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4

New oral anticoagulants after acute coronary syndrome

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New oral anticoagulants (NOACs) have been developed that may further decrease the mortality and morbidity of ACS by complementing antiplatelet therapy. Optimal use of these agents can be achieved by maximum reduction in thrombotic events at the minimum bleeding risk when combining a long-term oral anticoagulant with anti-platelet therapy in patients with coronary heart disease. Although, based on the pharmacokinetics and -dynamics of NOACs, these agents could improve the current management of ACS patients, multiple trials consistently demonstrate a trend toward increased major and clinically relevant non major bleeding almost diminishing the benefits in reduction of ischemic events. Therefore, some critical issues need to be further evaluated in future trials.

Introduction

During the past decade, many advances have been made regarding short- and long-term outcomes for patients after an acute coronary syndrome (ACS) event [1]. ACS is the term which consists of a clinical triad of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA and NSTEMI are together referred to as NSTE-ACS [2].

ACS has worldwide a large burden of disease. Improvements in ACS-management, international guidelines regarding ACS-management and compliance to these, have already improved outcomes of coronary heart disease (CHD). It has resulted in a 47% decrease in CHD-deaths [3] and a significant

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decrease in in-hospital mortality from 10.4% in 1994 to 6.3% in 2006 in the US [4]. However, the residual acute and long-term morbidity and mortality of ACS remains high. Therefore, further improvement ACS-management remains of utmost importance [3].

ACS is initially managed by the acute administration of antiplatelet and anticoagulant agents, and by revascularization when indicated [2]. Secondary prevention consists of long-term antiplatelet therapy and other secondary prevention drugs such as statins and β-blockers [3]. It is estimated that 17% of patients without secondary prevention surviving an ACS event will experience recurrent events within 1 year [4,5]. However, the GRACE-registry [6], a long-term study recruiting and following ACS patients for a median of 5 years, showed that despite secondary prevention a mortality rate of almost 20% remains. In addition, most of these deaths occurred after hospital discharge. In the PCI-CURE-trial [7], including patients whom were treated with Percutaneous Coronary Intervention (PCI) plus stenting, the incidence of death or myocardial infarction (MI) at 1 year was 11.7% in patients given aspirin and 8.7% in patients given aspirin plus clopidogrel. Furthermore, a meta-analysis of 12 trials [8] demonstrating the efficacy of secondary prevention with antiplatelet therapy, showed that 13.5% of patients receiving antiplatelet therapy still experienced vascular events in 2 years follow-up. These numbers make a strong suggestion that (dual) antiplatelet therapy (as recommended by current international guidelines) alone as secondary prevention after ACS might be suboptimal, urging for more effective ACS-management [1,3].

The mentioned residual risk may be related in part to excess thrombin generation that persists beyond the acute presentation in ACS-patients [9]. Although platelet activation and adhesion is essential for atherothrombosis, it is thrombin that remains the factor leading to thrombus formation [10]. Moreover, studies have shown that the coagulation system remained considerably activated during months if not longer after an ACS [9]. Therefore, there has been growing interest in evaluating the role of oral anticoagulants after an acute coronary syndrome.

This review will focus on the new oral anticoagulants and their use in ACS. We will discuss the role of these agents in the area of ACS and provide the most recent updates on their clinical trials.

Oral anticoagulants in acute coronary syndrome

The most common used anticoagulants are oral vitamine K antagonists (VKAs). VKAs inhibit the vitamin K-dependent synthesis of biologically active forms of the four clotting factors II, VII, IX and X resulting in broad inhibitory action within the coagulation cascade [1,11].

In the past, there have been many studies regarding adding anticoagulants to antiplatelet therapy in ACS [12]. In a meta-analysis [13] consisting of 5938 patients, warfarin combined with aspirin compared to aspirin monotherapy post ACS resulted in a significantly lower risk of MI, ischemic stroke, and revascularization without differing in mortality rates. However, major bleeding increased with an overall absolute annual risk of 1.5%. Other studies evaluating anticoagulation in ACS failed to show a significant benefit for the addition of VKAs compared to aspirin monotherapy due to increase in bleeding events [14–16]. Furthermore, in the OASIS-2 trial [17] it was concluded that a significant reduction of ischemic events was only seen in countries with high rates of compliance to oral anticoagulation.

Current international guidelines regarding ACS-management recommend dual antiplatelet therapy (DAPT), aspirin in combination with a P2Y12-receptor antagonist, in long-term management of ACS [2]. When adding VKAs for triple therapy (DAPT and anticoagulant) one can reason that bleeding events will only increase further. A Danish registry [18] reported that in real-world use of aspirin, clopidogrel and VKAs, nonfatal and fatal bleeding events were greater in patients receiving clopidogrel plus VKA (12.3%/y) or triple therapy (12%/y) than in patients receiving aspirin and clopidogrel (3.7%/y) or aspirin monotherapy (2.6%/y). Again, the benefits of adding anticoagulants seemed to diminish because of an increase in bleeding events. Due to these findings uncertainty remained about the safety of combining oral anticoagulation and DAPT. However, recently the WOEST-trial [19] investigated the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting. This trial reported a large reduction in overall TIMI-bleeding, reduction of ischemic events and a significant reduction in all-cause mortality in patients receiving dual therapy with VKA plus clopidogrel compared