

Overcoming “resistance” to aspirin and clopidogrel with tirofiban: fact or fiction?

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What is the optimal antithrombotic therapy in high-risk patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI)? This has been a hot research and clinical issue for several decades, and the attitude of cardiovascular specialists has changed considerably as new antithrombotic agents were approved and introduced in clinical practice, as well as new means to appraise antithrombotic efficacy were proposed. Another major paradigm shift has occurred recently with the ever increasing emphasis placed not only on efficacy (i.e. antithrombotic effect), but also on safety (risk of bleeding) (1). Finally, a major change has been led by the diffuse view that some patients may be “resistant”, i.e. respond poorly or incompletely, to commonly used antiplatelet agents such as aspirin, ticlopidine or clopidogrel (2, 3).

Nowadays several antithrombotic agents are already (or will shortly be) available: a) antiplatelet drugs such as aspirin, thienopyridines (i.e. ticlopidine, clopidogrel, or prasugrel), intravenous glycoprotein IIb/IIIa inhibitors (i.e. abciximab, eptifibatid and tirofiban), or cangrelor; and b) anticoagulant drugs such as unfractionated heparin, low-molecular-weight heparins (e.g. enoxaparin or dalteparin), and direct thrombin inhibitors (e.g. argatroban or bivalirudin). Given the wealth and partial redundancy of these agents, physicians are faced with the challenge of identifying the most appropriate cocktail for the specific patient under their care. While some evidence-based suggestions can and have been proposed (4, 5), there remains much room for improvement and research. The article by Ivandic et al. (6) in this issue of *Thrombosis and Haemostasis* is a very useful addition to the current literature on this topic, providing intriguing data on the role of tirofiban in high-risk patients with acute coronary syndromes.

It is well known that those presenting with ACS and undergoing PCI are far better off when treated with abciximab on top of aspirin and front-loaded (600 mg) clopidogrel than when treated with aspirin and front-loaded clopidogrel alone (7). Whether this holds true also for other glycoprotein IIb/IIIa inhibitors was a matter of debate. However, Ivandic et al. elegantly

demonstrate in a 100-patient randomized trial that tirofiban, on top of aspirin and 600 mg of clopidogrel, further inhibits platelet aggregation leading to significant reductions in the occurrence of post-procedural myocardial necrosis (as measured by cardiac troponin T levels), despite a non-significant increase in minor bleedings. While this effect did not translate into major reductions in more traditional cardiac markers such as creatine kinase and creatine kinase-MB in this relatively small study, its results shed new light on the hot and debated topic of “resistance” to antiplatelet agents.

Indeed, Ivandic et al. (6) poignantly show that, peri-procedurally, aspirin “resistance” (i.e. non-responsiveness) occurred in 28% and clopidogrel “resistance” in 69% of those not treated with tirofiban, whereas corresponding prevalences were 4% and 2% in the tirofiban group. Moreover, combined “resistance” to aspirin and clopidogrel was demonstrated in as many as 26% of patients not treated with tirofiban, whereas only one subject in the tirofiban group responded poorly to both aspirin and clopidogrel. In addition, among the few patients treated for at least 120 minutes before reaching the catheterization laboratory and being assessed for platelet function, aspirin and/or clopidogrel “resistance” occurred less frequently in both groups, also supporting the important role of time since administration of the specific agent in determining responsiveness.

What can we conclude from this interesting randomized study, albeit limited by the reliance on surrogate end-points and relatively small sample size (Fig. 1)?

- Patients with non-ST-elevation acute coronary syndromes should be given aspirin and a 600 mg loading dose of clopidogrel as soon as a diagnosis is made and excessive bleeding risk is ruled out (e.g. in the Emergency Department or even in the ambulance) (8).
- High-risk subjects with non-ST-elevation acute coronary syndromes, without a bleeding diathesis, and planned for coronary angiography and/or intervention should be given a glycoprotein IIb/IIIa inhibitor either before reaching the catheterization laboratory (in which case tirofiban or eptifi-

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ST-ELEVATION ACUTE CORONARY SYNDROMES	NON-ST-ELEVATION ACUTE CORONARY SYNDROMES	STABLE CORONARY ARTERY DISEASE
ASPIRIN 600 mg OF CLOPIDOGREL	ASPIRIN 600 mg OF CLOPIDOGREL	ASPIRIN 600 mg OF CLOPIDOGREL
BIVALIRUDIN <i>or</i> HEPARIN PLUS GLYCOPROTEIN IIB/IIIA INHIBITORS *	HEPARIN <i>for low ischemic and bleeding risk</i> HEPARIN PLUS GLYCOPROTEIN IIB/IIIA INHIBITORS <i>for high ischemic but low bleeding risk</i> BIVALIRUDIN <i>for low ischemic but high bleeding risk</i>	HEPARIN OR BIVALIRUDIN† GLYCOPROTEIN IIB/IIIA INHIBITORS as <i>bail-out</i>

Figure 1: Schematic algorithm for the management of antithrombotic therapy in patients with coronary artery disease undergoing invasive management [*bivalirudin provides a survival benefit, but increases the risk of early stent thrombosis; †depending on bleeding risk].

- batide are probably of similar benefit) (6) or in the catheterization laboratory (in which case abciximab, tirofiban or eptifibatide are probably of similar benefit, even if the weight of evidence is mainly on abciximab) (7), combined with unfractionated heparin.
- Whenever bleeding risk is at least moderate, aspirin, clopidogrel and bivalirudin can be considered in patients with non-ST-elevation acute coronary syndromes, even if this latter agent may provide a suboptimal antithrombotic efficacy in comparison to heparin plus glycoprotein Iib/IIIA inhibitors (9).
- Given the recent results from the HORIZONS trial, patients with ST-elevation myocardial infarction may fare better with aspirin, clopidogrel and bivalirudin, even if the early increase in stent thrombosis seen in the bivalirudin arm in this recent trial in comparison to the heparin plus glycoprotein Iib/IIIA inhibitors arm warrants further analyses (10).

- All stable coronary patients (e.g. those with effort angina or silent myocardial ischemia) undergoing PCI are likely best managed with aspirin and 600 mg of clopidogrel plus an anti-coagulant agent (heparin or bivalirudin, depending on bleeding risk). In this setting, glycoprotein Iib/IIIA inhibitors have a more limited elective role, but they remain crucial whenever complications arise (i.e. in a bail-out indication) or possibly, when non-responsiveness to aspirin and/or clopidogrel is demonstrated despite adequate pre-treatment time.

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Conflicts of interest

Dr. Biondi-Zoccai has lectured for Bristol-Myers Squibb and Sanofi Aventis.

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