New drugs for the treatment of coronary artery syndromes; otamixaban and ticagrelor


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Abstract

Background: Acute coronary syndromes are a major cause of mortality and morbidity. Objectives/Methods: The objective of this evaluation is to review the clinical trials of two new drugs being developed for the treatment of acute coronary syndromes. The first drug is the anti-coagulant otamixaban, and the trial compared otamixaban with unfractionated heparin and eptifibatide in acute coronary syndromes. The second drug is the anti-platelet ticagrelor, and the trial compared ticagrelor with clopidogrel in acute coronary syndromes. Results: In the SEPIA-ACS1 TIMI 42 trial, the primary efficacy endpoint occurred in 6.2% of subjects treated with unfractionated heparin and eptifibatide, and to a significantly lesser extent with otamixaban. In the PLATO trial, the primary efficacy endpoint had occurred less in the ticagrelor group (9.8%) than in the clopidogrel group (11.7%) at 12 months. Conclusions: Two new drugs for acute coronary syndromes, otamixaban and ticagrelor, have recently been shown to have benefits in subjects undergoing percutaneous interventions compared to the present standard regimens for this condition.

Key words acute coronary syndromes, clinical trials, otamixaban, ticagrelor
1. Introduction

The term acute coronary syndrome is used to encompass a variety of acute myocardial ischaemic states including unstable angina, non-ST segment elevation myocardial infarction, and ST segment elevation infarction. Acute coronary syndromes are a major cause of mortality and morbidity.

Underlying acute coronary syndromes there is usually a coronary thrombosis associated with a disrupted atherosclerotic plaque. Anti-platelet and anti-coagulant drugs are used to prevent the further formation of the coronary thrombus, and to prevent coagulation associated with coronary surgery.

This evaluation is of the clinical trials of two new drugs being developed for the treatment of acute coronary syndromes. The first drug is the anti-coagulant otamixaban, and the trial compared otamixaban with unfractionated heparin and eptifibatide in acute coronary syndromes ([1] Section 2). The trial is the SEPIA-ACS1 TIMI 42 trial (Study Program to Evaluate the Prevention of Ischemia with direct Anti-Xa inhibition in Acute Coronary Syndromes 1 – Thrombolysis in Myocardial Infarction 42).

The second drug is the anti-platelet ticagrelor, and the trial compared ticagrelor with clopidogrel in acute coronary syndromes ([2] Section 3). The trial is the PLATO trial (The Study of Platelet Inhibition and Patient Outcomes).

2. Otamixaban

2.1 Introduction

The heparins and vitamin K antagonists (e.g. warfarin) are the standard anti-thrombotic drugs, with the heparins being used for an immediate effect, and warfarin for long term prevention of excessive coagulation. As acute coronary syndromes and the surgery associated with them require an immediate anticoagulant effect, the heparins have been the standard agents for some time.

Fondaparinux was the first selective direct inhibitor of factor Xa to gain registration as an anticoagulant. Fondaparinux is used subcutaneously in the prevention of thromboembolism. Otamixaban is a new selective short-acting inhibitor of factor Xa, which is being developed for intravenous use in coronary events.

Otamixaban has already been tested in a Phase II clinical trial of 947 subjects who were about to undergo non-urgent percutaneous coronary intervention [3]. This trial compared 5 bolus intravenous doses of otamixaban followed by a 3 hour infusion with bolus intravenous unfractionated heparins and, at the treating physician’s choice, with and without a GPIIb/IIIa inhibitor [3]. Subjects were also recommended to take aspirin and clopidogrel [3]. Prothrombin fragments 1 + 2 were used as a measure of thrombin activity, and it was shown that the highest dose of otamixaban tested (0.140 mg/kg followed by a 3 hour infusion of 0.200 mg/kg/hour) had a greater ability to reduce thrombin activity than the unfractionated heparin [3]. However, significantly more bleeds occurred with the two highest doses of otamixaban than with the unfractionated heparins [3]. This trial was not powered to
show effects on clinical endpoints, but it did show that there were fewer of the composite of death, myocardial infarction, or target-vessel revascularization in 30 days, with otamixaban at 0.080 mg/kg followed by 0.120 mg/kg/hour dose (3.8%) or 0.120 mg/kg followed by 0.160 mg/kg followed by 0.160 mg/kg/hour dose (2.5%) than with unfractionated heparin (5.6%) [3]. This data provided the basis for another Phase II study, SEPIA-ACS TIMI 42 trial [1].

2.2 Methods and results

The methods and results of the SEPIA-ACS TIMI 42 trial [1] are summarized in this section. SEPIA-ACS1 enrolled 3241 subjects who were within 24 hours of having an acute coronary syndrome e.g. new ST-segment deviation of 0.1 mV, and scheduled to have coronary angiography. Excluded subjects included those who had had treatment with an anticoagulant in the last 24 hours, those requiring treatment with an oral anticoagulant, and those prone to haemorrhage.

The subjects enrolled had a mean age of about 62 years old, were predominantly men (~70%), about 55% had ST deviation of ≥ 0.1 mV, and about 80% had elevated troponin or creatine kinase. Most of the subjects had a history of hypertension (~70%), about half had dyslipidemia requiring treatment, nearly 30% had diabetes mellitus, and about 20% had had a previous myocardial infarction. Aspirin and clopidogrel were recommended to subjects, and almost all took these. Most subjects were also taking β-adrenoceptor antagonists (~80%) and statins (~87%).

Five doses of otamixaban (0.08 mg/kg followed by 0.35, 0.70, 0.105, 0.140 or 0.175 mg/kg/hour) were compared to unfractionated heparins (60 IU/kg intravenous bolus followed by12 IU/kg/hour) and the GPIIb/IIIa inhibitor eptifibatide. The otamixaban and heparin were administered until the end of the percutaneous coronary intervention, whereas eptifibatide was administered until 18-24 hours after the procedure. The Independent Data Monitoring Committee, reviewing safety during the trial, recommended that the lowest dose of otamixaban be discontinued because of inadequate anti-coagulation, and the results with this dose are not discussed.

The primary efficacy endpoint was a composite of all-cause death, myocardial infarction, severe recurrent myocardial ischaemia requiring urgent revascularisation, or bailout use of a glycoprotein IIb/IIIa inhibitor for recurrent ischaemia or for a thrombotic complication during percutaneous intervention up to 7 days. This primary endpoint occurred in 6.2% of subjects treated with unfractionated heparin and eptifibatide (28 of 449 subjects) and to a significantly lesser extent with otamixaban at 0.70 (4.6%, 31/676), 0.105 (3.8%, 25/662), 0.140 (3.6%, 24/658), and 0.175 (4.3%, 29/671) mg/kg/hour. The major component of the lesser primary endpoint with otamixaban was a reduced rate of myocardial infarction, which occurred in 3.1% of subjects with heparin/eptifibatide, and in 1.6, 1.4, 2.0 and 1.8% of subjects treated with otamixaban at 0.70, 0.105, 0.140, and 0.175 mg/kg/hour, respectively.

The primary safety endpoints was TIMI major or minor bleeding not related to coronary-artery bypass grafting (4% of subjects underwent coronary-artery bypass) in the 7 days. In this, the lower doses of otamixaban had similar abilities to the heparin/eptifibatide to cause bleeding (2.7% with
heparin/eptifibatide; 1.6, 3.1 and 3.4% with otamixaban with 0.70, 0.105 and 0.140 mg/kg/hour). However, the highest dose of otamixaban caused more bleeding (5.4% with 0.175 mg/kg/hr) than did the heparin/eptifibatide.

About 65% of the subjects underwent a percutaneous coronary intervention, and in this group, the higher doses of otamixaban (0.105, 0.140 and 0.175 mg/kg/hour) had similar abilities to causing thrombotic complications as the heparin/eptifibatide (2.4%) but the lower dose of otamixaban caused more thrombotic complications (5.0% with 0.070 mg/kg/h) than the heparin/eptifibatide.

2.3 Discussion

Unfractionated heparin is still recommended for treatment of high risk subjects with non-ST-elevation acute coronary syndromes, but several other anticoagulants have been compared to unfractionated heparin [1]. For instance, the low-molecular-weight heparin enoxaparin has a similar efficacy to unfractionated heparin in early intervention invasive surgery for acute coronary artery syndrome with non-ST-segment elevation [1].

In addition to otamixaban, some of the other new anticoagulants may have advantages over unfractionated heparins. The direct thrombin inhibitor bivalirudin has been compared to unfractionated heparin and a GPIIbIIIa inhibitor and shown to have similar efficacy with lower bleeding [1]. The indirect factor Xa inhibitor, fondaparinux also has similar efficacy to unfractionated heparin and causes less bleeding than unfractionated heparin [1]. These findings and their implications are further discussed in Section 4.

3. Ticagrelor

3.1 Introduction

Aspirin and clopidogrel are the standard anti-platelet drugs, and they are often both used in the treatment of acute coronary syndromes. Clopidogrel is a prodrug that is metabolised in the liver to become an irreversible inhibitor at the platelet-specific ADP receptor P2Y_{12}, and to inhibit ATP platelet activation. Ticagrelor is a long-lasting reversible inhibitor of the P2Y_{12} receptor, and does not need to be metabolised for activation, prior to inhibiting ATP platelet aggregation.

Ticagrelor (90 or 180 mg po, bid) has been compared to clopidogrel (75 mg po, daily) in the Phase II DISPERSE–2 (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogrel in non-ST-segment Elevation myocardial infarction)-2 trial, in 990 subjects with acute coronary syndromes with non-ST-segment elevation [4]. DISPERSE-2 showed that ticagrelor inhibited platelet aggregation to a greater extent than clopidogrel at the doses tested [4]. There was a lower incidence of myocardial infarction with ticagrelor than with clopidogrel, P=0.047 [5]. Dyspnoea was the most common adverse effect in ticagrelor groups, and occurred more frequently than in the clopidogrel group [5]. These Phase II results formed the basis for undertaking the Phase III PLATO clinical trial with ticagrelor.
3.2 Methods and results

The methods and results of the PLATO trial [2] are combined and summarised in this section. PLATO enrolled subjects who had been hospitalised for an acute coronary syndrome, with or without ST-segment deviation. For those without ST-segment deviation, they had to have 2 of 3 of (i) ST-segment changes on ECG indicating ischaemia, (ii) a biomarker of myocardial necrosis or (iii) a risk factor such as previous myocardial infarction or coronary-artery bypass grafting.

The trial enrolled 18,624 subjects with a mean age of 62 years old. Those enrolled were predominantly men (~72%), white (~92%), with hypertension (~65%), dyslipidemia (~47%), diabetes mellitus (~25%) and/or smokers (~36%) with previous myocardial infarction (~21%). The most frequent diagnosis was ST-segment depression (~51%), followed by persistent ST-segment elevation (~38%), and T-wave inversion (~32%). Most subjects were already taking aspirin, prior to randomisation (~94%). In hospital many subjects received unfractionated heparin (~57%) and/or low-molecular-weight-heparin (~51%), and some received GPIIb/IIIa inhibitors (~27%).

All subjects received aspirin (75-100 mg), and were randomised to ticagrelor (loading dose of 180 mg, followed by 90 mg bid) or clopidogrel (loading dose of 300 mg, followed by 75 mg daily). Subjects, undergoing a percutaneous coronary intervention, received either an additional 90 mg of ticagrelor or 300 mg of clopidogrel. In subjects undergoing coronary artery bypass grafting, the clopidogrel was withheld for 5 days, and the ticagrelor for 24-72 hours.

Slightly more subjects discontinued ticagrelor (23.4%) than clopidogrel (21.5%). In the ticagrelor group, 0.9% of subjects discontinued treatment due to dyspnoea, whereas only 0.1% discontinued clopidogrel because of dyspnoea.

The primary efficacy endpoint was the time to the first occurrence of the composite of death from vascular causes, myocardial infarction or stroke. At 12 months, this endpoint had occurred less in the ticagrelor group (9.8%; 864 of 9333 subject) than in the clopidogrel group (11.7%; 1014/9291). This reduction was due to a reduced rate of death from vascular caused (ticagrelor, 4.0%; clopidogrel, 5.1%) and myocardial infarction (5.8% vs 6.9%), but not stroke.

The primary safety endpoint was the first occurrence of major bleeding, and these were similar in the ticagrelor (11.6%) and clopidogrel groups (11.2%). There was no difference in coronary artery bypass grafting major bleeding; but there was a difference in the subjects not having grafting with more major bleeding in the ticagrelor group (4.5%) than in the clopidogrel group (3.8%).

Dyspnoea was more common in the ticagrelor (13.8%) than the clopidogrel group (7.8%). During Holter monitoring there were more ventricular pauses ≥ 3 seconds with ticagrelor (5.8%) than with clopidogrel (3.6%) but there was no difference in pauses ≥ 5 seconds.

3.3 Discussion
The authors concluded that ticagrelor was more efficacious than clopidogrel with similar effects on bleeding [2]. The authors also point out that the new P2Y12 inhibitor prasugrel has not been shown to reduce mortality when compared to clopidogrel [6], whereas their trial comparing ticagrelor and clopidogrel showed that ticagrelor reduced mortality when compared to clopidogrel.

4. Expert Opinion

4.1 Comparator clinical trials with otamixaban

SEPIA-ACS TIMI 42 compared otamixaban with unfractionated heparin and eptifibatide, and showed that, at 0.070-0.140 mg/kg/hour, otamixaban is more efficacious and causes similar bleeding as the unfractionated heparin with eptifibatide [1]. Previous studies have suggested that enoxaparin is as efficacious as unfractionated heparin in treating non-ST segment elevation acute coronary syndromes, but that it has a tendency to cause more bleeding [7,8]. This suggests that otamixaban may be better than enoxaparin in this condition, but this can only be definitely be determined in a comparator trial of otamixaban with enoxaparin.

The direct thrombin inhibitor bivalirudin has been compared to unfractionated heparin or enoxaparin and a GPIIbIIIa inhibitor and shown to have similar efficacy with lower bleeding [9]. Fondaparinux binds antithrombin to inhibit factor Xa. Fondaparinux has been compared to enoxaparin in subjects with unstable angina or myocardial infarction without ST segment elevation, and shown to be similar to enoxaparin at reducing short term ischaemic events, but to cause less bleeding than enoxaparin [10]. Direct comparator trials of bivalirudin and fondaparinux with otamixaban are required, to determine whether these agents have similar or different effects, in treating non-ST segment elevation acute coronary syndromes.

4.2 Comparator clinical trials with ticagrelor

The PLATO results suggest that ticagrelor may be more efficacious than clopidogrel at reducing vascular death and nonfatal myocardial infarction, and that ticagrelor and clopidogrel have similar effects on bleeding. Prasugrel, like clopidogrel, is a prodrug with a metabolite that inhibits the P2Y12 receptors on platelets. In subjects with acute coronary syndromes scheduled for percutaneous coronary intervention, compared to clopidogrel, prasugrel reduced the rates of myocardial infarction, urgent target-vessel revascularisation, and stent thrombosis [6]. Major bleeding was also less with prasugrel than clopidogrel [6]. As both seem to have advantages over clopidogrel, a comparator trial of ticagrelor and prasugrel is indicated.

4.3 Dyspnoea versus benefit with ticagrelor

In the DISPERSE-2 trial, dyspnoea was the most common adverse event in ticagrelor-treat patients (9.6 and 15.8% in the 90 and 180 mg dose groups, respectively) and occurred more frequently than in the clopidogrel group (6.4%) [5]. At this stage, there were no clinical endpoint studies with ticagrelor, and the similarity of ticagrelor to clopidogrel on bleeding, suggested that the dyspnoea with ticagrelor
may be a barrier to the development and use of this drug [11]. In PLATO, dyspnoea was also more common in the ticagrelor 90 mg (13.8%) than the clopidogrel group (7.8%) [2]. However, in the ticagrelor group, only 0.9% of subjects discontinued treatment due to dyspnoea, compared to 0.1% with clopidogrel [2]. Furthermore, the clinical endpoints showed that ticagrelor was superior to clopidogrel [2]. Thus, it remains unfortunate, that ticagrelor causes an excess of dyspnoea, but most people seem to tolerate this, and consequently dyspnoea may be a small price to pay for improved clinical outcomes with ticagrelor compared to clopidogrel.

4.4 Conclusions

Despite many advances in the last few decades, cardiovascular disease remains a leading cause of mortality and morbidity. Two new drugs for acute coronary syndromes, otamixaban and ticagrelor, have recently been shown to have benefits in subjects undergoing percutaneous interventions compared to the present standard regimens for this condition. This suggests that steady progress continues in the treatment of cardiovascular disease.

References