplatelet therapy

The choice of antiplatelet drug combinations, in particular the decision on the duration of treatment with multiple antiplatelet drugs, is always based on an assessment of risk of atherothrombotic events and the risk of bleeding in each individual; it may be extended to more than one year or even shortened (Figure 1).

2.1 Antiplatelet drugs

The basis of prevention after a cardiovascular event is antiplatelet therapy with low doses of aspirin. This is not a novelty as aspirin was first synthesized in 1897. Initially, it served as an antipyretic and anti-inflammatory drug (in higher doses), but the discovery of antithrombotic activity marked its breakthrough in the field of cardiovascular prevention. Aspirin inhibits the formation of thromboxane A2 even at very low doses and prevents platelet aggregation (8). As early as 1988, the ISIS-2 study showed that aspirin reduced the risk of myocardial infarction recurrence by 49% and mortality by 23% compared to placebo in the five weeks after myocardial infarction (9). A subsequent meta-analysis confirmed the validity of its use in long-term secondary prevention after myocardial infarction: it showed a 19% reduced risk of serious vascular events and a 20% reduced risk of coronary events, but no increased risk of cerebral haemorrhage (10). Thus, long-term treatment with low-dose aspirin (75-100 mg) after myocardial infarction is recommended in the guidelines with a grade of recommendation *I A* (2,3,7).

For the treatment of acute coronary syndrome, dual antiplatelet therapy (DAPT) with aspirin and ticagrelor or prasugrel is recommended for 12 months after

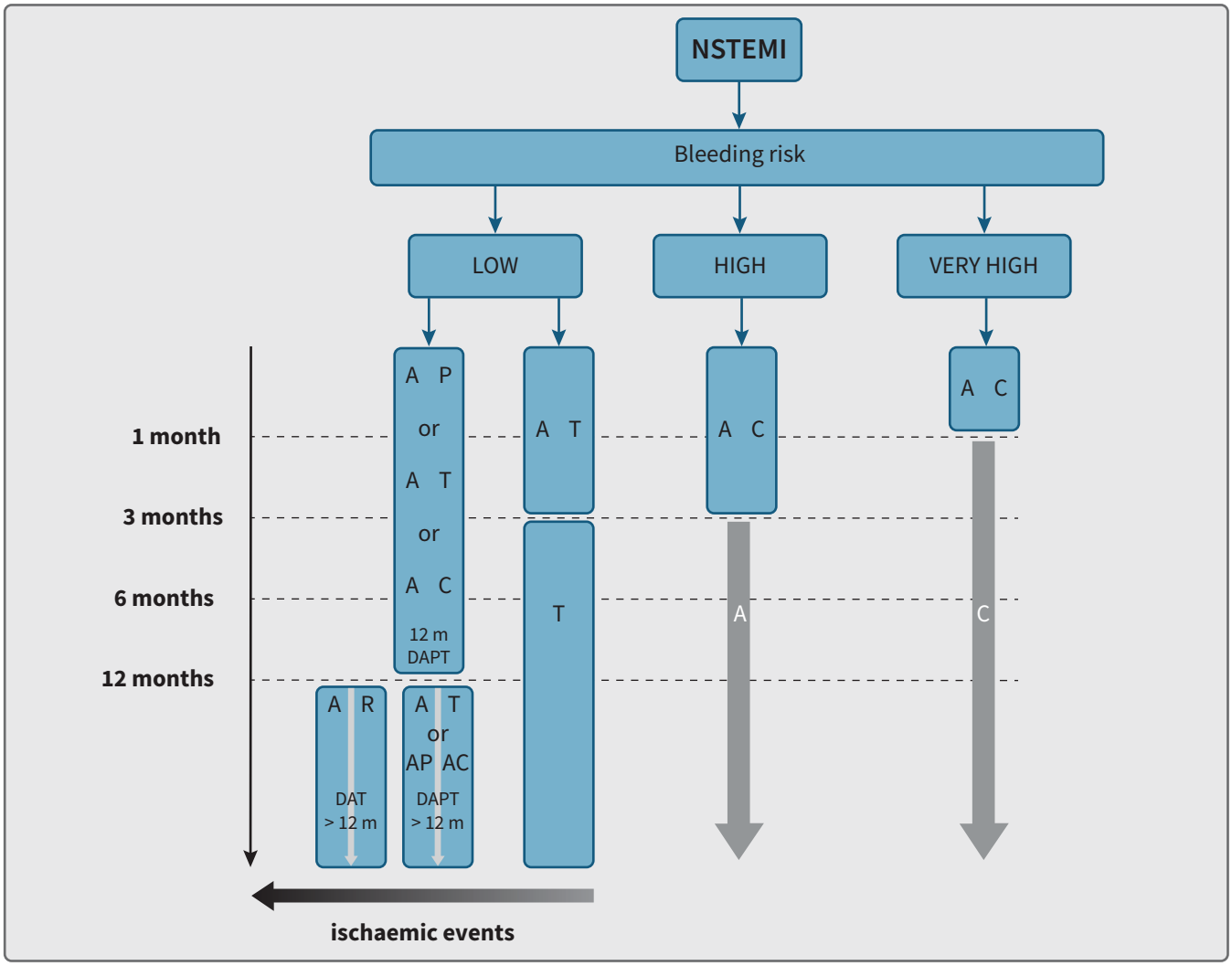


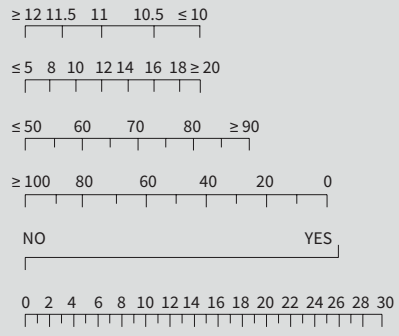
Figure 1: Algorithm for the choice of antiplatelet therapy after PCI for myocardial infarction. Adapted from Collet JP, et al., 2020 (2).

A high bleeding risk translates into increased risk of spontaneous bleeding while on DAPT (e.g. PRECISE-DAPT score ≥ 25 points). A very high risk of bleeding is, by definition, recent bleeding in the last month and/or urgent surgery.

Legend: NSTEMI – non-ST-elevation myocardial infarction; DAPT – dual antiplatelet therapy; DAT – dual antiplatelet therapy (here, this means aspirin + rivaroxaban); A – aspirin; C – clopidogrel; P – prasugrel; R – rivaroxaban; T – ticagrelor; m – month.

the event (especially after percutaneous coronary intervention, PCI); if the latter two drugs are not available, are contraindicated or the risk of bleeding is too great, treatment with clopidogrel is recommended (grade of recommendation *I A*) (Figure 1) (2,3). These are adenosine diphosphate P2Y12 antagonists. At first, the effectiveness of clopidogrel was described, which, when used in combination with aspirin, reduced the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and strokes by 20%, but increased the risk of major bleeding by 38% (11). Further studies in dual antiplatelet therapy compared clopidogrel to potent receptor P2Y12 antagonists prasugrel and ticagrelor, which act faster and inhibit platelets to a greater extent than clopidogrel. They confirmed a further reduction in the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and stroke (prasugrel by 19%, ticagrelor by 16%). Prasugrel increased the risk of major bleeding by 32%, while ticagrelor did not significantly increase the overall risk of major bleeding with only the risk of major non-CABG associated bleeding being increased by 19% (12,13). On the other hand, a recent ISAR-REACT 5 study found that prasugrel and ticagrelor had a similar effect on bleeding risk, while prasugrel was more effective in reducing the risk of ischaemic outcomes. With ticagrelor, the risk of the composite outcome of death, myocardial infarction and stroke was

Table 1: DAPT and PRECISE-DAPT as a support in deciding the duration of dual antiplatelet therapy. Adapted from Valgimigli M, 2017 (6).

	DAPT risk calculator		PRECISE-DAPT risk calculator
When to use	After 12 months of DAPT without events		At the time of coronary artery stenting
Duration strategies	standard (12 months) vs. extended (30 months)		short (3–6 months) vs. standard/extended (12–24 months)
Factors	Age • ≥ 75 • 65 do < 75 • < 65 Cigarette smoking Diabetes mellitus MI at presentation Prior MI or PCI Paclitaxel-eluting stent Stent diameter < 3 mm CHF or LVEF < 30% Vein graft stent	 –2 points –1 point 0 points +1 points +1 points +1 points +1 points +1 points +1 points +2 points +2 points	Hb WBC Age CrCl Prior bleeding Score points 
Range	–2 to 10 points		0 to 100 points
Proposed cut-off limits	≥ 2 points→ extendedDAPT < 2 points→ standard DAPT		≥ 25 points → short DAPT < 25 points → standard/extended DAPT
Calculator	www.daptstudy.org		www.precisedaptscore.com

Legend: DAPT – dual antiplatelet therapy; MI – myocardial infarction; PCI – percutaneous coronary intervention; CHF – congestive heart failure; LVEF – left ventricular ejection fraction; Hb– haemoglobin; WBC – white blood cell count; CrCI – creatinine clearance.

36% higher than with prasugrel in one year (14). Based on this study, the guidelines favour prasugrel over ticagrelor for the choice of P2Y12 receptor antagonist in patients undergoing PCI (grade of recommendation *IIa B*) (2).

Based on the favourable results of the study with ticagrelor in the first 12 months after acute coronary syndrome, PEGASUS-TIMI 54 investigated whether prolonging dual antiplatelet therapy could also be of benefit. In prolonged secondary prevention in the stable phase after myocardial infarction, ticagrelor was tested as an adjunct to aspirin at doses of 90 mg bid and 60 mg bid. Both doses significantly reduced the risk of the composite outcome of death from cardiovascular disease, myocardial infarction and stroke compared to placebo (15% and 16%, respectively), but the higher dose increased the risk of bleeding more than the lower dose (relative risk 2.69 and 2.32, respectively) (15). Therefore, the STEMI guidelines allow the prolongation of dual antiplatelet therapy with ticagrelor 60 mg bid and aspirin for up to three years (grade of recommendation *IIb B*) in patients with high risk for ischaemic events (over 50 years of age and ≥ 1 of the criteria: age over 65 years, previously treated diabetes mellitus, multivessel coronary artery disease, chronic kidney disease with GRF <60 ml/min/1.73 m2) without bleeding complication (Figure 1) (3). Therefore, individual adjustment based on weighing the risk of ischaemic events and bleeding is crucial. The decision on the duration of dual antiplatelet therapy can be assisted by using a validated DAPT risk calculator with prolongation of treatment for more than 12 months being recommended at the score of ≥ 2 points, and on the other hand by using the PRECISE-DAPT risk calculator in which a score of ≥ 25 (which means high risk of bleeding) means consideration should be given to discontinuing the P2Y12 receptor antagonist 3–6 months after myocardial infarction (Table 1) (2,6,16). Based on the DAPT study, if there is doubt regarding the prolongation of dual antiplatelet therapy with ticagrelor, prasugrel or clopidogrel may be used instead. Each treatment regimen has a different relationship between the anti-ischaemic benefit and bleeding risk, but a direct comparison between treatment regimens is not possible with different study designs (Figure 1) (2).

Based on the TWILIGHT study, only three months

of dual antiplatelet therapy with a combination of aspirin and ticagrelor, followed by prolongation to 12 months with ticagrelor alone is possible in patients with low risk for bleeding and ischaemic complications (Figure 1). The group that received only ticagrelor from the third month onwards had a significantly lower risk of bleeding (a 44% reduction in risk). The study was not designed to identify ischaemic complications, but in verifying the non-inferiority of ticagrelor alone; increased risk of mortality, myocardial infarction and stroke was not detected (17).

In the field of antiplatelet therapy after myocardial infarction, changes can be expected with the development and wider use of new generations of vascular splints (ultrathin, biodegradable splints, polymer-free splints) (18). In any case, a personalized approach is required, taking into account coronary pathology and the specifics of the performed procedure as well as the broader clinical characteristics of the patient.

2.2 Direct oral anticoagulants

When cardiovascular risk persists despite dual antiplatelet therapy, concurrent inhibition of the coagulation cascade is an option for additional antithrombotic activity.

2.2.1 Acute coronary syndrome

In studies of acute coronary syndrome, rivaroxaban and apixaban, direct and selective inhibitors of coagulation factor Xa, have been tested. In the ATLAS ACS-2-TIMI 51 study, rivaroxaban was administered at low doses of 2.5 mg bid, 5 mg bid, or placebo concurrently with dual antiplatelet therapy with aspirin and clopidogrel/ticlopidine. Both doses significantly reduced risk of the composite of death from cardiovascular causes, myocardial infarction and stroke by 15-16%. Interestingly, only the lower dose (2.5 mg bid) significantly reduced mortality from cardiovascular causes (by 34%) or from any cause (by 32%). On the other hand, the combination of both drugs significantly increased the risk of major bleeding 3 to 4-fold (e.g. the relative risk of for cerebral haemorrhage was 3.28; for major non-CABG-related bleeding, it was 3.96) (19). The risks thus outweighed the benefits. However, based on the study, the guidelines issued a grade *IIb B* recommendation that in patients with a low risk of bleeding, high risk of ischaemic complications and no history of stroke, supplementation with low-dose rivaroxaban (2.5 mg bid) should be considered in addition to dual antiplatelet therapy with aspirin and clopidogrel (2,3). Given the limitations of the study (a high rate of missing data, different impact of two doses on individual components of the primary end point), the proposed treatment regimen has not transitioned into clinical practice. Additionally, the Health Insurance Institute of Slovenia (HIIS) does not cover the cost of rivaroxaban's prescription for this indication.

An increase in major bleeding was also reported in the APPRAISE-2 study, in which therapeutic doses of apixaban (5 mg bid) were added to antiplatelet therapy after acute coronary syndrome. Unlike the ATLAS study, there was no significant reduction in recurrent ischaemic events (20).

Recently, the question has arisen if aspirin could be replaced by low-dose rivaroxaban. In the GEMINI-ACS-1 study, rivaroxaban 2.5 mg bid was compared with aspirin 100 mg in addition to clopidogrel or ticagrelor in patients with acute coronary syndrome. There were no significant differences between rivaroxaban and aspirin in either bleeding or ischaemic events (21). The findings suggest that rivaroxaban in very low doses is a possible alternative to aspirin, which could mean the end of low-dose aspirin usage as the basis of acute coronary syndrome treatment.

2.2.2 Stable coronary artery disease

Subsequently, research into low doses of direct oral anticoagulants focused on stable coronary artery disease. The pivotal COMPASS study (Table 2) proved that the addition of low-dose rivaroxaban (2.5 mg bid) to aspirin in almost all phases of stable coronary artery disease reduced morbidity and mortality. When compared to aspirin alone, the combination of drugs reduced the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and stroke by 26% and mortality by 23%. The outcome was similarly improved in patients after myocardial infarction (representing 69% of all subjects) and in those without a history of myocardial infarction. The results did not differ based on the time from myocardial infarction (between groups of patients who were two years, 2–5 years and 5–20 years after myocardial infarction). The benefits of combining rivaroxaban with aspirin were similar between the group that had followed guidelines for adequate secondary prevention (non-smokers, beta blocker, ACE inhibitor, lipid-lowering drugs) and the group that did not. The combination also resulted in an increased risk of bleeding (by 66%), but the bleeding was mainly gastrointestinal and there was no

Table 2: An overview of some key large clinical trials in recent years.

Study (year of publication)	Drug	Duration	Number of patients	Patients after a myocardial infarction	Primary outcome (other outcomes in brackets)	Results (study drug vs. control drug)	Relative reduction in cardiovascular risk	Side effects	Risk of side effects (drug vs. control)
COMPASS-CAD (2018)	Rivaroxaban 2.5 mg bid + aspirin 100 mg (R+A) vs. rivaroxaban 5 mg bid (R) vs. aspirin 100 mg (A)	An average of 1.95 years	27,395 Coronary artery disease: 24,824	MI in the last 20 years (69%)	Composite outcome – death from CV cause, MI, stroke (mortality) (overall clinical benefit - events)	R vs. A: NS R+A vs. A: 4% vs. 6% (NNT 50) 3% vs. 4% 5% vs. 6%	 26% 23% 22%	Major bleeding	R+A vs. A: 3% vs. 2% (HR 1.66)
ODYSSEY (2018)	Alirocumab 75 mg/2 weeks sc. (increased to 150 mg or discontinuation – target LDL cholesterol 0.6-1.3 mmol/L) vs. placebo	Median 2.8 years	18,924	ACS 1–12 months ago (median 2.6 months), LDL cholesterol ≥ 1,8 / non-HDL cholesterol ≥ 2.6 mmol/L / apolipo B 80 mg/dcL	Composite outcome – death from coronary artery disease, MI; ischaemic stroke-non-fatal/fatal, UA-hospitalization (LDL cholesterol - 12 months) (mortality)	9.5% vs. 11.1% (NNT 63) 2.38→1.1 mmol/lL 3.5% vs. 4.1%	15% NS	Injection site reaction	3.8% vs. 2.1%
REDUCE-IT (2019)	Icosapent ethyl 22 mg bid (omega-3 PUFA) vs. placebo	Median 4.9 years	8,179	CV diseases (71%) or DM + at least one risk factor TG > 1,52 mmol/L	Composite outcome - death from CV cause, MI, stroke, UA, coronary revascularization (Death from CV cause)	17.2% vs. 22% (NNT 21) 4.3% vs. 5.2%	25% 20% (p=0.03)	Severe bleeding	2.7% vs. 2.1% (NS)
COLCOT (2019)	Low-dose colchicine 0.5 mg vs. placebo	Median 22.6 months	4,745	30 days after MI	Composite outcome – death from CV cause, cardiac arrest with successful resuscitation, MI, stroke and emergency hospitalizations due to angina pectoris leading to coronary revascularisation	5.5% vs. 7.1% (NNT 63)	23%	Pneumonia	0.9% vs. 0.4%

Study (year of publication)	Drug	Duration	Number of patients	Patients after a myocardial infarction	Primary outcome (other outcomes in brackets)	Results (study drug vs. control drug)	Relative reduction in cardiovascular risk	Side effects	Risk of side effects (drug vs. control)
REWIND (2019)	Dulaglutide once weekly sc. (GLP1-RA) vs. placebo	Median 5.4 years	9,901	CV diseases (31,5%), risk factors, 20,6% after MI/stroke	Composite outcome - death from CV cause, MI, stroke (death – any reason)	12% vs. 13.4% (NNT 71) Group with CV diseases: 17.9% vs. 20.3% NS	12% 13%	Gastrointestinal	47.4% vs. 34.1%

Legend: R – rivaroxaban; A – aspirin; MI – myocardial infarction; HR – risk ratio; ACS – acute coronary syndrome; NNT – number needed to treat (calculated for primary outcome); LDL – low density lipoprotein; ne-HDL – non-high-density lipoprotein; UA – unstable angina; CV – cardiovascular; NS - non-significant, PUFA – polyunsaturated fatty acids; DM – diabetes mellitus; TG – triglycerides; GLP1-RA – glucagon-like peptide 1 receptor agonists.

significant increase in cerebral haemorrhage or fatal haemorrhage. At the same time, the risk of bleeding was higher in the first year than in subsequent years while the reduction in major cardiovascular events persisted throughout. The overall benefit thus spoke in favour of the use of a combination of low-dose rivaroxaban and aspirin. There is no data on why the subjects were poorly compliant with therapy in the introductory phase of the study, and in the study, myocardial infarction was not classified by individual types, which limits the importance of the study. The study was stopped early after meeting the primary end point, which could overestimate the treatment effect (22). Based on the inclusion criteria for the COMPASS study, Slovenian recommendations for the use of low doses of rivaroxaban in combination with aspirin were adopted. This combination can be prescribed to patients with coronary artery disease without concurrent indications for anticoagulation, dual antiplatelet therapy or other contraindications and who are older than 65 years and patients younger than 65 years but with at least two-vessel coronary artery disease or at least two additional risk factors, which are listed here: smoking, diabetes mellitus, GRF < 60 ml/min, heart failure or non-lacunar ischaemic stroke ≥ 1 month ago (23).

In the latest ESC guidelines for the treatment of NSTEMI, the grade of recommendation for extended dual antiplatelet therapy is the same for both the combination of aspirin and low-dose rivaroxaban and dual antiplatelet therapy (Figure 1). It is only considered in patients without an increased risk of major bleeding. However, if there is a high risk of ischaemic events (complex coronary artery disease and at least one additional criterion), the grade of recommendation is *IIa*, and in the case of a moderate risk of ischaemic events, IIb (Figure 1) (2). If no events occur with dual antiplatelet therapy, it is usually extended after 12 months and not later, after one antiplatelet drug had already been discontinued. If we are deciding on treatment later, given the design of the study, the addition of a low-dose rivaroxaban is appropriate.

3 Beta-adrenergic receptor blockers and angiotensin-converting-enzyme (ACE) inhibitors

There has been no significant research in this area in recent years. An older meta-analysis has confirmed that beta blockers reduce mortality by 19% (24). The guidelines recommend beta blockers in patients after myocardial infarction who have left ventricular systolic

dysfunction or heart failure with a reduced ejection fraction ≤ 40% (grade of recommendation *I A*) (2,7). In acute coronary syndrome, intravenous beta blockers may be used if there are no signs of acute heart failure and systolic blood pressure is above 120 mmHg. In the guidelines, routine use of beta blockers in all patients after STEMI (without contraindications) has a grade of recommendation *IIa B*. It should be noted that beta blockers have been tested in patients with a normal ejection fraction in the period before modern methods of revascularization. To date, there is no evidence to suggest discontinuation of treatment would be beneficial in patients that tolerate them well (3,7). In addition to its preventive role, beta blockers are also effective as anti-ischaemic agents. In the acute phase after infarction, guidelines recommend the continuation of chronic treatment with beta blockers (except in cases of worsening heart failure) (I C) (2).

In the past, numerous studies have confirmed the long-term beneficial cardiovascular effects of ACE inhibitors and angiotensin II receptor blockers (ARBs). One of these is the EUROPA study, which reduced the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and cardiac arrest by 20% with perindopril (25). Furthermore, several studies (e.g. SOLVD, AIRE, TRACE) have confirmed that ACE inhibitors prevent cardiovascular events as well as myocardial remodelling in patients with reduced left ventricular ejection fraction (26). The ESC guidelines for STEMI management recommend treatment with an ACE inhibitor within 24 hours of myocardial infarction in patients with heart failure, left ventricular systolic dysfunction, diabetes or anterior wall infarction (grade of recommendation *I A*). In case of ACE inhibitor intolerance, treatment with an ARB is recommended, preferably valsartan (grade of recommendation *I B*). Again, the grade of recommendation for use in all patients (without the above criteria, if there are no contraindications) is lower (*IIa A*) (3). The latest ESC guidelines for NSTEMI management recommend the introduction of an ACE inhibitor (or in the case of intolerance, an ARB) in patients with myocardial infarction who have heart failure with a reduced ejection rate ≤ 40%, diabetes, or chronic kidney disease, in order to reduce overall cardiovascular mortality and morbidity (grade of recommendation *I A*) (2). Similarly, the guidelines for the treatment of patients with chronic coronary syndrome recommend ACE inhibitors when comorbidities are present (heart failure, hypertension or diabetes) with a grade of recommendation *I A*, and in patients with a very high risk of cardiovascular events with a grade of recommendation *IIa A* (7).

4 Lipid-lowering therapy

4.1 Statins

Research has confirmed that lower LDL cholesterol levels achieved with high-intensity statins (compared to medium-intensity statins) were associated with a greater reduction in both first and overall cardiovascular events. Long-term clinical benefits have been attributed, at least in part, to the beneficial pleiotropic effects of statins: effects on inflammation, oxidative stress, endothelial function, and antiplatelet activity (27). A meta-analysis confirmed that initiating statin therapy prior to PCI reduced the risk of myocardial within 30 days compared with initiation after PCI (relative risk reduction of 62% vs. 15%). Earlier initiation of treatment also meant fewer other cardiovascular events. In addition to its beneficial effects in the first month, the meta-analysis also confirmed the long-term efficacy of statins in preventing major cardiovascular events (28). Thus, in all patients with acute coronary syndrome who have no contraindications, the introduction of a high-intensity statin is recommended as soon as possible, regardless of baseline LDL cholesterol (grade of recommendation *I A*). After 4-6 weeks, it is necessary to check whether the target values have been reached: reduction of LDL cholesterol by ≥ 50% from baseline and LDL cholesterol <1.4 mmol/L. Low-intensity statins should only be considered in patients at increased risk of adverse reactions, i.e. in the elderly, in case of kidney failure, liver failure or anticipated drug-drug interactions (2,4).

The guidelines also suggest the possible use of a loading dose of a statin in patients undergoing PCI (grade of recommendation *IIa B*) (4). A recent SECURE-PCI study speaks against the use of statin loading doses in general in all patients with acute coronary syndrome. In all subjects included in the study, a significant reduction in the 30-day risk of major cardiovascular events was not demonstrated with the atorvastatin 80 mg loading dose (before and 24 hours after PCI). This reduction in risk was confirmed in the group of subjects who had PCI (65% of all patients; the rest were treated with surgical coronary revascularization or drugs). In these patients, the risk of death, myocardial infarction, stroke and unforeseen coronary revascularization was reduced by 28%. However, the decrease in risk was even more pronounced in patients treated with PCI during STEMI (by 46%) (29).

4.2 EZETIMIBE

It has been shown that combination lipid-lowering therapy improves clinical outcomes. In the IMPROVE-IT study, ezetimibe, a drug that reduces the intestinal absorption of cholesterol, was added to simvastatin; this addition lowered LDL cholesterol levels by approximately 24%. Combination therapy significantly reduced the risk of events during a median follow-up period of six years, such as: death from cardiovascular causes, myocardial infarction, stroke, unstable angina (requiring hospitalization) and coronary revascularisation ≥ 30 days after randomization with an overall risk reduction of 9%. Of these, 56% were first events and 44% subsequent events, confirming the importance of continuing combination lipid-lowering therapy after the first cardiovascular event (30,31). In patients with acute coronary syndrome, the guidelines recommend initiating treatment with ezetimibe after 4-6 weeks of the maximum tolerated statin dose if the target LDL cholesterol level has not been reached (grade of recommendation *I B*) (2,4).

4.3 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

An important, perhaps revolutionary, step forward in the field of lipid-lowering therapy is the discovery of monoclonal antibodies that inhibit the proprotein convertase subtilisin/kexin type 9 (PCSK9) and thus prevent the degradation of LDL receptors. Due to the increased density of LDL receptors on hepatocytes, the removal of LDL cholesterol from plasma is increased. PCSK9 inhibitors, such as evolocumab and alirocumab, reduce LDL cholesterol levels by approximately 60%.

Inhibition of PCSK9 by evolocumab as a statin adjunct in the FOURIER study led to a significant reduction in cardiovascular events in patients with atherosclerotic cardiovascular disease. There was a 15% reduction in the risk of composite outcome of death from cardiovascular causes, myocardial infarction, stroke, hospitalization for unstable coronary artery disease and coronary revascularisation. With evolocumab, the median LDL cholesterol was reduced from 2.4 mmol/L to 0.78 mmol/L; therefore, patients benefited from lowering LDL cholesterol below target values. Among the patients, 81.1% had a history of myocardial infarction (with a median of 3.35 years since the last event) (32). These were included in a further analysis of the FOURIER study and it was confirmed that the clinical benefit of evolocumab depends on the degree and extent of coronary artery disease. Patients who had a myocardial infarction in the last two years, those with a history of at least two myocardial infarctions and patients with persistent multivessel coronary artery disease were identified as high-risk subgroups. These characteristics have been shown to be an independent predictor of worse cardiovascular outcomes. The relative risk reduction with evolocumab was significantly higher in these high-risk subgroups in the remaining patients: in the subgroup with a myocardial infarction in the last two years by 20% (vs. 5%), in the subgroup with at least two myocardial by 18% (vs. 7%) and in the group with persistent multivessel coronary artery disease by 21% (vs. 7%). Thus, in these subgroups, the reduction of LDL cholesterol with evolocumab led to a greater and earlier cardiovascular risk reduction. Therefore, it is sensible to identify the most at-risk groups among patients after a myocardial infarction. Based on this type of research, personalized medicine will become increasingly important in the future (33).

The reduction in recurrent ischaemic events was also confirmed with alirocumab in the ODYSSEY study (Table 2). Patients with a median of 2.6 months after acute coronary syndrome were included. Patients received alirocumab as a high-intensity statin adjunct (atorvastatin or rosuvastatin) at the highest tolerated dose. The composite outcome of death from coronary artery disease, myocardial infarction, all ischaemic strokes and hospitalizations due to unstable angina decreased by 15% over a median follow-up period of 2.8 years. The greatest reduction in cardiovascular risk was in subjects with baseline LDL cholesterol ≥ 2.6 mmol/L (34).

No effects on cardiovascular mortality have been demonstrated in studies with evolocumab and alirocumab, which may be related to the main limitation of the studies - relatively short follow-up. Except for injection site reactions, no side effects were reported. As these are novel drugs, none of the studies can predict the long-term safety of PCSK9 monoclonal antibody therapy. The studies have also been limited by not using ezetimibe, which is, per the guidelines, a prerequisite for the introduction of a PCSK9 inhibitor (32,34). The guidelines recommend treatment with PCSK9 inhibitors if target LDL cholesterol levels are not reached after 4–6 weeks of treatment with a combination of a statin at the highest tolerated dose and ezetimibe (grade of recommendation *I B*) (2,4). The same recommendations, which recommend treatment with a statin, followed by the addition of ezetimibe and finally a PCSK9 inhibitor until target lipid levels are reached, also apply

to patients with chronic coronary syndrome (7). Prescribing PCSK9 inhibitors is not as widespread in any of the European countries as recommended by the ECS guidelines. In Slovenia, the HIIS will cover the cost of prescription for a PCSK9 inhibitor as part of secondary atherosclerosis prevention in comorbidities that increase cardiovascular risk (severe/generalized atherosclerosis, rapid progression of atherosclerotic vascular disease, familial hypercholesterolaemia, diabetes mellitus with target organ failure or additional risk factors or Lp(a) concentration >500 mg/L) if with the combination of a statin (at the highest tolerated individual dose) and ezetimibe, LDL cholesterol levels remain elevated above 2.6 mmol/L and in the absence of these comorbidities, above 3.6 mmol/L. As part of secondary atherosclerosis prevention, a PCSK-9 inhibitor may also be prescribed at Lp(a) concentrations >1000 mg/L and concurrent documented progression of atherosclerosis. A prescription is also possible if the patient's intolerance to statins is documented (35).

4.4 Omega-3 polyunsaturated fatty acids

The studies of omega-3 polyunsaturated fatty acids are contradictory. A recent meta-analysis using n-3 polyunsaturated fatty acids did not confirm a reduction in the risk of mortality, myocardial infarction or major vascular events, as was the case with the group with known coronary artery disease (36). Therefore, the guidelines do not recommend routine treatment (4). However, research suggests that patients at high cardiovascular risk, especially those with elevated triglycerides, could benefit from omega-3 fatty acid therapy (37). The results of the REDUCE-IT study, which included patients with elevated triglycerides at baseline, are promising (Table 2). Compared to other studies, the REDUCE-IT also used higher doses of omega-3 fatty acids, namely icosapent ethyl (purified and stable ester of eicosapentaenoic acid) at 2 g bid. Over a median follow-up period of 4.9 years, a 25% reduction in the risk of composite outcome of death from cardiovascular causes, myocardial infarction, stroke, unstable angina and coronary revascularisation was achieved. This improvement occurred independently of the achieved level of triglycerides in one year, which means that other metabolic effects, including antiplatelet activity, membrane stabilization effects, membrane stabilization, coronary artery plaque stabilization or reduction, and anti-inflammatory activity, also contributed to the favourable cardiovascular profile (38). The new EVAPORATE study has confirmed that icosapent ethyl at a daily dose of 4 g reduces atherosclerotic plaques (including vulnerable ones) (39).

5 Anti-inflammatory drugs

Low-grade chronic inflammation is an important aetiological factor in the continuous process of atherosclerosis. The CANTOS study suggested that reducing inflammation could reduce residual cardiovascular risk in patients with a history of myocardial infarction (stable phase) and hsCRP levels above 2 mg/L. Canakinumab, a monoclonal antibody targeting interleukin-1β, was investigated. Canakinumab 150 mg (administered subcutaneously every three months) has been shown to reduce the risk of cardiovascular event recurrence by 15% (composite outcome of death from cardiovascular causes, myocardial infarction and stroke) without affecting lipid levels. There was no effect on mortality, but a number of fatal infections were associated with canakinumab (40).

COLCOT, the most recent major clinical trial in the field of anti-inflammatory activity (Table 2) studied a low dose of colchicine, a drug otherwise used to treat gout and pericarditis. The study included patients in the acute phase (mean 13.5 days) after myocardial infarction with a median follow-up duration of 22.6 months. A low colchicine dose (0.5 mg daily) compared with placebo significantly reduced the risk of the composite outcome of death from cardiovascular causes, cardiac arrest with successful resuscitation, myocardial infarction, stroke and emergency hospitalizations due to angina pectoris leading to coronary revascularisation, by 23%. A higher incidence of pneumonia was reported in the colchicine group (41). Additional analysis showed that the group that received low doses of colchicine very early (first three days) after a myocardial infarction benefited the most. In this group, the risk of cardiovascular ischaemic events was reduced by as much as 48% compared to placebo, thus favouring the early introduction of colchicine in hospital treatment (42).

This is an interesting concept of anti-inflammatory action, which is currently limited to research, as these drugs are not yet registered for the secondary prevention of atherosclerosis.

6 Diabetes treatment in patients after myocardial infarction

Among patients with coronary artery disease, approximately 20–30% have diabetes mellitus, and in approximately 70% of the remaining patients, an oral

glucose tolerance test is expected to confirm the diagnosis of de novo diabetes mellitus or impaired glucose tolerance. Metformin, which has been shown to improve the long-term outcomes of cardiovascular conditions, remains the basis of treatment. However, in patients with myocardial infarction, favourable new therapeutic options in type 2 diabetes treatment appeared with the introduction of drugs that significantly reduced cardiovascular events: glucagon-like polypeptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors (5,43).

The LEADER study demonstrated a 13% reduction in the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and stroke in diabetic patients at high cardiovascular risk (30.7% of the patients were after myocardial infarction) after treatment with a GLP-1 receptor agonist liraglutide. Liraglutide also had a significant effect on reducing the risk of mortality (22% from cardiovascular causes and 15% from any cause). Notable side effects included acute gallbladder disease, injection site reactions, nausea, vomiting, diarrhoea, decreased appetite and abdominal discomfort (44). Dulaglutide in the REWIND study also significantly reduced the risk of the composite outcome of death from cardiovascular causes, myocardial infarction and stroke by 12% (median follow-up duration of 5.4 years) (Table 2). The study covered a wider population of cardiovascular patients, of whom only 20.6% had a history of myocardial infarction or stroke (45). Among GLP-1 receptor agonists, lixisenatide was also investigated after acute coronary syndrome, but did not lead to a significant reduction in cardiovascular events. Patients after a myocardial infarction were also included in the Harmony Outcomes study, in which albiglutide, which has since been discontinued, reduced serious cardiovascular events by 22% (5).

Among SGLT-2 inhibitors, empagliflozin (EMPA-REG OUTCOME study, in which 46.6% of subjects had a history of myocardial infarction) was shown to be effective in preventing deaths from cardiovascular causes, myocardial infarctions and strokes, but not dapagliflozin (DECLARE -TIMI 58, in which 40.6% of the subjects had cardiovascular disease). Empagliflozin reduced the risk of this combined outcome by 14%. By separating the group with empagliflozine and placebo in the favourable direction only two months into the study, the reduction of death from cardiovascular causes by 38% significantly contributed to this risk reduction. Empagliflozin also significantly reduced the risk of overall mortality by 32%. SGLT-2 inhibitors, whose mechanism of action is to reduce glucose reabsorption in the proximal renal tubule and increase glucosuria, have also been shown to be effective in reducing hospitalizations due to heart failure. Empagliflozin reduced the risk of the latter by 35% and dapagliflozin reduced the risk of the composite outcome of death from cardiovascular causes and hospitalization due to heart failure by 17%. Ketoacidosis was a side effect of dapagliflozin treatment that appeared significantly more frequently compared to placebo, and the risk of genital infections was significantly increased in patients with SGLT2 inhibitors compared to placebo (46,47).

Studies suggests that GLP-1 receptor agonists are likely to be beneficial primarily in reducing atherosclerotic events, and SGLT2 inhibitors in reducing outcomes associated with heart failure. The latest guidelines take into account these research findings. In patients with type 2 diabetes and cardiovascular disease or with a very high cardiovascular risk, the use of GLP1 receptor agonists (liraglutide, semaglutide or dulaglutide) or the use of SGLT2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) is recommended to prevent cardiovascular events. Treatment with liraglutide or empagliflozin is recommended to reduce the risk of death (recommendation level *I B*) (5).

7 Conclusion

Optimizing drug treatment after a myocardial infarction tends to combine drugs in both antiplatelet and lipid-lowering therapy. Interestingly, low-dose drugs have proven to be beneficial in the long term as part of dual antiplatelet therapy. In terms of improving patient participation, treatment regimens that allow periodic treatment are tempting. In patients after a myocardial infarction, treatment of diabetes with beneficial cardiovascular effects is now possible. We can conclude that recent research offers the possibility of various additional routes through which we can influence the slowed process of atherosclerosis and thus improve the prognosis of patients after a myocardial infarction.

Conflict of interest

None declared.

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