Intern Emerg Med (2009) 4:275–276
DOI 10.1007/s11739-009-0271-2

IM - COMMENTARY

Perioperative handling of antiplatelet therapy: watching the two sides of the coin

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Received: 25 May 2009 / Accepted: 26 May 2009 / Published online: 17 June 2009

The last quarter of a century has witnessed the most formidable progress in the treatment of ischemic cardiovascular disorders, with a striking decrease of cardiovascular mortality that translated in more than 300,000 fewer deaths in 2000 as compared to 1980 in the USA. Among the causes of this decline in coronary heart disease mortality, antithrombotic treatment, and in particular the progressive improvement of antiplatelet therapy, has played an important role [1, 2]. However, despite great progress, current antiplatelet therapy has still got serious limitations and a number of important unmet medical needs still remain. In particular: suboptimal clinical efficacy, with only about one-fourth of all the cardiovascular events prevented and an unacceptably high residual rate of recurrent ischemic events under antiplatelet treatment; variability of the response to treatment, which has been shown to have a negative prognostic impact on cardiovascular events; bleeding risk, especially when more aggressive therapeutic protocols are employed. The efficacy, and therefore the benefit, of antiplatelet therapy is especially great in conditions at high risk of cardiovascular events, and in particular in acute coronary syndromes [3]. Thus, the inappropriate withdrawal of the most effective antiplatelet regimen may generate a great burden of serious adverse cardiovascular events in these patients [4, 5]. On the other hand, even a relatively small improvement of the efficacy or of the rapidity of the initiation of action of the antiplatelet effect, such as for instance that generated by prasugrel as compared with clopidogrel in patients undergoing percutaneous coronary interventions [6], may further reduce consistently the incidence of serious cardiovascular events and cardiovascular mortality.

One of the main reasons for the early discontinuation of antiplatelet therapy is the need for surgery, either urgent coronary artery bypass graft surgery in patients failing PCI or incidental surgery for other conditions [7]. The fear for excessive bleeding, especially by surgeons and anesthesiologists, often leads to inappropriate or too prolonged discontinuation of antiplatelet therapy, sometimes substituted for by empirically prescribed heparin. Unfortunately, most of the information so far available on the risk of early antiplatelet discontinuation and on the most appropriate timing and duration of interruption of the treatment before surgery comes from retrospective studies or meta-analyses of small observational studies, with no direct evidence coming from prospective studies [7].

The effort to establish a consensus between surgeons, anesthesiologists and experts in cardiovascular medicine on the perioperative handling of patients on antiplatelet therapy who require surgery, based on the systematic scrutiny of the available literature, such as that reported in the current issue of *Internal and Emergency Medicine*, is therefore very appropriate [8].

While it is important to recommend not to inappropriately discontinue antiplatelet therapy in patients at high cardiovascular risk, it must also be considered that also major bleeding has a strongly negative prognostic value in patients at high risk of cardiovascular events [9, 10], with a striking increase not only in total mortality, but also of cardiovascular mortality in patients who suffer a major hemorrhagic complication. A paradigmatic example of this is the recent Horizons-AMI trial, comparing bivalirudin with heparin plus a GPIIb/IIIa antagonist in patients undergoing primary PCI for STEMI [11]. In this study, a highly

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significant decrease in 30-day cardiovascular mortality in the bivalirudin arm was entirely explained by the significantly lower incidence of major bleeding and not by better prevention of major ischemic events that were, on the contrary, even somewhat higher in the first 10 days of treatment in the bivalirudin group [11].

The probability of developing a major cardiovascular event in the individual patient is proportional to the strength of its risk and to the duration of the exposure to it; on the other hand, the likelihood of major bleeding during surgery depends on the type and duration of surgery and on the efficiency of the hemostatic system at the moment of surgery, therefore a careful assessment of these two sides of the coin must be made in the individual patient. A number of useful considerations along these lines are reported in the consensus document by Di Minno and coworkers [8].

Of course, more conclusive information may only come from prospective clinical trials comparing different strategies for the perioperative handling of patients on antiplatelet therapy who require surgery. By analogy with the ongoing studies testing the modification of antiplatelet dosage guided by platelet response (e.g. GRAVITAS trial), a laboratory-driven strategy, based on the disappearance of the platelet inhibitory effect as detected by one of the platelet function tests currently under evaluation for the monitoring of antiplatelet therapy, could also be envisaged. Indeed, a one-size-fits-all strategy may not always be appropriate because if it is true that current antiplatelet agents (aspirin and clopidogrel) block irreversibly their target on platelets, it is also likely that platelet turnover, and therefore the timing of resumption of a normal platelet function, may vary from patient to patient.

A possible way out to the apparently insoluble dilemma of avoiding bleeding without provoking ischemic events may come from novel antiplatelet agents in development. The new PAR-1 antagonists, currently in phase III clinical testing, have given promising preclinical and preliminary clinical results, showing an effective antiplatelet action without any associated significant bleeding, and future novel approaches may provide further options in this sense [12, 13].

While waiting for new evidence to emerge on the best antiplatelet regimen to be used, the full implementation of the entire pharmacologic armamentarium of proven efficacy is highly warranted and may contribute to further reduce mortality from ischemic cardiovascular disease in patients with atherothrombosis [14], considering that the application of treatments of proven efficacy is still far from optimal [15].

Conflict of interest statement The author declares that he has no conflict of interest related to the publication of this manuscript.

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