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Review

The antithrombotic therapy of atrial fibrillation in patients with coronary heart disease

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Abstract: Coronary heart disease (CHD) is the most common cardiovascular disease, while atrial fibrillation (AF) is the most common heart rhythm disorder. These diseases have common risk factors such as hypertension, diabetes, sleep apnea, obesity and smoking. The frequency of CHD in patients with AF ranges from 17.0 to 46.5%, while the prevalence of AF among patients with CHD is low and is estimated at only 0.2–5.0%. AF is a well-known factor of unfavorable short-term and long-term prognosis in patients with acute myocardial infarction; it is associated with a significant increase in overall mortality. It is assumed that in 5-15% of cases of AF, coronary artery stenting and, accordingly, triple therapy with Aspirin, Clopidogrel or Ticagrelor and oral anticoagulant will ever be required. This requires very careful consideration of balanced antithrombotic therapy, taking into account the high risk of bleeding, the risk of stroke and stent thrombosis followed by acute coronary syndrome. Co-administration of oral anticoagulants with antiplatelet drugs, and in particular triple therapy, significantly increases the absolute risk of serious bleeding. In addition, severe bleeding is associated with a fivefold increase in the risk of adverse outcome after acute coronary syndrome. The presence of atrial fibrillation with coronary heart disease worsens the prognosis even in patients undergoing careful treatment.

Keywords: coronary artery disease, atrial fibrillation, prevention, antithrombotic therapy.

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Introduction

Coronary heart disease (CHD) is the most widely spread cardiovascular disease [1], while atrial fibrillation (AF) is the most common heart rhythm disorder [2]. The frequency of angina pectoris in women increases from 5-7% at the age of 45-64 years to 10-12% at the age of 65-84 years. In turn, angina pectoris in male aged 45-64 years is observed in 4-7% and aged 65-84 years - in 12-14% [3]. In 2013, CHD was the leading cause of death worldwide. The mortality from CHD increased from 5.74 million (12%) in 1990 to 8.14 million (16.8%) in 2013 [4].

The prevalence of atrial fibrillation is generally 2% and increases with age: 0.14% in people younger than 50 years, 4% aged from 60 to 70 years, 14% in people older than 80 years [2, 5]. CHD and AF have common risk factors such as hypertension, diabetes, sleep apnea, obesity and smoking. Moreover, inflammation plays a great role in the development of both diseases [6].

The frequency of CHD in patients with AF ranges from 17% to 46.5% [7]. In large studies such as ROCKET-AF [8] and RELY [9], CHD was detected in 17% of patients with AF. In the study which had been carried out by Van Gelder et al., the prevalence of coronary heart disease was 18% in patients with a constant form of atrial fibrillation [10]. In the study performed by Kralev et al., 13% of patients with AF subjected to coronary angiography were diagnosed with hemodynamically significant coronary artery stenosis, and the frequency of a constant form of arrhythmia was almost identical in both groups - with and without coronary artery disease (30% and 27%, respectively) [11]. In turn, the frequency of concomitant AF among patients with CHD is only 0.2-5.0% [12].

Atrial fibrillation and myocardial infarction as concomitant events

The acute myocardial infarction (AMI) is an established risk factor for AF, which occurs in 6-21% of patients in this category [13]. One patient from ten with AMI has the AF in history. Moreover, one from four patients after the AMI has AF. The study of 2,460 patients after myocardial infarction showed that the damage of the atrial branches is a risk factor for AF, regardless of age, sex, left ventricular ejection fraction, left atrial size, time of reperfusion or coronary blood flow on the TIMI scale after intervention [14].

AF is a factor of unfavorable short-term and long-term prognosis in patients with AMI. It also contributes to a significant increase in overall mortality. In patients with AMI and concomitant AF in history, mortality rates are higher than in patients without arrhythmia. The half of the first reported cases of supraventricular arrhythmias had developed within one month after acute coronary syndrome (ACS). The risk of mortality associated with AF varies and depends on terms, for example, the risk of death in the case of arrhythmia occurring within 30 days after AMI, twice as high as in patients without AF. In a large study involving more than 6,000

patients with AMI, it was noted that the first developed AF is a frequent and lethal complication of myocardial infarction. It is also noted that this arrhythmia is associated with a higher risk of death in the hospital and repeated hospitalizations within 30 days. Moreover, during hospitalization in patients with AMI and AF the risk of acute cerebrovascular accident increases twice [15]. These results are relevant to the GRACE study, which noted that patients with ACS and newly developed AF have a 3 times increased risk of death during hospitalization compared to those without arrhythmia [16]. In addition, these patients were almost twice as likely to have complications in the form of heart failure, and more than 3 times more often - in the form of cardiogenic shock [15]. In a large single-center study, while comparing the results of different types of AF, among 2,980 patients with AMI, only with a constant and newly developed form of AF, a significantly higher short-term and long-term mortality was noted, compared with patients without arrhythmia. The patients with documented paroxysmal AF had the lowest 30-day mortality (7.3%) among subgroups with arrhythmia, similar to the group without AF (5.2%). The 10-year mortality rate was high and did not differ significantly among subgroups [17].

In some cases, patients with AF developed thromboembolic AMI [18]. This arrhythmia is associated with signs of systemic inflammation, which can contribute to the prothrombotic state and, finally, to AMI [19]. The systemic inflammation may depend on arrhythmia as well, as on the presence of concomitant classical atherosclerosis risk factors, which are usually also associated with AF. In addition, there is another mechanism for the development of AMI in AF. For example, episodes of such arrhythmia with a high frequency of ventricular contractions can lead to the second type of AMI, which is characterized by an imbalance between the need of oxygen and the blood supply to the myocardium and is usually not manifested by the elevation of the ST segment [20]. In a large randomized ROCKET-AF study, AMI developed in 101 patients in the Rivaroxaban group and 126 patients in the Warfarin group (0.9% and 1.1% per year, respectively) [8]. The RELY study reported a lower incidence of myocardial infarction: 0.53% per year while taking Warfarin, 0.72% per year while taking Dabigatran at 110 mg (twice a day) and 0.74% per year while taking Dabigatran at 150 mg (twice a day) [9].

Atrial fibrillation after coronary artery bypass grafting

The cardiac arrhythmias are not uncommon after heart surgery and occur in approximately 20-40% of patients after coronary artery bypass grafting (CABG) [21]. The postoperative AF usually develops in 2-4 days after surgery. This arrhythmia can be life-threatening, especially in the elderly and patients with left ventricular dysfunction. The postoperative AF is also associated with an increased risk of thromboembolic events, strokes and longer hospital stay. The study showed that the average duration of hospitalization after surgery in patients with AF was 15.3±28.6 days compared to 9.3±19.6 days in patients without arrhythmia [22].

Angiographic results in patients with atrial fibrillation

The patients with AF may experience chest pain, which is sometimes accompanied by transient changes in the ST segment of the ischemic character with slightly elevated cardiac markers, thus simulating coronary artery disease. The patients in this category often have a high frequency of ventricular contractions, which leads to the appearance of ST-segment depression that occurs in the background of the subendocardial ischemia. The study demonstrated that depression of ST segment was observed in 38% of patients with tachy-systolic type of the AF, and half of them according to the results of angiography were diagnosed coronary artery disease [23]. Only 4% of patients with tachy-systolic type of AF without changes of ST segment on electrocardiogram (ECG) were positive noninvasive stress tests and coronary artery disease according to the results of coronary angiography [24].

ST segment depression often occurs during tachycardia even in the absence of coronary artery disease and is not specific to ischemia, especially if depression is <2 mm [25]. In one study, the author found the release of troponin in 15% of patients with AF and symptoms of myocardial ischemia, with normal angiography data [26]. In a retrospective analysis of the database of patients who underwent coronary angiography, the presence of AF at the time of the procedure or in history was a factor associated with initial coronary heart disease [27]. Thus, patients with isolated AF and the absence of risk factors for coronary heart disease should be searched for the causes of arrhythmia. On the other hand, one study showed that patients of this group who underwent percutaneous coronary interventions (PCI) had more frequent atherosclerotic changes in the right coronary artery compared to patients without AF [11]. The authors of this work emphasized that the presence of significant stenosis in the proximal segment of the right coronary artery and the left circumflex artery before the branches of the atria, increases the probability of supraventricular arrhythmias. A retrospective analysis of 3,220 patients who underwent selective coronary angiography showed that only 43% of patients with coronary artery disease and AF had atherosclerotic changes in the right coronary or left circumflex arteries. In addition, only 2/3 of patients with stenoses in the coronary arteries were localized before the atria branches [28]. The single-center retrospective analysis showed that CHD in patients with AF proceeds with a higher degree of severity. In addition, patients with arrhythmia and AMI had a significantly higher number of affected coronary arteries [29].

Antithrombotic therapy after acute coronary syndrome and percutaneous coronary intervention

It is supposed that 5-15% of patients with AF will require coronary artery revascularization and, accordingly, triple therapy with Aspirin, Clopidogrel or Ticagrelor and oral anticoagulant. This necessitates careful consideration of balanced antithrombotic therapy, taking into account the risks of bleeding, stroke or stent thrombosis followed by acute coronary syndrome [2].

The co-administration of oral anticoagulant with antiplatelet drugs, in particular, triple therapy, increases the absolute risk of serious bleeding [30]. Several retrospective and prospective analyses compared triple therapy (dual antiplatelet therapy with oral anticoagulants) with dual therapy (dual antiplatelet therapy or oral anticoagulants with a single antiplatelet drug). The results of these studies show an increased risk of bleeding in triple therapy, an average of 50% higher compared to double therapy [31]. However, several large registries reported that the risk of serious bleeding in triple therapy is 3-4 times higher than in the case of oral anticoagulant monotherapy or using the one antiplatelet drug. It was also shown that profuse bleeding was associated with a fivefold increased risk of mortality after acute coronary syndrome [32-34].

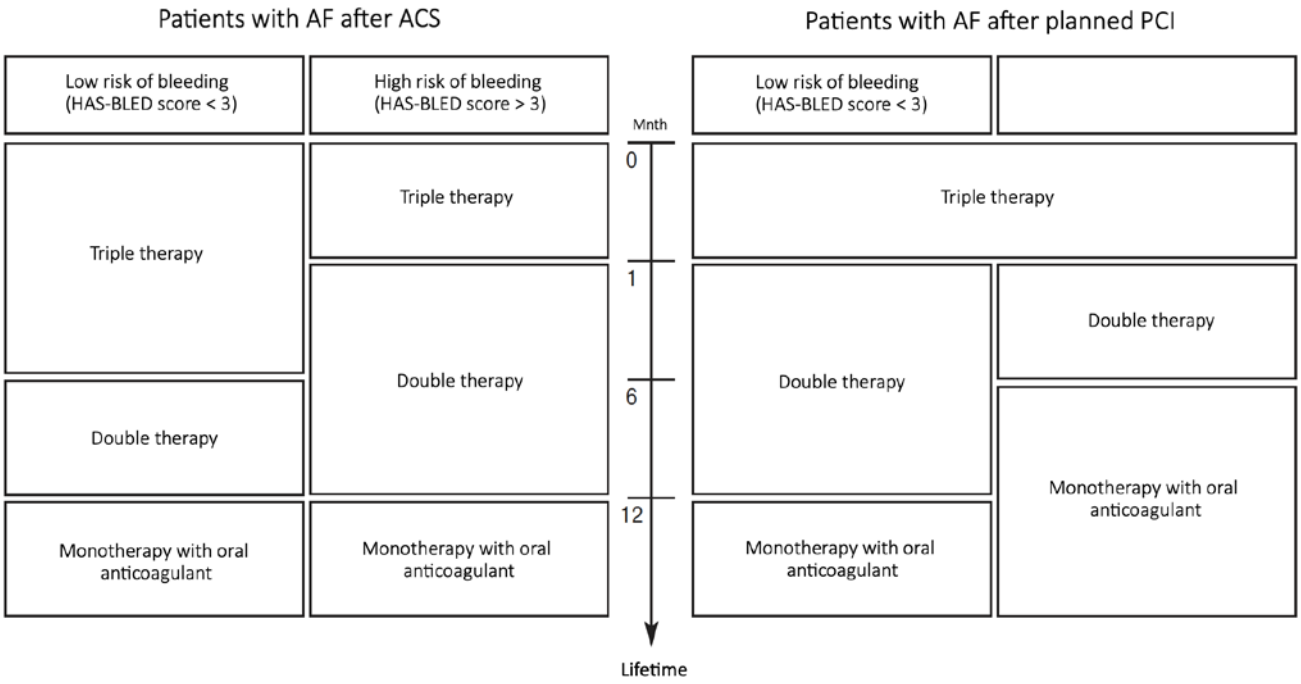

Figure 1. The treatment of atrial fibrillation depending on clinical conditions [2].

The PIONEER AF-PCI study involved patients with AF of non-valvular genesis after PCI with coronary artery stenting. The administration of either a low dose of Rivaroxaban (15 mg once a day) with P2Y12 inhibitor for 12 months or a very low dose of Rivaroxaban (2.5 mg twice a day) with dual antiplatelet therapy for 1, 6 or 12 months was associated with a lower incidence of clinically significant bleeding than standard Vitamin K antagonist therapy with dual antiplatelet therapy for 1, 6 or 12 months [35]. At the same time, all three groups had similar efficiency.

The patients with AF who have undergone coronary artery stenting were prescribed either Rivaroxaban 15 mg daily with P2Y12 inhibitor or Rivaroxaban 2.5 mg twice daily. The double antiplatelet therapy is associated with a reduced risk of mortality or re-hospitalization compared to the standard triple treatment regimen [36].

In the WOEST study there have been 573 patients who received oral anticoagulants (mainly because of the AF) and needed for PCI patients randomized to the standard group triple therapy (oral anticoagulants, Aspirin and Clopidogrel) and dual therapy (Clopidogrel and oral anticoagulants). This work has shown that dual therapy significantly reduced the risk of bleeding, and was associated with a lower risk of death or thrombosis. During one year of treatment, episodes of bleeding have been observed in 19.4% of patients receiving double therapy, against 44.4% – with triple scheme [37].

The ISAR-TRIPLE study, in which patients have been randomized in groups of 6-week or 6-month Clopidogrel therapy in addition to aspirin and oral anticoagulants after drug-coated stent implantation, revealed no significant differences between the groups in mortality rates, AMI frequency, stroke, thrombolysis in myocardial infarction or major bleeding (primary end point) [38]. In addition, there have been no differences in the combined secondary end point (cardiac death, AMI or ischemic stroke). These findings suggest that physicians should carefully balance the risk of ischemic events against the risk of serious bleeding while choosing a short-term or long-term triple therapy.

In the Re-dual-PCI study, the use of Dabigatran and P2Y12 inhibitors was studied in 2,725 patients with non-valvular atrial fibrillation who underwent planned PCI. There was an unreliable increase in the level of individual thromboembolic endpoints in the group of double therapy with Dabigatran at a dose of 110 mg (2 times a day), but according to the authors, these results should be evaluated with caution, due to insufficient evidence. Nevertheless, a significant reduction in the frequency of bleeding was demonstrated with the use of dual therapy.

The other studies on various aspects of oral anticoagulants and antithrombotic therapy are still ongoing.

The patients with AF and risk of stroke, as well as mechanical valves and recent or recurrent deep vein thrombosis or pulmonary embolism, should take oral anticoagulants during and after stenting. A short period of triple therapy (oral anticoagulants, Aspirin, Clopidogrel) is recommended, and then should be followed by a period of double therapy (oral anticoagulants with one antiplatelet drug) (*Figure* 1).

After planned stenting of coronary arteries, patients with AF and stable angina at risk of stroke, combined triple therapy with Aspirin, Clopidogrel and oral anticoagulant should be administered within 1 month to prevent coronary and cerebral ischemic events.

After acute coronary syndrome and stent implantation in patients with AF and stroke risk, combined triple therapy with Aspirin, Clopidogrel and oral anticoagulant should be administered within 1-6 months to prevent coronary and cerebral ischemic events [2].

After acute coronary syndrome without stent implantation, patients with AF and risk of stroke, dual therapy with oral anticoagulant and Aspirin or Clopidogrel should be prescribed for up to 12 months to prevent coronary and cerebral ischemic events.

The combined antithrombotic therapy, especially triple therapy, should be prescribed for a limited period of time, warning the perceived risk of recurrent coronary events and serious bleeding. The double therapy with any oral anticoagulant and Clopidogrel (75 mg per day) can be considered as an alternative to triple therapy for individual patients [2].

While using new oral anticoagulants, it is recommended to prescribe the lowest effective dose for the prevention of stroke in AF [2]. The recommended combination of oral anticoagulants, antithrombotic therapy and duration of such combined therapy for patients with AF after PCI is shown in *Figure* 1.

In patients after acute coronary syndrome with high (uncorrectable) risk of bleeding, the duration of triple therapy can be reduced from 6 to 1 month or, in some cases, immediately replaced by double therapy (with Aspirin or Clopidogrel). The more longer-term triple therapy (up to 12 months) may be considered in individual patients who have been implanted with a first-generation drug-coated stent, as well as in the case of very high anti-thrombotic risk (e.g. ≥118 on the GRACE scale) in combination with a low risk of bleeding on the HAS-BLED scale [39].

All patients with coronary artery disease and AF should switch to oral anticoagulants monotherapy in 1 year, except for those patients who have a very high risk of coronary events and a sufficiently low risk of bleeding [40].

Conclusion

In patients with AF, the general prevalence of CHD is relatively high. The number of patients with AF who underwent PCI or CABG is also high, especially among those over 70 years. An increase in the number of risk factors for cardiovascular disease necessitates a thorough examination of patients with AF, either to exclude or to establish a diagnosis of coronary artery disease. This may contribute to a timely and safe therapeutic strategy, including oral administration of oral anticoagulants in combination with antiplatelet drugs.

Conflict of interest

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