Is there an acceptable ceiling for bleeding for an antithrombotic drug dose to be tested in a phase 3 trial?

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The SEPIA-ACS1 TIMI 42 (Study to Evaluate the Pharmacodynamics, the Safety and Tolerability, and the Pharmacokinetics of Several Intravenous Regimens of the Factor Xa Inhibitor Otamixaban (XRP0673), in Comparison to Intravenous Unfractionated Heparin-Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction) trial is a well performed trial. It tested otamixaban, which is a short-acting i.v. direct factor Xa inhibitor with a half-life of 30 min, compared with unfractionated heparin (UFH) plus eptifibatide in patients with non-ST elevation acute coronary syndrome (NSTEACS). The trial identified a signal for reduction in ischaemic events with otamixaban but also a signal associated with increased bleeding.

This is an important study with a high rate of angiography (98%) and guideline-recommended medications. The trial was a large dose-ranging trial in 3241 patients with NSTEACS following a dose-ranging trial in 947 patients undergoing urgent percutaneous coronary intervention (PCI; SEPIA PCI trial).¹

This is to be compared with a previous era when small numbers of patients were investigated in order to select a dose for a phase III trial, e.g. in GUSTO² <100 patients were tested with the streptokinase–tissue plasminogen activator (tPA) combination, and in GUSTO IIa <50 patients were tested with the hirudin dose that was evaluated in GUSTO IIa.³

The patients enrolled in SEPIA-ACS1⁴ were at high risk for ischaemia (ST deviation ≥0.1 mV in the UFH plus eptifibatide group 57%, elevated biomarker in the UFH plus eptifibatide group 79%) and underwent a planned early invasive strategy. The primary endpoint was a composite of death, myocardial infarction (MI), urgent revascularization, and bail-out IIb/IIIa antagonists for an ischaemic or thrombotic endpoint.

Five doses of otamixaban were tested (0.08 mg/kg bolus followed by infusions of 0.035, 0.070, 0.105, 0.140, or 0.175 mg/kg/h) or a control of UFH plus eptifibatide with a single bolus of eptifibatide rather than two boluses: 180 µg/kg and infusion for 18–24 h with renal adjustment. This is different from the double bolus 180 µg/kg 10 min apart used in the ESPIRT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy)⁵ and EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome)⁶ trials and would not be expected to achieve blockade of >90% of available glycoprotein IIb/IIIa receptors in >90% of patients.

The primary safety endpoint was TIMI major or minor bleeding not related to coronary artery bypass graft (CABG). This raises the question of what definition of bleeding should be used.

There are many different definitions of bleeding. Also, different bleeds have different meanings, e.g. intracranial haemorrhage has quite a different clinical meaning than a fall in haemoglobin. Over what time period should we capture the information about bleeding? Perhaps it should be 96 h with PCI with a landmark analysis out to 30 days or 120 h with medical treatment with a landmark analysis out to 30 days.

Also is there an acceptable ceiling for major bleeding? The Table 1 shows rates of TIMI major bleeding in recent trials. In the EARLY ACS trial TIMI major bleeding with upstream eptifibatide was 2.6% at 120 h vs. 1.8% for patients who received eptifibatide in the catheterization laboratory.⁶ Clearly we need a common template to be available so trials can be compared. There is also a need to have reversible agents so that, once present, bleeding can be stopped.

Bleeding is associated with increased morbidity and mortality (OASIS 5)⁷ and it would seem reasonable to test a dose with decreased bleeding compared with control. Clearly there is much to be gained in capturing minor bleeding, but for selection of a drug dose to move into phase III trials, perhaps we should be more focused on what is a ceiling for unacceptable bleeding. This ceiling may be gleaned from major bleeding data.

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The primary endpoint in SEPIA-ACS included adjudicated thrombotic and non-thrombotic procedural complications during the index PCI [including abrupt or threatened closure, new intracoronary thrombus, side branch closure, distal embolization, no-reflow, thrombus in catheter or adherent to guidewire, coronary dissection with decreased flow, difficulty in reaching or crossing the lesion, unplanned stent use, suboptimal results, and coronary perforation (tamponade)].

The 0.035 mg/kg/h dose was stopped because of clinical evidence of inadequate anticoagulation. The primary endpoint was reduced from 6.2% in the combined UFH plus eptifibatide arm to 4.6, 3.8, 3.6, and 4.3% (P trend = 0.34) for the four doses of otamixaban respectively. For death and MI there was a similar 42–48% reduction for the otamixaban doses (2.8, 2.6, 2.7, and 2.8%) compared with UFH plus eptifibatide.

Rates of the primary safety endpoint of TIMI major and minor bleeding across the five otamixaban doses were 1.6, 1.6, 3.1, 3.4, and 3.4% (P trend = 0.0001); the rate in the control arm was 2.7%.

Patients treated with 0.070 mg/kg/h tended to have higher rates of bail-out glycoprotein IIb/IIIa inhibitor; 1.99 (95% CI 0.73–5.44), whereas higher doses of otamixaban had similar use to that observed with UFH plus eptifibatide.

In SEPIA-PCI there were eight catheter thromboses. Perhaps supplemental UFH should be considered to prevent contact thrombosis with otamixaban as with the indirect factor X inhibitor fondaparinux (OASIS 5, OASIS 6). It would be interesting to know how many cases of new intracoronary, catheter, or guidewire thrombus occurred in the current trial.

MI was part of the composite endpoint and used the universal definition for MI and PCI, but not for CABG, where only 5-fold elevation of biomarkers or new Q waves was required and not both, or evidence of new graft or native coronary artery occlusion. The universal redefinition of MI recommended that a universal definition template be available with different definitions and cut-off points for biomarkers, and hopefully that will be available online, so we can make comparisons with other trials.

The investigators of the SEPIA-ACS trial suggested that ‘Otamixaban 0.105–0.140 mg/kg/h appears to be the best range for further study as a replacement for UFH plus glycoprotein IIb/IIIa’. However the lower dose of otamixaban (0.07 mg/kg/h) had similar efficacy for the primary endpoint, and for death and MI. In addition, it had the lowest bleeding compared with the next two doses (51 and 47% lower for major and minor bleeding) and was 59% lower than control; 1.6% vs. 2.7%. Importantly TIMI major bleeding was also similar in the 0.07 mg/kg/h group to control (1.8%), and 52 and 69% lower than the next two higher doses, but there were increased thrombotic complications and 2.2% vs. (1.1% control) use of IIb/IIIa antagonists compared with bivalirudin in the ACUITY trial where 7% of bail-out IIb/IIIa antagonists were used. However, this should be evaluated from the point of view as to whether hard clinical adverse events ensued.

There continues to be an unmet need for patients with acute coronary syndromes for both ischaemia and the new paradigm for bleeding. SEPIA-ACS14 provides new information which will enable appropriate dose selection for a phase III trial.

### Conflict of interest
none declared.

### References