Triple antiplatelet treatment in patients presenting with non-ST-segment elevation acute coronary syndromes

Michel E. Bertrand* and Eric Van Belle

Lille Heart Institute, Hôpital Cardiologique, Boulevard du Professeur Leclercq, 59037 Lille, France

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Introduction

Over the last 20 years, it has been clearly demonstrated that antiplatelet drugs played a major role in the management of acute coronary syndromes (ACSs). There are three major classes of antiplatelet drugs, namely aspirin, thienopyridines, and glycoprotein (Gp) IIb/IIla receptor inhibitors. Aspirin inhibits cyclo-oxygenase-1 and blocks the formation of thromboxane A2. This blockade is irreversible and lasts until the formation of new platelets. Three trials have consistently shown that aspirin decreases the rate of death or MI in patients with unstable angina.1–4 A meta-analysis showed that 75–150 mg aspirin was as effective as higher doses.5

Thienopyridines include ticlopidine and clopidogrel, two ADP receptor antagonists. The largest body of information concerning ACS was provided by the CURE trial6 conducted in non-ST-elevation acute coronary syndromes (NSTE-ACS) and by the CLARITY7 and COMMIT trials8 conducted in ST-elevation ACSs. In addition, the CREDO9 trial provided interesting data concerning patients undergoing percutaneous coronary interventions (PCIs). New compounds (Prasugrel, CS-747; Cangrelor, ARC-69931 MCX and AZ-6140) are under evaluation.

GpIIb/IIla receptors are expressed on the surface of activated platelets. They link to fibrinogen to form bridges between activated platelets, leading to formation of platelet thrombi. Direct inhibitors of the glycoprotein (Gp) IIb/IIla receptors have been developed and have been tested in various conditions where platelet activation plays a major role, in particular, in patients undergoing PCI, in patients admitted with ACSs, and in patients receiving thrombolytic therapy for acute myocardial infarction. Several studies and a meta-analysis10 have clearly defined the impact of GpIIb/IIla receptor inhibitors on outcome in NSTE-ACS. Overall, the rate of death and MI is modestly but significantly reduced at 30 days [OR 0.91 (0.84–0.98)].10 A significant risk reduction was shown for small molecules (tirofiban11,12 and eptifibatide13) but not for abxicimab.14 GpIIb/IIla receptor inhibitors are effective in patients with elevated troponins and in those undergoing PCI.10 A significant risk reduction for death and MI and also for cardiovascular death was shown in a meta-analysis addressing the efficacy of GpIIb/IIla receptor inhibitors in diabetic patients.15

* Corresponding author.
E-mail address: mbcardio@club-internet.fr

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The guidelines of the European Society of Cardiology (ESC)\textsuperscript{16,17} and the ACC/AHA guidelines\textsuperscript{18,19} recommend dual antiplatelet treatment (aspirin + clopidogrel) for the management of all patients presenting with NSTE-ACS. Triple antiplatelet treatment including aspirin, clopidogrel, and GpIIb/IIIa receptor inhibitors is recommended for the management of moderate-to-high-risk patients, namely those with recurrent ischaemia, ST-segment depression, elevated troponins, and diabetic patients, or as defined by the TIMI risk score. This proposal resulted from an extrapolation of trials conducted with GpIIb/IIIa receptor inhibitors\textsuperscript{20} but has never (until recently) been validated by randomized clinical trials.

In this article, the rationale for triple antiplatelet treatment, the clinical impact of this strategy, and the current clinical indications will be reviewed.

Rationale for a triple antiplatelet treatment

The rationale for triple antiplatelet treatment results from clinical and biological studies. Steinhubl et al.\textsuperscript{21} assessed the occurrence of major adverse clinical events (MACE) in 500 patients submitted to PCI with planned use of GpIIb/IIIa receptor inhibitors based on the level of platelet inhibition. Platelet inhibition was measured with the Ultegra rapid platelet function assay (Accumetrics). In this study,\textsuperscript{21} the level of platelet inhibition was related to the rate of MACE [a composite of death, MI, and urgent target vessel revascularization (TVR)]: patients whose platelet function was inhibited $>90\%$ at 24 h experienced the lowest event rate (2\%) compared with an average of 9.7\% for the patients with lower platelet inhibition levels ($P = 0.13$).

In the TOPSTAR trial,\textsuperscript{22} 96 patients with stable coronary disease underwent PCI and stent implantation, with clopidogrel 300 mg and aspirin administered the day before intervention. They were also randomized to receive either tirofiban (bolus 10 $\mu$g/kg followed by 0.15 $\mu$g/kg/min for 18 h) or placebo. Blood samples were drawn at baseline, 30 min, and 2, 6, 12, 24, and 48 h to assess platelet aggregation. The triple antiplatelet treatment induced marked platelet inhibition with partial recovery at 24 h after administration of tirofiban. Platelet aggregation was almost completely restored at 48 h (Figure 1).

In the PEACE study,\textsuperscript{23} Dalby et al. assessed GpIIb/IIIa receptor expression and anti-fibrinogen binding in 32 patients with NSTE-ACS and elevated troponins. Blood samples were collected on EDTA for platelet count and on PPACK to avoid calcium chelation. Measurements were performed at baseline, 3 h after clopidogrel, and $>12$ h after additional prescription of eptifibatide. The activated GpIIb/IIIa receptor expression and fibrinogen-binding findings confirmed that a significant potent antiplatelet activity was induced by eptifibatide in addition to the effect exerted by aspirin and clopidogrel.

All in all, these different studies provide evidence that additional anti-platelet activity can be achieved when GpIIb/IIIa receptor inhibitors are prescribed on top of dual anti-platelet therapy.

**Figure 1** The level of platelet level inhibition in the TOPSTAR trial. Marked platelet inhibition is obtained with triple antiplatelet treatment. Solid bar, tirofiban ($n = 50$); open bar, placebo ($n = 46$). $P < 0.05$; $**P < 0.001$. Data $\pm$ SEM.\textsuperscript{22}

Interest of triple antiplatelet treatment: clinical evidence

Most of the contemporary trials related to PCIs or to ACSs included dual antiplatelet treatment (e.g. CAPTURE,\textsuperscript{24} PRISM,\textsuperscript{11} PRISM-PLUS,\textsuperscript{12} PURSUIT,\textsuperscript{13} PARAGON A and B,\textsuperscript{25,26} GUSTO IV-ACS,\textsuperscript{14} EPIC,\textsuperscript{27} EPILOG,\textsuperscript{28} EPISTENT,\textsuperscript{29} ESPRIT,\textsuperscript{30} RESTORE\textsuperscript{31}). Only a few trials have studied triple antiplatelet treatment, and only some provided evidence in favour of this regimen.

In the ESPRIT trial,\textsuperscript{30} 2064 patients undergoing elective stenting were pre-treated with aspirin and randomized to receive either eptifibatide or placebo. Thienopyridines were administered before the procedure in some patients, at the operator’s discretion. The lowest event rate was observed in patients with triple anti-platelet therapy, comprising aspirin and thienopyridine + eptifibatide (Figure 2).

In the TARGET trial,\textsuperscript{32} two regimens of GpIIb/IIIa receptor inhibitors were compared: a monoclonal antibody (abciximab 25 mg/kg bolus $+125 \mu$g/kg/min 12 h infusion) and a small molecule (tirofiban 10 $\mu$g/kg bolus followed by 15 $\mu$g/kg/min 18–24 h infusion) in a cohort of 4809 patients. At 30 days, tirofiban was shown to be inferior to abciximab, but this difference was no longer apparent at 1-year follow-up.\textsuperscript{33}

As in the ESPRIT study, a certain number of patients received clopidogrel (300 mg loading dose 2–6 h prior to PCI followed by 75 mg/day for 29 days). As shown in Figure 3, there was a lower event rate in patients who received triple anti-platelet therapy, with a rate of death + MI + urgent TVR of 5.9 vs. 7.3\% in those without triple anti-platelet therapy.

In the TOPSTAR trial\textsuperscript{22} mentioned earlier, the rate of troponin release after intervention was significantly lower in patients who received triple antiplatelet treatment when compared with dual antiplatelet therapy. At 9 months, the rate of death, MI, and urgent TVR was significantly lower in the triple anti-platelet therapy group.
However, the sample size of this study was quite small, so these results could be due to chance. In a similar study, Assali et al. observed similar results in 299 patients with unstable angina. The rate of MACE was 5.5% with triple anti-platelet therapy when compared with 14% with dual anti-platelet therapy ($P = 0.03$).

In the ADVANCE trial, which included 202 high-risk diabetic patients with NSTE-ACS, submitted to planned multi-stage PCI, a strategy with a high bolus of tirofiban (25 $\mu$g/kg: 3 min + 0.15 $\mu$g/kg/min during 24-48 h) was compared with placebo. All patients received dual anti-platelet therapy as a baseline treatment. The rate of death, MI, or urgent TVR was significantly reduced from 31 to 20%, with triple vs. dual anti-platelet therapy, respectively, $P = 0.04$.

Other trials did not show any superiority of triple anti-platelet therapy over dual therapy but in different settings. In the EPISTENT trial, 2399 patients undergoing elective or urgent angioplasty with stenting were randomized to receive either abciximab or placebo, with or without pre-treatment with ticlopidine, which was the only thienopyridine available at the time. Abciximab significantly reduced the rate of 30-day MACE, but no clear effect of pre-treatment with ticlopidine was identified (5.2 vs. 5.5%, respectively).

The first two ISAR studies carried out in the setting of planned PCI and diabetes failed to show any difference between dual and triple anti-platelet therapy. The goal of these studies was to compare a high loading dose of clopidogrel on top of aspirin in patients randomized to receive either abciximab or placebo in the setting of PCI. These two studies compared two different regimens of anti-platelet treatment: double vs. triple anti-platelet therapy.

The ISAR-REACT study enrolled 2159 patients undergoing elective PCI. There was no significant difference for death (Q-wave or non-Q-wave) MI or urgent TVR. The composite endpoint did not show a significant difference (4.2 vs. 4%). However, this study was conducted in a low risk population in whom it is known that GpIIb/IIIa receptor inhibitors have no efficacy, as shown by previous trials and the meta-analysis of Boersma et al. In ISAR-REACT, patients with ACSs or elevated troponin, insulin-dependent diabetics, and patients with thrombus-containing lesions were excluded.

In the ISAR-SWEET trial, 701 diabetic patients undergoing planned PCI were submitted to the same regimen. No significant difference was observed between groups in the rate of MACE (5.1 vs. 4% at 30 days and 8.3 vs. 8.6% at 1 year).

However, this study was seriously underpowered because of a miscalculation of the sample size, based on an overestimation of the event rate. The population actually included in this study was at rather low risk.

The ISAR-REACT II study addressed a totally different patient population, namely high-risk patients with ongoing ACS. The same regimen as the ISAR-REACT and ISAR-SWEET studies was used, evaluating the efficacy of treatment with abciximab compared with placebo among patients undergoing PCI and treated with high-dose clopidogrel (600 mg) + aspirin. Inclusion criteria selected a high-risk population: recent episode of angina (<48 h) and elevated troponin T level or new ST-segment depression of >1 mV or transient ST-segment elevation of >0.1 mV or new presumed left bundle-branch block and significant angiographic lesions in a native coronary vessel or saphenous vein graft amenable to and requiring PCI. In total, 2022 patients (mean age 66 years) were enrolled. All patients were pre-treated with 600 mg loading dose of...
clopidogrel + aspirin at least 2 h pre-procedure and randomized to abciximab (1012 patients) or placebo (1010 patients). The primary composite endpoint of death, MI, or urgent TVR was significantly reduced in the triple vs. dual antiplatelet group (8.9 vs. 11.9%, \( P = 0.03 \)) at 30 days. The rate of death and MI was also significantly reduced (8.6 vs. 11.5%, \( P = 0.05 \)). The rate of urgent TVR was low and non-significantly influenced by triple anti-platelet therapy.

These results warrant several comments.

- Only patients with elevated troponins (>0.03 \( \mu g/L \)) benefited from triple antiplatelet treatment: reduction of the primary endpoint from 18.3 to 13.1% (\( P = 0.02 \)).
- In contrast, patients with negative troponins did not derive any benefit from an aggressive strategy including three antiplatelet drugs (4.6% in both groups).
- No significant excess of bleeding was observed, despite the intense anti-platelet regimen with three drugs (Figure 5).
- Contrary to the meta-analysis of Roffi et al.,\(^{15}\) no significant benefit on the primary endpoint was observed in diabetic patients (\( n = 536 \)), with aspirin + clopidogrel + abciximab (10.3%) vs. aspirin + clopidogrel (11.3%) [OR = 0.91 (95% CI: 0.51–1.62), \( P = 0.72 \)]. Actually, the non-diabetic patients derived the best benefit from triple antiplatelet treatment: 8.4 vs. 12.1% [OR 0.69 (95% CI 0.49–0.99), \( P = 0.03 \)]. These results require further investigation.

All in all, this study confirms that in high-risk patients submitted to PCI, triple anti-platelet therapy comprising abciximab, clopidogrel, and aspirin leads to a better risk reduction in the occurrence of MACE, when compared with dual anti-platelet therapy.

**Conclusions**

There is now a large body of information which makes it possible to draw firm conclusions concerning triple anti-platelet treatment. Biological assays have shown that a higher level of platelet inhibition was obtained with a combination of aspirin, thienopyridine, and GpIIb/IIIa receptor inhibitors. A high level of platelet inhibition is associated with a lower rate of major cardiac events in patients with ACSs. Post hoc analysis of several trials has suggested that triple anti-platelet therapy would lead to better clinical outcome.

The ISAR-REACT II trial confirmed that triple anti-platelet therapy leads to better outcome in terms of death + MI, and death, MI, or urgent TVR in high-risk patients submitted to PCI, particularly patients with elevated troponin levels.

These results validate the recommendations in the ESC and ACC/AHA guidelines. All patients presenting with non-ST-segment elevation ACS should receive a baseline treatment with two antiplatelet drugs, i.e. aspirin + clopidogrel. High-risk patients should also receive a GpIIb/IIIa receptor blocker on top of aspirin and clopidogrel. This population is characterized by patients who have recurrent chest pain and ischaemia, ST-segment depression, elevated troponins, and the diabetic patients (and moderate-to-high-risk patients according to the TIMI risk score). This information will be incorporated into future updates of these guidelines.

Conflict of interest: none declared.

**References**


