DOI: 10.20514/2226-6704-2020-10-5-348-356

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Modern Approaches to Optimal Antithrombotic Therapy for Stable Ischemic Heart Disease

Abstract

The article highlights the practical aspects of the use of antithrombotic therapy in patients with stable (chronic) coronary artery disease (CAD). The CAD verification using modern functional and anatomical diagnostic methods are considered. Patients with stable CAD represent a heterogeneous group, having various clinical scenarios. Information is provided on the main risk factors for ischemic and hemorrhagic complications that determine the choice of optimal antithrombotic therapy regimens. Modern views on the monotherapy and clopidogrel in CAD are presented. The data of the largest international studies CHARISMA and PEGASUS-TIMI 54 on the use of double antiplatelet therapy in patients with stable IHD reflected in modern guidelines are highlighted. Features of new antiplatelet agents (prasugrel and ticagrelol) are described. Based on the results of the COMPASS study, indications for the administration of small doses of rivaroxaban in combination with aspirin for the secondary prevention of cardiovascular complications in patients with stable manifestations of atherosclerosis with a low risk of bleeding are considered.

The use of antithrombotic therapy is associated with an increased risk of bleeding and particularly with gastrointestinal bleeding. The information on the use of drugs for the prevention of gastrointestinal bleeding is provided.

Antithrombotic therapy can reduce the risk of complications associated with atherothrombosis, however, to improve prognosis a multipurpose intervention is required, including correction of risk factors and the use of drugs from different groups with proven effectiveness. Optimal medical therapy, including antithrombotic drugs, is vital for patients with CAD and can successfully prevent adverse outcomes.

Key words: *coronary artery disease, ischemic risk, hemorrhagic risk, antithrombotic therapy, antiplatelet agents, dual antiplatelet therapy, rivaroxaban, optimal medical therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.06.2020
Accepted for publication on 18.08.2020

For citation: Roytberg G.E., Slastnikova I.D. Modern Approaches to Optimal Antithrombotic Therapy for Stable Ischemic Heart Disease. The Russian Archives of Internal Medicine. 2020; 10(5): 348-356. DOI: 10.20514/2226-6704-2020-10-5-348-356

ACS — acute coronary syndrome, ASA — acetylsalicylic acid, ATT — antithrombotic therapy, BP — blood pressure, CHD — coronary heart disease, cCHD — chronic coronary heart disease, CCS — chronic coronary syndrome, CVCs — cardiovascular complications, DATT — dual antiplatelet therapy, HR — heart rate, LDL-C — low density lipoprotein cholesterol, MI — myocardial infarction, ODT — optimal drug therapy, PCI — percutaneous coronary interventions, PPI — proton pump inhibitors, stress ECHO-CG — stress echocardiography

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Thrombotic complications are among the most dangerous complications of atherosclerotic vascular disease that lead to myocardial infarction, stroke, and contribute to premature death. Antithrombotic therapy (ATT) can reduce the risk of complications associated with atherothrombosis. However, for optimal therapy regimen, many factors associated with the special features of antithrombotic drugs and the peculiarities of disease course in a particular patient should be considered. Successful treatment also requires controlled long-term management of the patient using, along with ATT, all complex measures aimed at improving prognosis and quality of life.

Special Aspects of the Disease

The first required step is the verified diagnosis of coronary heart disease (CHD). According to the current view, CHD is a pathological process characterized by atherosclerotic plaques in epicardial coronary arteries, and the process can be both obstructive and non-obstructive [1]. CHD course includes stable and unstable periods; these are classified, respectively, as chronic coronary heart disease (cCHD) or chronic coronary syndrome (CCS), and acute coronary syndrome (ACS). Patients with a stable CHD course may have very different clinical manifestations and risk of cardiovascular complications (CVCs) such as death and myocardial infarction.

Today, all cases of CCS can be divided into 6 groups:

1) Angina and/or dyspnea in patients with suspected CHD;
2) Recent cardiac insufficiency or decreased left ventricular function in patients with suspected CHD;
3) No symptoms or stable symptoms for less than one year after ACS or recent myocardial revascularization;
4) No symptoms or stable symptoms for more than one year after diagnosis or revascularization;
5) Suspected vasospastic or microvascular angina;
6) No symptoms in the presence of CHD found during screening [1].

Present-day diagnosis of coronary heart disease includes several stages. At the initial stage, patients with possible unstable angina should be identified: prolonged episodes of angina at rest, recent onset of angina (new onset of angina), increased intensity and severity of attacks during the previous brief period of time (progressive angina); other forms of ACS should also be excluded.

At subsequent stages, the detected symptoms and comorbidities should be evaluated, clinical examinations and laboratory tests should be performed, along with the analysis of the probability of CHD and diagnostic tests.

CHD overdiagnosis is often observed in actual clinical practice. Up to 50% of patients referred for coronary angiography with a diagnosis of "stable angina" have intact coronary arteries [2]. Additional examination in some patients may reveal a non-obstructive cause of ischemia (microvascular or vasospastic angina) without atherosclerotic damage to epicardial coronary vessels. In order to detect obstructive CHD, functional or anatomical methods are typically used. Present-day non-invasive functional tests for ischemia (stress echocardiography (stress EchoCG), magnetic resonance imaging, single-photon emission computed tomography) are highly informative. Stress echocardiography is the most accessible imaging method. Multispiral computed tomography of coronary vessels can be used as the initial anatomical method. This method is preferable in patients with no history of CHD and its low clinical probability. Selective coronary angiography for diagnostic purposes in stable patients should be considered only when non-invasive methods have provided no information for making a definite diagnosis [1].

According to large randomized trials, using antiplatelet agents in the absence of CHD (primary prevention), even in patients with a high risk of cardiovascular events, can have a negative effect due to side effects (increased bleeding) [3].

Assessment of the risk of cardiovascular events is the most important factor for choosing the optimal treatment. In cases of cCHD, risk stratification is based on parameters used for establishing the diagnosis: clinical signs of the disease (severity of myocardial ischemia), involvement of anatomical structures and severity of coronary artery atherosclerosis, systolic function of the left ventricle, comorbidities and additional risk factors.

Risk assessment should be performed for patients with CHD taking into account different clinical

variants; it will allow identifying patients with a high risk of events (risk of cardiac mortality > 3% per year) and changing management tactics to improve prognosis [2].

According to the REACH register, the annual mortality rate among patients with CHD varied by a factor of 6, from 0.63% in patients with non-obstructive coronary artery disease to 3.8% in patients with myocardial infarction (MI) and coexistent diabetes mellitus [4].

The history of MI is one of the main factors determining the prognosis of cCHD. According to the APOLLO register, one in five patients (18.3%) develops major CVCs (MI, stroke, cardiovascular death) during the first year after MI, and another 20% of patients — during the next 3 years [5]. A high risk of events is also observed in patients with common multivascular coronary artery disease. The prevalence of multivascular disease in patients with non-ST elevation ACS varies from 40 to 80% [6].

Factors of high and moderate risk of ischemic events in patients with cCHD are presented in Table 1.

The use of ATT is associated with an increased risk of bleeding. The choice of ATT and its duration can vary significantly in patients with different hemorrhagic risk. Factors contributing to the high risk of bleeding are shown in Table 2.

ATT in patients with a high risk of both ischemic and hemorrhagic complications is a challenging task. According to the PARIS register, 40% of patients with a high risk of bleeding had a high ischemic risk [8].

Table 1. *Factors of high and moderately increased risk of ischemic events in patients with CAD*

1. Clinical characteristics [1]
A high risk of ischemic events: diffuse multivessel CAD with at least one of the following:
✓ DM requiring medication
✓ Recurrent MI
✓ PAD
✓ CKD with eGFR 15-59 ml/min /1,73 m^2
A moderately increased risk of ischemic events: the presence of at least one of the following:
✓ Multivessel/ diffuse CAD
✓ DM requiring medication
✓ Recurrent MI
✓ PAD
✓ Heart failure
✓ CKD with eGFR 15-59 ml / min / 1,73 m^2
2. Angiographic characteristics and complex PCI [7]
✓ Previous stent thrombosis
✓ Stenting of last remaining patent artery
✓ Simultaneous stenting of three or more stents
✓ Simultaneous intervention on three or more stenoses
✓ Stenting of bifurcation with two stents implanted
✓ Stent length >60 mm
✓ Treatment of chronic total occlusion

Note: CAD — coronary artery disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; HF — heart failure; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention

Table 2. *Factors of high bleeding risk [2]*

High bleeding risk
✓ Prior history of intracerebral haemorrhage or ischaemic stroke
✓ History of other intracranial pathology
✓ Recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss
✓ Other gastrointestinal pathology associated with increased bleeding risk
✓ Liver failure
✓ Bleeding diathesis or coagulopathy
✓ Extreme old age or frailty
✓ Renal failure requiring dialysis or with eGFR <15 mL/min/1,73 m^2

Note: eGFR = estimated glomerular filtration rate

Choosing Antithrombotic Therapy

Thrombosis occurs due to the activation of both platelet and plasma components of hemostasis. Platelets play the most critical role in the development of atherothrombotic events. Antiplatelet agents (antiaggregants) form the basis of ATT in patients with CHD. Drugs of this group can be prescribed for both monotherapy and dual antiplatelet therapy (DATT).

Monotherapy with antiplatelet agents

Acetylsalicylic acid (ASA) is the most common and affordable antiplatelet agent. For many years, all patients with cCHD and sinus rhythm were recommended to use ASA in low doses (75-150 mg per day), if there were no contraindications. This recommendation was related to class I recommendations (*This type of treatment is proven to be useful and*

effective) with high strength in the European Society of Cardiology guidelines for stable coronary heart disease (ESC, 2016) [9].

What has changed? The accumulated experience of using ASA showed that the frequency of ischemic complications of CHD decreases with increase in the number of bleedings. Patients with a high risk of complications have the best risk-benefit ratio when using ASA, which was mentioned in the ESC Guidelines 2019 [1]. The former class I recommendation was left in place not for all patients with cCHD but only for patients after MI and revascularization (daily intake of ASA 75–100 mg). The risk of ischemic complications in patients without MI and revascularization is relatively low. Therefore, the benefit from ASA in these cases only slightly exceeds the negative consequences. The use of ASA 75–100 mg daily can be considered in such patients, with CHD that is reliably confirmed with advanced imaging methods (class IIb *"Usefulness/efficacy is less well established by evidence/opinion").*

Clopidogrel (75 mg/day) remains an alternative to ASA in patients with stable CHD and is a second-line drug for patients with ASA intolerance. Clopidogrel causes reduced antiplatelet response in some patients, which is associated with several factors, including genetic polymorphism, as well as intake of drugs that disrupt the conversion of clopidogrel to its active metabolite [10].

In the CAPRIE study, in a subgroup of patients with symptomatic lower limb atherosclerosis, clopidogrel had an advantage over ASA in reducing the risk of CVCs and cardiovascular mortality and was equally safe [11]. Clopidogrel may be preferred over ASA in patients with CHD combined with lower limb atherosclerosis (class IIb) [1, 12].

Monotherapy with prasugrel or ticagrelol is not officially recommended in patients with CHD, although their actual clinical off-label use in stable patients has increased in recent years [13]. The risk of bleeding with these drugs can be unjustifiably high compared with the number of prevented ischemic events. Currently, monotherapy with prasugrel or ticagrelol is not used in stable patients with CHD and without a history of coronary stenting.

Dual antiplatelet therapy with the combination of ASA and one of P2Y12 receptor blockers is the basis of ATT in patients with ACS and/or percutaneous coronary interventions (PCI) [7].

After planned PCI with stenting in patients with cCHD, it is recommended to prescribe DATT (ASA + clopidogrel) for six months, if there is no high risk of bleeding (class I), in order to achieve an optimal balance of efficacy and safety. Premature withdrawal of clopidogrel can lead to increased risk of stent thrombosis. In patients with a high risk of bleeding, DATT can be reduced to three months (class IIa *"Weight of evidence/opinion is in favor of usefulness/efficacy"*) or minimum to 1 month (class IIb) [1, 7].

After elective coronary artery bypass surgery, unlike elective stenting, ASA monotherapy is usually prescribed to patients with cCHD [7]. There is currently no convincing evidence base for using DATT after coronary artery bypass surgery in patients with CHD, although there is evidence for a reduced risk of venous (not arterial) shunt thrombosis associated with DATT [14, 15].

DATT in stable patients was studied in comparison with ASA monotherapy in large studies CHARISMA (ASA + clopidogrel/prasugrel) and PEGASUS-TIMI 54 (ASA + ticagrelol) [16, 17]. A significant decrease in major CVCs, including MI, stroke and cardiovascular death, without a significant effect on overall mortality, was demonstrated in both studies (in CHARISMA study, in the subgroup of patients with confirmed CHD). The greatest benefit of DATT was observed in patients with a history of MI. At the same time, both studies showed a significant increase in the number of major bleedings but no increase in fatal bleedings.

The duration of DATT after ACS is advisably at least one year [7]. Prolonged DATT leads to a lower risk of ischemic complications but increased bleeding in proportion to the duration of administration. Special scales were developed to implement personalized treatment and find the optimal duration of DATT for a particular patient. The best known among them are DAPT and PRECISE-DAPT. Both scales are fairly easy to use; results can be obtained with the help of online calculators. The DAPT scale is used when deciding between termination and continued use of DATT 12 months after stenting if the patient has no hemorrhagic and ischemic complications while taking two antiplatelet agents. The DAPT scale uses scoring for the following parameters: age, smoking, diabetes mellitus, myocardial infarction, history of PCI or myocardial infarction,

using a stent coated with paclitaxel, a stent with a diameter of < 3 mm, cardiac insufficiency or decreased LVEF < 30%, stenting of venous shunts. A DAPT score ≥ 2 points indicates a high risk of ischemic complications, and DATT prolongation (up to 30 months) is recommended for such patients. If the result is < 2 points, the standard duration of DATT (12 months) without further prolongation is recommended [18].

The PRECISE-DAPT scale is used immediately after coronary stenting to assess the risk of community-acquired bleeding and possible reduction of DATT duration. This scale includes five prognostic factors: age, creatinine clearance, hemoglobin, WBC and the history of spontaneous bleedings in patients treated with DATT. A PRECISE-DAPT score ≥ 25 points indicates a high hemorrhagic risk. Therefore, DATT duration may be reduced to six months in cases of stenting for ACS and three months in cases of elective stenting for cCHD. If the risk of bleeding is low (PRECISE-DAPT <25 points), DATT duration can be standard or prolonged [19].

The abovementioned scales have several limitations. They are not validated for patients taking ticagrelol or prasugrel as P2Y12 receptor blockers; the DAPT scale factors in a stent with paclitaxel, which is rarely used at present; the PRECISE-DAPT scale does not consider special features of coronary disease and PCI. DAPT and PRECISE-DAPT scales can be considered when determining the possible duration of DATT (class IIb) [7]. However, to this day, these scales have not been confirmed in large randomized trials, and so their significance in determining DATT duration remains unclear.

Results of studies on the risk-benefit ratio of long-term DATT in patients with a history of MI were analyzed in a large meta-analysis [20]. Prolonged DATT was shown to reduce the number of major CVCs and stent thrombosis but had no effect on overall mortality. The effect observed was accompanied by increased bleedings. Analysis of different subgroups of patients treated with prolonged DATT revealed that patients with previous MI and high risk of ischemic complications and no high risk of bleeding benefit the most from this treatment. The necessary condition for DATT prolongation is good tolerance to the antiplatelet drugs used with no ischemic or hemorrhagic complications during the first year. It should be noted that the most favorable effect of DATT is observed with no break in the administration of antiplatelet agents after MI. If DATT was restarted after a long break (more than one year), this strategy had no positive effect [21]. The possibility of prolonging treatment with P2Y12 receptor blockers as part of DATT is indicated for clopidogrel at a dose of 75 mg/day, prasugrel at a dose of 10 mg or 5 mg/day (with body weight < 60 kg or age > 75 years) and ticagrelor at a dose of 60 mg twice a day. Clopidogrel remains the best-studied drug for long-term DATT. Prasugrel should not be used in patients with a history of ischemic stroke; there are restrictions for patients aged >75 years or with low body weight (less than 60 kg). Ticagrelol can cause dyspnea, which is often transient, but in some cases, it should be replaced with another drug. At present, according to the ECS Guidelines (2019), when it comes to stable patients with previous MI, the possibility of using prolonged DATT should be considered in patients with a high risk of ischemic complications (class IIa) and can be considered in patients with a moderately high risk (class IIb) with no high hemorrhagic risk [1].

New regimens of antiplatelet therapy are currently being studied. Several studies have been carried out on the use of antiplatelet agents after PCI as a part of short-term DATT (1–3 months) followed by long-term administration of a P2Y12 antiplatelet agent as monotherapy without ASA. Information obtained from the studies (STOPDAPT-2, SMART-CHOICE, GLOBAL LEADERS, TWILIGHT) suggests the advantage of such regimens in terms of treatment safety (decreased bleedings), along with no decrease in antiischemic effect (no worse than standard DATT) [22]. A thorough analysis of the results of these treatment regimens is underway, but they have not yet been included in the accepted international and national recommendations.

Combined antithrombotic therapy: antiplatelet agent + anticoagulant

Along with platelet activation, the activation of the blood coagulation system plays a crucial role in the pathogenesis of atherothrombosis. Both processes (activation of platelets and coagulation cascade) occur simultaneously, which leads to thrombus

formation. In this regard, the combination of antiplatelet agents and anticoagulants seems very reasonable in patients with atherothrombosis.

The study of oral non-vitamin K-dependent anticoagulant rivaroxaban in patients with sinus rhythm and stable manifestations of atherosclerosis (CHD, atherosclerosis of lower limbs) was carried out during the COMPASS study [23]. The addition of rivaroxaban at a dose of 2.5 mg twice a day to ASA treatment compared with ASA monotherapy significantly reduced not only the risk of major CVCs but also mortality from all causes; no such fact was previously observed for other ATT strategies. The risk of major bleeding in cases of combined ATT increased, but the number of fatal and intracranial bleedings showed no reliable increase. In general, combination therapy had an advantage over ASA monotherapy in terms of the sum of major CVCs and heavy bleedings. The risk of severe ischemic complications in lower limbs, including amputations, decreased further in patients with atherosclerosis of lower limbs. This regimen (ASA 75–100 mg + rivaroxaban 2.5 mg twice/day) can be discussed for secondary prevention at high (class IIa) or moderately high (class IIb) risk of ischemic events in patients with multivascular CHD or previous MI > 1 year with low hemorrhagic risk [1].

To increase ATT safety, the use of proton pump inhibitors (PPIs) is recommended in patients with a high risk of gastrointestinal bleeding in order to prevent bleeding from the upper gastrointestinal tract [1, 7]. PPIs have an inhibitory effect on cytochrome P450 enzymes, which can reduce the effectiveness of clopidogrel. Different PPIs produce a different degree of inhibition. Laboratory test results showed a stronger inhibitory effect of lansoprazole, omeprazole and esomeprazole. Pantoprazole and rabeprazole had a significantly lesser effect on cytochrome P450 enzymes [24]. It should be noted that no significant differences between the drugs were found in clinical trials [25]. Data on the effect of PPIs on the risk of CVCs are contradictory. The results on the high risk of adverse cardiovascular events in cases of combined use of PPIs and clopidogrel (both as monotherapy and as a part of DATT) were not confirmed in a number of clinical trials [25, 26].

Along with damage to the upper gastrointestinal tract, prolonged use of antiplatelet agents lead to mucosal lesions of the small intestine [27]. In order to reduce the risk of intestinal bleeding, literature discusses synthetic prostaglandins and other GI protectant drugs that enhance the synthesis of endogenous prostaglandins and have anti-inflammatory and antioxidant effect [28].

As a result, different ATT strategies are currently used in patients with CHD, depending on the risk of ischemic and hemorrhagic complications. In patients with a high risk of ischemic events, new ATT regimens are recommended; their specific choice is determined by the risk of bleeding, individual peculiarities of the patient, and comorbidity.

Additional Options for Prognosis Improvement

For the prevention of ischemic complications in patients with CHD (secondary prevention), present-day recommendations are aimed at lifestyle changes (smoking cessation, balanced healthy diet, alcohol restriction, weight loss, regular physical activity), prescription of drugs with proven effectiveness and revascularization in high-risk patients [1]. Properly chosen advanced drugs have an effect on different mechanisms of CHD and complement each other. Drug treatment of patients with CHD, along with ATT, should include statins, renin-angiotensin-aldosterone system blockers (RAASB) / angiotensin II receptor blockers, beta blockers (BB) and antianginal drugs, thus forming the optimal drug therapy (ODT) [1].

ODT includes regular risk assessment of both ischemic and hemorrhagic complications and management of existing cardiovascular risk factors. It is extremely important for effective therapy to achieve the following target values: low-density lipoprotein cholesterol (LDL-C), heart rate (HR), blood pressure (BP) and blood glucose. Unfortunately, the recommended target values are not achieved in most patients in clinical practice. It was demonstrated that only 8% of patients in the FREEDOM study, 18% in the COURAGE study, and 23% in the BARI-2D study achieved target values (levels of LDL-C, BP, blood glucose, and smoking cessation) [29]. According to the large CLARIFY register, a high heart rate (more than 70 beats/min) was registered in 41% of 33,177 patients with cCHD treated with BB therapy [30].

Effective ODT in patients with CHD significantly reduces mortality and risk of events. Most studies revealed that more active management of patients with CHD (elective myocardial revascularization) does not improve their prognosis compared with ODT in most patients [31]. The recent large-scale clinical ISCHEMIA study, which involved 5,179 patients with cCHD, could not prove the superiority of invasive methods over ODT. Analysis of separate subgroups revealed no categories of patients where the invasive strategy would give advantages. In the invasive treatment group, improvement in the quality of life was observed only in patients with initially frequent angina attacks [32]. In cases of cCHD, planned revascularization is advisable in patients with damage to the left coronary artery trunk, with a combination of low LV ejection fraction with multivascular coronary artery disease and ODT failure [33].

Thus, at present, advanced drug therapy is the basis for the management of patients with CHD, enabling to prevent most adverse outcomes. As an integral part of ODT, ATT significantly contributes to reducing risks and improving the prognosis for patients with CHD.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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