Tirofiban and NSTE-ACS: The Current Perspective

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Acute coronary syndromes without persistent ST segment elevation (NSTE-ACS) are common manifestations of coronary artery disease and represent one of the most important reasons for emergency medical care and hospitalisation, accounting for approximately 2.5 million hospital admissions annually worldwide [1]. Although conventional antithrombotic therapy (e.g. unfractionated heparin and aspirin) have proved to reduce the incidence of ischaemic complications, a substantial burden of death and (re-)infarction still remains.

Considerable progress has been made recently in the optimal management of these patients, particularly with regard to (1) the introduction of new powerful antiplatelet drugs (mainly the IIb/IIIa platelet receptor inhibitors) and (2) the demonstration that, in selected cases, an aggressive approach with early coronary angiography and percutaneous coronary interventions (PCI) can be safely performed with low risk of procedural complications and with improved in-hospital and long-term outcome.

IIb/IIIa Platelet Receptor Inhibitors

It has recently been shown that the addition of glycoprotein (GP) IIb/IIIa receptor inhibitors to unfractionated heparin and aspirin further improves the clinical outcome of patients with NSTE-ACS [2]. From basic research on the congenital platelet defect involved in Glanzmann thrombasthenia and the identification of the mechanisms responsible for fibrinogen binding to GP IIb/IIIa receptors, a chimaeric monoclonal antibody was developed by Coller [3], tested in a randomised double-blind placebo-controlled study [4],

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and subsequently approved for clinical use. Shortly thereafter, peptide and non-peptide compounds mimicking the RGD or KGD amino acid sequence responsible for fibrinogen binding to the GP IIb/IIIa receptor were synthesised. The three GP IIb/IIIa antagonists developed for parenteral use and extensively examined in clinical studies include the monoclonal antibody abciximab, the cyclic peptide eptifibatide, and the non-peptide tirofiban.

Several clinical trials have demonstrated a clear benefit from the use of GP IIb/IIIa inhibitors in reducing ischaemic complications in patients undergoing PCI and in patients with medically managed NSTE-ACS. Boersma et al. carried out a meta-analysis of all six large randomised place-bo-controlled trials of GP IIb/IIIa antagonists, which involved 31 402 patients with unstable angina or non-ST-elevation myocardial infarction (UA/NSTEMI) not routinely scheduled to undergo coronary revascularisation [5]. A small reduction in the odds of death or myocardial infarction (MI) in the active treatment arm was observed (11.8% vs 10.8%, OR = 0.91, 95% CI 0.84 to 0.98, P = 0.015).

Although not scheduled for coronary revascularisation procedures, 11 965 of the 31 402 patients (38%) actually underwent PCI or coronary artery bypass graft (CABG) within 30 days, and in this subgroup the OR for death or MI in the patients assigned to GP IIb/IIIa antagonist treatment was 0.89 (95% CI 0.80 to 0.98). In the other 19 416 patients who did not undergo coronary revascularisation, the OR for death or MI in the GP IIb/IIIa group was 0.95 (95% CI 0.86 to 1.05, NS). Thus, GP IIb/IIIa inhibitors are of substantial benefit in patients with NSTE-ACS who undergo PCI, whereas they are of questionable benefit in patients who do not undergo PCI. Hence the international guidelines recommend that a GP IIb/IIIa inhibitor be administered, along with acetylsalicylic acid (aspirin) and unfractioned heparin (UFH), to all of the patients with NSTE-ACS and high-risk features who are scheduled to undergo early catheterisation [6, 7].

Among the available GP IIb/IIIa antagonists, small molecules have been approved for medical treatment of patients with UA/NSTEMI, whereas abciximab is recommended in the setting of PCI. Small molecules are the drugs of choice for the 'upstream' or 'upfront' treatment of patients with NSTE-ACS during the waiting time for the scheduled coronary angiography. Abciximab is the preferred drug of this class to be used in the catheterisation laboratory for the 'downstream' treatment (i.e. immediately before and in the few hours after PCI). With contemporary trials favouring an early invasive strategy in the management NSTE-ACS, controversy has arisen regarding whether GP IIb/IIIa inhibitors should be started upstream for all patients or be reserved for use only for patients selected to undergo PCI. Multiple trials have shown that the benefit of upstream GP IIb/IIIa inhibitor therapy in NSTE-ACS is derived very early, during the period of medical management that precedes

revascularisation procedures – a key observation when considering strategies to optimise procedural outcomes in this high-risk patient population. A meta-analysis of the PRISM-PLUS, PURSUIT, and CAPTURE trials demonstrated a 34% reduction in the rate of death or MI with GP IIb/IIIa inhibition during the period of initial medical stabilisation that preceded revascularisation (2.5% vs 3.8%; $P = 0.001$), with further benefit seen following PCI [2].

The use of tirofiban for the medical management of higher risk patients with NSTE-ACS was explored by the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, [8] in which 1915 NSTE-ACS patients were randomised to receive either tirofiban/aspirin/heparin or aspirin/heparin. Patients were treated in a medical stabilisation phase for a minimum of 48 h before possible angiography. The results of PRISM-PLUS demonstrate significant reductions in death/MI, with benefits evident as early as 48 h (during the medical stabilisation phase) and persisting for at least 6 months.

The benefits of tirofiban in higher risk patients from PRISM-PLUS were observed in several subgroups, notably including patients with diabetes [9], patients with impaired renal function [10], and in the elderly [11]. In general, the higher the level of risk of the patients, the greater the benefits from the use of the drug, as shown in the study by Morrow et al. [12].

Similar to studies with other GP IIb/IIIa antagonists, 19 strong benefits of tirofiban were noted among patients treated with early PCI, with a 42% reduction in death/MI noted in these patients, compared to 23% among patients revascularised 72 h after randomisation [13].

Despite the data supporting GP IIb/IIIa inhibitors for high risk patients with NSTE-ACS and the consensus guidelines recommending their use, recent surveys suggest that there continues to be a low rate of use of these agents for eligible patients. This may be related to clinician confusion about which patients should receive GP IIb/IIIa inhibitors as well as the most appropriate timing for the initiation of treatment with these agents. The European guidelines suggest that in all of the patients with NSTE-ACS and high risk features the administration of IIb/IIIa inhibitors should start as soon as possible, in order to gain the higher benefit from the treatment [6].

Invasive Strategy

Patients with ACS undergoing early PCI are at increased risk of early ischaemic complications. This early hazard appears to be the result of a thrombin-mediated and platelet-dependent process that is initiated by mechanical plaque disruption and culminates in thrombus formation at the site of vessel injury. Distal embolisation of atherothrombotic debris into the

coronary microcirculation may also occur as a complication of the unstable plaque. For these reasons, early randomised trials such as the TIMI IIIB [14, 15] and VANQWISH trials [16] failed to demonstrate that routine use of an early invasive strategy improves the outcome compared to a conservative strategy. Furthermore, the VANQWISH trial showed a significant difference in favour of conservative treatment in the composite end-point of death and MI at 1-month and 1-year follow-up. In contrast, the FRISC II study showed a significant and clinically relevant decrease in death and MI at 6-month [17] and 1-year [18] follow-up in patients randomised to an early invasive strategy. The TACTICS-TIMI 18 trial [19] confirmed these findings by showing that in patients with ACS receiving tirofiban, an early invasive strategy with stent implantation resulted in a significantly lower rate of the primary end-point (death, non-fatal MI, and rehospitalisation for ACS), as well as a lower rate of death or non-fatal MI both at 30 days and at 6 months.

An invasive strategy appears to limit the increased risk conferred by raised levels of troponin (Tn). In both the FRISC II and the TACTICS-TIMI 18 trials, the benefit of the early invasive strategy was greater in high and intermediate risk patients with elevated levels of TnT.

More recently, the results of the third Randomised Intervention Trial of unstable Angina (RITA) study suggested that routine early invasive management was effective in reducing refractory or severe angina among patients at moderate risk of death after NSTE-ACS, but no reduction was seen in new MI [20].

In accordance with these studies two separate sets of guidelines, released by the European Society of Cardiology and by the American College of Cardiology/American Heart Association, respectively, recommended careful and prompt risk stratification in all patients with NSTE-ACS to identify those who will benefit more from an early invasive strategy [6, 7].

Risk Stratification

Patients with NSTE-ACS represent a heterogeneous population with a wide range of probability of cardiac events in the short and intermediate term. Identification of subsets of patients with different risk profiles is crucial in order to select the most appropriate therapy in each case. The patients considered to be at high risk on the basis of clinical, electrocardiographic, and biochemical characteristics benefit more from an aggressive strategy that includes powerful antithrombotic therapy and early angiography with revascularisation, if feasible. On the other hand, low risk patients need to be identified in order to avoid unnecessary resource use and the risks deriving from an unjustified aggressive approach. Risk stratification is a dynamic process

that starts at the time of admission and is continuously updated with new information obtained during the subsequent hospital stay. However, immediate risk stratification is the most important step for the appropriate management of these patients, since the probability of events is highest in the very early phase of the disease and progressively decreases thereafter. Simple clinical data derived from the patient's medical history and physical examination, a standard 12-lead electrocardiogram (ECG), and measurements of biochemical markers of myocardial damage can be easily obtained in the emergency room and serve as a guide for deciding appropriate medical management and optimal use of available resources.

Two different models of risk stratification have been developed. The first is based on the simple, dichotomous description of a series of variables, whose presence, even when isolated, is sufficient to identify high risk patients. This method is currently suggested by the ESC guidelines. The second takes into account the prognostic information derived from a number of clinical, electrocardiographic, and biochemical parameters, analysed in a comprehensive manner [21]. These models have the advantage of allowing the identification of patients at the highest risk of events.

Timing of Intervention

The optimal time to intervene is not well defined as it was significantly different among clinical trials comparing invasive to conservative strategy in NSTE-ACS: this interval was 4–6 days in FRISC 2, while it was less than 48 h in TACTICS-TIMI 18 and in RITA 3. The ESC guidelines recommend that coronary angiography be performed within 48 h of admission, and earlier ('as soon as possible') for patients at very high risk such as those presenting with major arrhythmias, haemodynamic instability, a history of prior CABG, or early post-MI unstable angina.

Recently, the Intracoronary Stenting with Antithrombotic Regimen Cooling-off (ISAR-COOL) study [22] added further support to the combination of GP IIb/IIIa antagonism with early invasive management. ISAR-COOL compared routine invasive management among a high risk NSTE-ACS patient population treated either with prolonged medical stabilisation (with the combination of heparin, aspirin, clopidogrel, and tirofiban for a mean of 86 h) or by proceeding directly to the catheterisation laboratory within the first 24 h (mean 2.3 h) with the same medical therapy. The ISAR-COOL results suggested that expedited catheterisation with GP IIb/IIIa antagonism pretreatment was associated with a significant reduction in death/MI relative to the delayed invasive group (5.9% vs 11.6%, $P = 0.04$), due entirely to reductions in pre-PCI MI.

These results suggest that the benefits of early invasive therapy may outweigh those of prolonged pharmacological pretreatment. However, whether a strategy of immediate coronary angiography (within hours of presentation) leads to a significant clinical benefit in comparison with the overall accepted intervention within 48 h is unknown, and a larger randomised trial testing the two strategy will be needed.

Conclusions

The globality of current evidence strongly suggests that in high risk patients with ACS an early combined invasive strategy and treatment with GP IIb/IIIa antagonists considerably improves short- and long-term outcome.

As adjunctive therapies improve, lessening the risk associated with invasive cardiac procedures, we may well be moving to an era of rapid risk assessment and triage, initial medical stabilisation with very potent antithrombotic medications, and rapid transfer to cardiac centres of excellence for diagnostic and therapeutic procedures within 48 h of presentation. This should allow to patients admitted to peripheral hospitals to have access to the same type of care as those patients directly admitted to tertiary centres. A unified systematic approach to NSTE-ACS that incorporates all evidence-based therapies and interventions would be expected to maximise the positive impact of such strategies on long-term clinical outcome.

How best to incorporate this new knowledge into a better process of care for patients will need to be shown by prospective cohort studies showing how clinicians actually deliver care to their patients in 'real-life'.

References

1. Braunwald E, Antman EM, Beasley JW et al (2000) ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 102:1193–1209
2. Boersma E, Akkerhuis KM, Theroux P et al (1999) Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. Circulation 100:2045–2048
3. Coller BS (1995) Blockade of platelet GP IIb/IIIa receptors as an anti-thrombotic strategy. Circulation 92:2373–2380
4. The EPIC Investigators (1994) Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 330:956–961
5. Boersma E, Harrington RA, Moliterno DJ et al (2002) Platelet glycoprotein IIb/IIIa

inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 359:189–198

6. Bertrand ME, Simoons ML, Fox KAA et al (2002) Management of acute coronary syndromes in patients presenting without ST-segment elevation. Eur Heart J 23:1809–1840

7. Braunwald E, Antman EM, Beasley JW et al (2002) ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 106:1893–1900

8. Theroux P, Alexander J Jr, Pharand C et al (2000) Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infarction: results from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. Circulation 102:2466–2472

9. Januzzi JL, Snapinn SM, DiBattiste PM et al (2002) Benefits and safety of tirofiban among acute coronary syndrome patients with mild to moderate renal insufficiency. Circulation 105:2359–2364

10. Januzzi JL Jr, Sabatine MS, Wan Y et al (2003) Interactions between age, outcome of acute coronary syndromes, and tirofiban therapy. Am J Cardiol 91:457–461

11. Morrow DA, Antman EM, Snapinn SM et al (2002) An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. Eur Heart J 23:223–229

12. Morrow DA, Antman EM, Snapinn SM et al (2002) An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. Eur Heart J 23:223–229

13. Roffi M, Chew D, Mukherjee D et al (2002) Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes: gradient of benefit related to the revascularisation strategy. Eur Heart J 23:1441–1448

14. The TIMI IIIB Investigators (1994) Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: the results of TIMI IIIB trial. Circulation 89:1545–1556

15. Anderson HV, Cannon CP, Stone PH et al (1995) One year result of the TIMI IIIB clinical trial: a randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q-wave myocardial infarction. J Am Coll Cardiol 26:1643–1650

16. Boden WE, O'Rourke RA, Crawford MH et al (1998) Outcomes in patients with acute non-Q-wave MI randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 338:1785–1792

17. Anonymous (1999) Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 354:708–715

18. Wallentin L, Lagerqvist B, Husted S et al (2000) Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary artery disease: The FRISC II invasive randomised trial. Lancet 356:9–16

19. Cannon CP, Weintraub W, Demopoulos LA et al (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
20. Fox KA, Poole-Wilson PA, Henderson RA et al (2002) Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 360:743–751
21. Antman EM, Cohen M, Bernink PJ et al (2000) The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 284:835–842
22. Neumann FJ, Kastrati A, Murray GP et al (2003) Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes. JAMA 290:1593–1599