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# Dual antiplatelet therapy and antithrombotic treatment: Recommendations and controversies

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## Abstract

*Dual antiplatelet therapy is currently recommended for all patients with acute coronary syndromes, independent of whether they receive pharmacological treatment or undergo percutaneous coronary intervention. Antiplatelet agents are the cornerstone of pharmacological treatment in interventional cardiology. However, there is a clear need for randomized trials to assess the treatment strategy of dual antiplatelet therapy in patients who also need long-term antithrombotic treatment (such as those with atrial fibrillation, prosthetic heart valve, mitral valve regurgitation or stenosis, deep vein thrombosis, pulmonary embolism, or pulmonary hypertension). In this paper we discuss trials and analyses on the use of dual antiplatelet treatment in combination with antithrombotic therapy in particular diseases, with a focus on the risk of hemorrhagic events connected with this treatment, as well as recent guidelines of the European Society of Cardiology, the American College of Cardiology, and the American Heart Association.* (Cardiol J 2009; 16, 2: 179–189)

**Key words: antiplatelet therapy, antithrombotic treatment, acetylsalicylic acid, clopidogrel, oral anticoagulants, acute coronary syndromes, atrial fibrillation**

## Introduction

The need for simultaneous dual antiplatelet and oral anticoagulant (OAC) therapy is increasing. Dual antiplatelet therapy is currently recommended for all patients with acute coronary syndromes (ACS), independent of whether the patients are treated pharmacologically or with percutaneous coronary interventions (PCI) [1, 2]. Antiplatelet agents are the cornerstone of pharmacological treatment in interventional cardiology. Their use is necessary owing to the activation of platelets caused by damage to the endothelium and deeper layers of the vessel during percutaneous coronary intervention [3].

The number of patients of advanced age with ACS is increasing as life expectancy increases [4]. These patients are also more often diagnosed with atrial fibrillation (AF). Age greater than 75 years is an important risk factor for thromboembolic events, but also increases the risk of hemorrhagic complications. Many trials have shown that antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel is less effective than OAC therapy for the prevention of stroke, myocardial infarction (MI), or peripheral embolism in patients with AF and at high risk of thromboembolic events [5, 6]. On the other hand, oral anticoagulation alone is not recommended in patients who have undergone a coronary stent procedure, because it is associated with a 50% increased risk of death or MI caused by subacute embolism in stents [7, 8].

There is still a lack of data from large randomized trials to determine the best strategies for

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therapeutic management of patients with indications for dual antiplatelet therapy and for long-term antithrombotic treatment such as AF, prosthetic heart valves, thrombus in the left ventricle, or venous thrombotic disease. Use of dual antiplatelet therapy in ACS patients with simultaneous indications for OAC therapy seems reasonable, although the statements from cardiology societies are not unequivocal.

## Acute coronary syndromes

The degree of vessel stenosis caused by atherosclerotic lesions is not thought to play a major role in the pathophysiology of ACS. Instability of the atherosclerotic lesion, inflammatory processes, and thrombotic factors are now considered the main causes of ACS that determine the risk of thrombus formation on rupturing or ruptured lesions [4].

Damage of the vascular wall, resulting from the rupture of unstable atherosclerotic lesions (70% of ACS) or ulceration of critical lesions, makes the adhesion, activation, and aggregation of platelets possible, which in turn results in thrombus formation and regional decreases in blood flow with reduced tissue perfusion [9]. Acute thrombosis is often accompanied by vessel spasm, which further limits the flow of blood. During ST elevation myocardial infarction (STEMI), a thrombus rich in fibrin, causes total occlusion of the vessel. In patients presenting with non-ST elevation acute coronary syndrome (NSTE-ACS), the thrombus is rich in platelets and causes partial or total, but short-lasting, occlusion. Thrombi rich in platelets can break down into small pieces, and translocation in the blood can cause embolism of small arteries or capillary vessels. This process leads to small areas of myocardial necrosis and increased levels of markers of myocardial necrosis [10, 11]. The goal of antiplatelet treatment in NSTE-ACS is the disruption of thrombi rich in platelets, stabilization of atherosclerotic lesions and prevention of total vessel occlusion. Therapeutic management in STEMI is focused on restoration of blood flow in infarcted arteries.

Discovery of markers of thrombin formation and platelet activation, and demonstration of the benefits of antithrombotic treatment have contributed to a better understanding of the role of thrombosis in ACS [12]. Trials in patients with coronary artery disease have shown that use of OACs, with international normalized ratio (INR) level greater than 2, in combination with ASA significantly reduces total mortality and the incidence rates of MI and stroke, but is also associated with an increased risk of hemorrhagic complications compared with ASA alone [13–19]. Compared with ASA alone, the combination of ASA and OAC, with INR level less than 2, is not beneficial in preventing ischemic events, but increases the risk of hemorrhagic complications [18, 20, 21].

The process of platelet activation should be considered not only as acute rupture of atherosclerotic lesions but also as a factor that increases the risk of recurrent events due to atherosclerosis in patients with inflammatory processes in the vessel wall and systemic circulation. The duration of this increased risk after ACS is unknown. It is known that the processes mentioned above play important roles in the recurrence of acute ischemic incidents, which is why antiplatelet treatment is crucial during ACS and as chronic supportive therapy [2, 22––24]. Dual antiplatelet therapy with ASA and clopidogrel after PCI is superior to therapy with ASA [25, 26] or warfarin alone or the combination of ASA and warfarin [8, 25, 27]. The addition of clopidogrel to ASA significantly reduces the risk of recurrent MI and angiovascular mortality in patients with ACS [26]. Dual antiplatelet therapy is particularly important after implantation of drug-eluting stents (DES), the use of which is associated with an increased risk of late stent thrombosis compared to bare metal stents (BMS). According to the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/Society for Coronary Angiography and Interventions (ACC/AHA/SCAI) guidelines for PCI [3, 28] and the use of anticoagulants in heart disease [29], it is reasonable to avoid DES and use BMS as a safer option in patients requiring concomitant therapy with ASA, clopidogrel, and OAC.

## Atrial fibrillation

Atrial fibrillation is the most common indication for chronic antithrombotic therapy. It occurs in about 5–20% of patients with ACS. Some of these patients present with AF before ACS. In others, it is a consequence of the acute phase of ACS, which results in further poor prognosis. There are a few reasons for the coexistence of ACS and AF: both AF and ACS are common in patients of advanced age; dysfunction of the left ventricle, metabolic processes, inflammatory reaction of the pericardium, increased levels of catecholamines, or use of drugs stimulating beta receptors are factors that occur in ACS and can cause AF; and infarction or ischemia of the atria directly increases muscular excitability of the atria, thereby predisposing it to manifestation of arrhythmia.

Trials performed before [30–36] and after the era of fibrinolytic therapy [37, 38] showed that mortality in patients with both ACS and AF is two times greater compared with the population without AF [39–42]. One-year observational studies in patients with AF and ACS who were treated with invasive procedures clearly show that AF is an independent risk factor and increases mortality. It has also been shown that PCI is associated with a reduced rate of AF occurrence compared with thrombolysis [40]. The GUSTO study showed that patients with AF presented with more intense atherosclerosis of the coronary arteries and poorer reperfusion of infarcted vessels. Three-vessel disease and reduced ejection fraction of the left ventricle were more common in these patients, and they are at increased risk of in-hospital complications such as recurrent MI or ischemic events, heart failure, cardiogenic shock, ventricular arrhythmias, disturbances of atrioventricular conduction, acute mitral regurgitation, rupture of the interventricular septum, or systemic thrombosis. Patients with persistent AF were at increased risk of cerebrovascular events than patients with sinus rhythm [41, 37].

## Overview of studies on simultaneous use of dual antiplatelet therapy and antithrombotic therapy

Previous analyses have shown great variability in the regimens used in patients with indications for concomitant dual antiplatelet therapy and OAC (triple therapy).

Lip et al. [43] performed a retrospective analysis of 1,234 patients who had undergone PCI, 35 of whom presented AF. At the time of hospital admission, 19 of these 35 patients had pre-existing AF, 11 patients were receiving warfarin, 5 aspirin, 2 clopidogrel, and 1 patient was receiving no antithrombotic therapy. All patients receiving OAC had it discontinued prior to PCI and 65.7% were treated with low-molecular-weight heparin in addition to ASA and clopidogrel. At discharge from hospital, dual antiplatelet therapy was prescribed to 71.4% of patients, whereas 6 patients received triple therapy (17.1%), 2 received clopidogrel (5.7%), and 2 received warfarin plus one antiplatelet drug (5.7%). Further ambulatory management was heterogeneous: 10 patients were administered 1-year clopidogrel treatment plus lifelong ASA, 4 patients were treated with lifelong ASA and clopidogrel, and 8 patients were told to stop one of their antiplatelet drugs and replace it with warfarin. The use of triple therapy is relatively low owing to concerns of life-threatening bleeding. There were no bleeding complications requiring hospitalization after 30 days of follow-up.

In the study conducted by Karjalainen et al. [44], 239 patients with an indication for long-term OAC [such as AF, prosthetic heart valve, prior venous thrombotic disease (VTD)] treated with PCI were identified. Persistent AF was the most common indication for OAC treatment (70%). DESs were implanted in 40% of patients. The mean INR value was 2.19 ± 0.54 on the day of PCI. After coronary stenting, 48.4% of patients received triple therapy. A total of 15.5% of patients switched from warfarin to dual antiplatelet therapy with ASA and clopidogrel, 15.1% received warfarin and ASA, and 0.5% received warfarin alone. The duration of clopidogrel treatment was significantly shorter in the triple therapy group (about 4.14 months) but longer in patients receiving DES (5.88 months) than in patients with BMS (4.09 months). During the follow-up period, stent thrombosis (15.2%) or MI (18.2%) occurred in patients not receiving clopidogrel, and there was an increased risk of stroke in the group not receiving warfarin. Bleeding complications were most common with triple therapy or the combination of warfarin and clopidogrel; intracranial bleeding occurred in 3 patients, gastrointestinal events in 2, groin hematoma in 4, retroperitoneal bleeding in 1, urinary bleeding in 1, and a decrease in blood hemoglobin level (4 g/dL) in 17 patients. These data support the view that triple therapy is an optimal therapeutic option in patients who have undergone PCI and have indications for OAC.

In a prospective analysis that included 70 patients who had undergone coronary stenting and were receiving long-term anticoagulation therapy, the effective treatment prescribed on discharge from hospital was triple therapy in 64.2% of patients, ASA plus clopidogrel in 25.4%, and OAC plus clopidogrel in 3%. Withdrawal of dual antiplatelet therapy within 1 year was common in all patients groups, but was more marked for clopidogrel, which was prescribed to 92.3% of patients in the first month and to 43.5% 1 year after PCI. The overall percentage of patients who received triple therapy was 55.4% in the first month, 32.8% in the sixth month, and 16.9% at 1 year after PCI. Only half of the patients who underwent DES implantation continued with dual antiplatelet therapy 6 months after the procedure. Triple therapy has been shown to be an independent predictor of major bleeding risk, associated with a 5-fold increase in risk compared with dual antiplatelet therapy [45].

In a study including 426 patients who had undergone PCI with paroxysmal (39.9%) and

permanent (60.1%) AF, triple therapy was most often prescribed in the group with persistent AF (55.8%), compared with those with paroxysmal AF, for whom dual antiplatelet therapy was most common (49.5%). A lack of treatment with coumarins and advanced age were independent predictors of MI and target coronary revascularization [46].

Despite the demonstrated benefits of OAC in this group of patients, it was shown in RIKS-HIA analysis (6,182 patients) that only 30% of patients with indications were prescribed triple therapy. The patients who received OAC were younger, had no history of chronic pulmonary disease, and no dementia, but were more likely to have a history of stroke or coronary revascularization. Bundle-branch block, ST-segment elevation, or T-wave inversion on electrocardiogram had no effect on the use of OAC. ACE inhibitors, beta-blockers, digitalis, and statins were administered significantly more often to patients discharged with OAC [47].

The RICO Survey showed that, among patients with STEMI who were receiving dual antiplatelet therapy and OAC therapy, only 44% had an INR value between 2 and 3. The OAC group had a higher Killip class and lower left ventricular ejection fraction than the non-OAC group. The use of thrombolysis, heparin and antiplatelet drugs, and coronary angiography performance were much reduced in patients receiving OAC. The use of glycoprotein IIb/IIIa receptor antagonists did not differ between the two groups. The incidence rates of ventricular arrhythmia, cardiogenic shock, and stroke were similar for both groups. Of interest, prior OAC treatment was not an independent factor of major bleeding; advanced age and heart failure were shown to be predictors of bleeding events in this cohort. However, OAC was an independent predictor of in-hospital heart failure, together with age, diabetes, and low creatinine clearance rates [48].

## Hemorrhagic complications

Hemorrhagic complications are the most common complications during treatment for ACS (excluding ischemic events). When assessing the severity of bleeding, several clinical aspects should be considered (localization and influence on hemodynamic parameters), in addition to the need for blood transfusion and reductions in hemoglobin levels [49]. Bleeding can be classified as severe, life threatening, moderate, or mild. However, the cutoff values for these classifications can vary between studies, making it difficult to compare the frequency of bleeding among such studies. Data from many randomized trials show that frequency of these complications ranges from < 2% in OASIS-2, PRISM, and PURSUIT to > 8% in SYNERGY [50–52]. According to data from the European GRACE registry, which included 24,045 patients, the total frequency of severe bleeding is 3.9% in STEMI patients, 4.7% in NSTE-ACS patients, and 2.3% in unstable angina patients [53].

There are several independent prognostic factors associated with serious bleeding, including advanced age, female sex, history of prior bleeding, prior PCI, renal failure, and use of glycoprotein IIb/IIIa receptor antagonists. The risk of bleeding is also increased by administration of drugs at high doses that are too high, especially in women, elderly individuals, or patients with renal failure [54]. The increase in bleeding risk with worsening renal function shows a trend similar to the increase in risk of death in the GRACE registry, so physicians should be cautious when selecting aggressive invasive, antiplatelet, or antithrombotic treatment strategies in high-risk patients [29].

The incidence of bleeding events is related to the number and intensity of antiplatelet and antithrombotic therapies. In the study by Flaker et al. [55], the addition of ASA to warfarin treatment (with INR value between 2 and 3) increased the number of serious bleeding events (3.9% per year) in patients with AF compared with warfarin only (2.3% per year). Triple therapy (ASA + clopidogrel + + warfarin) was associated with an increased risk of serious bleeding by about 7% per year [56–60]. Bleeding events were reported in 3 patients receiving ASA, clopidogrel, and OAC (18.8%) and in 1 patient receiving dual antiplatelet therapy (16.7%) during a 30-day observation of 27 patients who had undergone PCI and who had indications for chronic anticoagulation [61]. However, another observation of PCI patients who required anticoagulation therapy showed that major bleeding events only occurred in patients receiving triple therapy (6.6%): two cases of gastrointestinal bleeding, four cases of nasal bleeding requiring surgery or blood transfusion, and one death caused by intracranial bleeding. Minor bleeding events were also more common in patients receiving triple therapy (14.9%) compared with those receiving dual antiplatelet therapy (3.8%) [57].

Many researchers have pointed out that incidence of bleeding depends on the antiplatelet drug dose and accurate control of the INR value. Orford et al. [59] conducted a retrospective study of 66 patients who were assigned triple therapy after PCI. No incidents of stent thrombosis, MI, or death were reported. Six patients suffered bleeding events, of

which two ended spontaneously, two required blood transfusion, and one occurred within 24 hours of discharge (with INR = 1) and was attributed to an interaction between ASA, clopidogrel, and enoxaparin. Although the incidence of bleeding complications was higher with triple therapy (9.2%) as compared to ASA and thienopyridine (1.8%) or ASA and OAC (6.5%), inappropriate use of OAC therapy was reported to be the main cause of increased risk of bleeding events [7, 8, 25, 62]. Of note, all serious bleeding events requiring intervention occurred at an INR value significantly greater than the therapeutic level [59]. Withdrawal of thienopyridine owing to bleeding was associated with increased risk of sudden death and MI during a 30-day observation period [7, 8, 25, 62]. Buresly et al. [63] investigated different combinations of antiplatelet and antithrombotic therapy in patients of advanced age (aged > 65 years) who had suffered an MI. Bleeding events occurred in 6.7% of patients, most of which were gastrointestinal (particularly in patients receiving antiplatelet drugs or ASA in combination with warfarin). Intracranial bleeding was most common in patients receiving ASA and warfarin. Dual antiplatelet therapy was associated with an increased risk of bleeding compared with ASA alone, but this increased risk was still lower than with the combination of ASA and warfarin. Only one patient receiving triple therapy suffered a bleeding event (hematuria).

## Current recommendations related to oral anticoagulation and dual antiplatelet therapy (Table 1)

### Venous thrombotic disease

Oral anticoagulants are the cornerstone of prevention and treatment of VTD, including deep vein thrombosis and pulmonary embolism. Anticoagulant treatment should be administered for at least 3 months in cases of reversible or transient-factor-caused prothrombotic conditions and 6 months in cases of thrombosis of unknown reason (class I, level of evidence A). Secondary prophylaxis in patients with malignant disease should be chronic or administered until recovery (class I, level of evidence C). In cases of recurrence or thrombophilia, long-term treatment should be used (class I, level of evidence C). It is reasonable to consider use of acenocumarol as the primary prophylaxis in patients with a particularly high risk of thrombosis after orthopedic or gynecologic surgery. It is not recommended that antiplatelet therapy be administered alone as prophylaxis or treatment of VTD [64].

### Atrial fibrillation

AF is connected with increased risk of thromboembolic complications, including ischemic stroke. Anticoagulant therapy is recommended for most patients with AF. According to ESC/ACC/AHA guidelines, strong indications for antithrombotic treatment relate to patients with AF and one major or two moderate thromboembolic risk factors (class I, level of evidence A). Major risk factors include history of previous stroke, transient ischemic attack, cerebral embolism, mitral stenosis, or prosthetic heart valve. Moderate factors include age more than 75 years, hypertension, heart failure, left ventricular ejection fraction less than 35%, and diabetes. Antiplatelet therapy with ASA is possible in cases of no or one moderate risk factor (class I, level of evidence A) [65].

### Prosthetic heart valves and valvular heart diseases

Chronic anticoagulant therapy is recommended in patients with mechanical prosthetic heart valves (class I, level of evidence C). The intensity of treatment depends on the type of valve, its localization, and coexisting thromboembolic risk factors. If additional risk factors are present (such as AF, MI, enlargement of the left atrium, low ejection fraction, or systemic embolism despite therapeutic INR) addition of ASA (75–100 mg/day) is recommended [66, 67].

Antithrombotic treatment is also recommended for the first 3 months after insertion of a bioprosthetic valve and for 3–12 months in patients with bioprosthetic valves who have a history of systemic embolism. For patients in sinus rhythm but without AF, long-term therapy with ASA is recommended [66, 67].

According to ESC/ACC/AHA guidelines, anticoagulation therapy is indicated in patients with mitral stenosis in sinus rhythm if they have a history of a prior embolic event, left atrium thrombus (class 1, level of evidence C), dense spontaneous contrast, or a left atrial dimension greater than or equal to 50 mm in echocardiography (class IIa, level of evidence C). In patients with mitral regurgitation, anticoagulant therapy should be administered to those with AF, a history of systemic embolism, or evidence of atrial thrombus, and during the first 3 months after mitral valve repair (no classification for this recommendation). There is no evidence to support the use of ASA as an alternative treatment in patients with heart disease of the mitral valve [68, 69].

### Other indications for antithrombotic therapy

Nowadays, anticoagulants are indicated for primary pulmonary hypertension (class IIa, level of

**Table 1.** Current recommendations for antithrombotic therapy.

| Disease | Indication for antithrombotic therapy | Recommended duration of treatment | Class and level of evidence | Guidelines |
|---|---|---|---|---|
| Venous thrombotic disease | Reversible or transient factor causing a prothrombotic condition | 3 months | I-A | Guidelines for management of patients with venous thrombotic disease [64] |
| | Thrombosis of unknown reason | 6 months | I-A | |
| | Malignant disease | Lifelong or until recovery | I-C | |
| | Recurrence of thrombosis or thrombophilia | Lifelong | I-C | |
| Atrial fibrillation | Presence of one major (previous stroke, TIA, cerebral embolism, mitral stenosis or prosthetic heart valve) or at least two moderate (age > 75 years, hypertension, HF, LVEF < 35%, diabetes) thromboembolic risk/s factors | Lifelong | I-A | ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation [65] |
| Mechanical prosthetic heart valve | All patients | Lifelong | I-C | Antithrombotic Therapy in Valvular Heart Disease — Native and Prosthetic: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (2004) [66]<br>Recommendations for the management of patients after heart valve surgery, ESC 2005 [67] |
| Bioprosthetic heart valve embolism | All patients | 3 months | I-C | |
| | History of prior systemic | 3–12 months | I-C | |
| Mitral stenosis | History of prior embolic event, left atrial thrombus | Lifelong | I-C | ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease: a report of American College of Cardiology/American Heart Association Task Force on Practice Guidelines [68]<br>Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology 2007 [69] |
| | Dense spontaneous contrast or left atrial dimension greater than or equal to 50 mm in echocardiography | Lifelong | IIa-C | |
| Mitral regurgitation | History of systemic embolism or evidence of atrial thrombus | Lifelong | N/A | |
| | After mitral valve repair | 3 months | N/A | |
| Primary pulmonary hypertension | All patients | Lifelong | IIa-C | Guidelines on diagnosis and treatment of pulmonary arterial hypertension The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology 2004 [70] |
| Secondary pulmonary hypertension | All patients | Lifelong | IIb-C | |
| Dissection of intracerebral arteries, intracranial vein thrombosis | All patients | 3–6 months, as an alternative to antiplatelet therapy | IIa-B | Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for health-care professionals from the AHA/American Stroke Association Council on Stroke 2006 [71] |

TIA — transient ischemic attack, HF — heart failure, LVEF — left ventricular ejection fraction, N/A—not applicable

**Table 2.** Current recommendations for dual antiplatelet therapy.

| Indication for dual antiplatelet therapy | Recommended duration of treatment | Class and level of evidence | Guidelines |
|---|---|---|---|
| NSTE-ACS independent of the treatment approach | 12 months | I-A | ESC Guidelines for the diagnosis and treatment of NSTE-ACS 2007 [2] |
| STEMI treated with PCI and DES | 12 months | I-B | 2007 Focused Update of the ACC/AHA 2004 Guidelines for the management of patients with ST-elevation myocardial infarction [1] |
| STEMI treated with PCI and BMS | For a minimum 1 month, 12 months is optimal | I-B | |
| STEMI treated with PCI without stenting or pharmacologically | Minimum 14 days | I-B | |
| STEMI treated with fibrinolysis or without reperfusion | Lifelong (e.g. for 12 months) | IIa-C | |
| BMS implantation | For a minimum of 1 month, 12 months is optimal | I-B | 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for percutaneous coronary intervention: a report of the ACC/AHA Task Force on Practice guidelines [28] |
| DES implantation | At least 12 months | I-B | |

NSTE-ACS — non-ST-elevation acute coronary syndrome, STEMI — ST-elevation myocardial infarction, PCI — percutaneous coronary intervention, DES — drug eluting stent, BMS — bare metal stent

evidence C) and permitted for secondary pulmonary hypertension (class IIb, level of evidence C) [70].

American Heart Association/American Stroke Association guidelines recommend the use of OAC in the dissection of intracerebral arteries for 3––6 months as an alternative to antiplatelet drugs (class IIa, level of evidence B) and for 3–6 months in intracranial vein thrombosis (class IIa, level of evidence B) [71].

## Dual antiplatelet therapy (Table 2)

When BMSs are implanted, dual antiplatelet therapy is recommended for 1 month and for at least 12 months if the patient has undergone DES intervention (class I, level of evidence B) [28].

It is well established that patients with ACS without ST elevation should receive concomitant treatment with ASA and clopidogrel for 12 months, independent of whether they are treated pharmacologically or by PCI (class I, level of evidence B) [2]. The efficacy of this combination treatment is greater than that of ASA alone or ASA and OAC [7, 8, 25, 62, 72–74]. According to ACC/AHA guidelines, the management of patients with ST elevation MI should involve ASA and clopidogrel treatment independent of use of fibrinolytic therapy (class I, level of evidence A), for at least 14 days (class I, level of evidence B). Long-term maintenance of dual therapy (for about 1 year) is reasonable in STEMI patients (new recommendation; class IIa, level of evidence C). There are no specific recommendations regarding the management of patients with STEMI who underwent PCI, although according to the guidelines it seems optimal to use this therapy for 12 months.

## Triple therapy (Table 3)

ESC/AHA/ACC guidelines for the management of patients receiving OAC treatment and presenting with NSTE-ACS suggest suspension of antithrombotic treatment [such as unfractionated heparin, low-molecular-weight-heparin, fondaparinux or bivalirudin] until the INR is $< 2$ during the acute phase. With long-term treatment, it is recommended that the lowest therapeutic level of INR be maintained, the shortest concomitant treatment with clopidogrel and OAC, and precise control of INR (class II, level of evidence C). However, treatment decisions should be made on an individualized basis and should take into account the bleeding and thromboembolic risks.

According to 2007 STEMI Focused Update Recommendations, for patients requiring warfarin, clopidogrel, and ASA, an INR of 2–2.5 is recommended with low-dose ASA (75–81 mg) and 75 mg clopidogrel.

ESC/AHA/ACC guidelines for the management of patients with AF suggest that clopidogrel (75 mg)

**Table 3.** Recommendations for concomitant dual antiplatelet and antithrombotic treatment in patients with indications for triple therapy.

| Guidelines | Recommendations | Class and level of evidence |
|---|---|---|
| ESC Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndrome 2007 | 1. Suspension of antithrombotic treatment until INR is < 2 during the acute phase<br>2. As long-term maintenance treatment with the lowest therapeutic level of INR, the shortest period of concomitant treatment with clopidogrel and OAC, and precise control of INR | Lack<br>II-C |
| 2007 Focused Update of the ACC/AHA 2004 Guidelines for the management of patients with ST-elevation myocardial Infarction | In patients requiring warfarin, clopidogrel, and ASA maintenance with INR 2–2,5; low dose ASA (75–81 mg) and clopidogrel 75 mg | I-C |
| ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation | In patients with ACS use of clopidogrel (75 mg) together with warfarin (INR 2–3) for 9–12 months as supportive treatment, if no recurrent ischemic event occurs, continue with warfarin alone | Lack |
| Antithrombotic and thrombolytic therapy. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) 2008 | 1. Use of ASA and OAC (with INR of 2–3) for at least 3 months in patients after MI and at high risk of thromboembolic events (such as AF, history of prior VTD)<br>2. Patients treated with PCI should receive triple therapy but the need for frequent control of INR to maintain the index at the lowest therapeutic level is crucial; use of proton-pump inhibitors can be considered when risk of gastrointestinal bleeding is increased | II-A<br>II-C |
| Recommendations for the management of patients after heart valve surgery ESC 2005 | Relative indications for triple therapy in patients who have undergone valvular surgery include:<br>1. coexistence of arterial disease<br>2. condition after coronary stenting<br>3. recurrent embolism, but only if followed by full diagnostics, correction of risk factors, and antithrombotic treatment, and when recurrent incidents could not be prevented<br>4. in patients with ball valve, dipyridamole should be the first choice of treatment | Lack |

OAC — oral anticoagulant, ACS — acute coronary syndrome, MI — myocardial infarction, AF — atrial fibrillation, VTD — venous thrombotic disease, ASA — acetylsalicylic acid, INR — international normalized ratio

and warfarin (INR 2–3) should be administered for 9–12 months as supportive treatment in patients with ACS. If no recurrent ischemic event occurs, the patient can continue with warfarin monotherapy (no classification for this recommendation) [65].

On the other hand, the earliest guidelines of the American College of Chest Physicians for antithrombotic therapy recommend the administration of ASA and OAC (with INR 2–3) for at least 3 months in patients after MI at high risk of thromboembolic events (such as those with AF, history of prior VTD) [75]. However, patients treated with PCI should receive triple therapy but with frequent control of INR to maintain the index at its lowest therapeutic level. Use of proton-pump inhibitors can be considered when the risk of gastrointestinal bleeding is increased. Further data are needed to determine if vitamin K supplementation is beneficial for the stabilization of INR. When choosing the type of stent in patients with indications for long-term anticoagulation it is better to use BMS, which allows the duration of triple therapy to be reduced to 4 weeks, followed by treatment with ASA and OAC [75].

The indications for triple therapy mentioned in the ESC guidelines for management of patients after valvular surgery include: coexistence of arterial disease, previous coronary stenting, recurrent embolism, but only when followed by full diagnostics, correction of risk factors and antithrombotic treatment when recurrent incidents could not be prevented; and in patients with ball valves, in whom dipyridamole should be the first choice of treatment.

Contraindications for triple therapy include: history of gastrointestinal bleeding and current chronic peptic ulcer disease or angiodysplasia, increased reaction after ASA administration with prolonged bleeding time, uncontrolled hypertension due to risk of intracranial bleeding and ineffectiveness of ASA in prophylaxis of stroke in hypertensive patients, advanced age, especially women aged > 75 years, concomitant administration of many drugs simultaneously or antibiotics, or significant fluctuations in INR value despite attempts to control it [67].

## Summary

Most recent trials and meta-analyses support the administration of long-term treatment with OAC in patients with AF and indications for dual antiplatelet therapy (such as prior MI or PCI). Therapeutic decisions should be made after individualized assessment of bleeding risk and the risks of thromboembolic events and stent thrombosis. Patients with AF and one major or at least two moderate factors of thromboembolic risk should receive antithrombotic treatment with maintenance of INR within the therapeutic level. Excluding patients with a high risk of bleeding, triple therapy consisting of ASA, clopidogrel, and OAC seems the most beneficial treatment strategy. If a patient receiving OAC requires coronary stenting, it is better to use BMS than DES because the former allows the duration of dual antiplatelet therapy to be reduced. Further trials are required to determine the optimal therapeutic strategy and control in these patients.

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