More evidence for a beneficial effect of platelet glycoprotein IIb/IIIa-blockade during coronary interventions. Latest results from the EPILOG and CAPTURE trials

Platelets play an important role in the pathophysiology of ischaemic complications during and after percutaneous transluminal coronary angioplasty (PTCA) or other coronary interventions such as atherectomy or stent deployment. Although aspirin, as a consequence, is routinely given to patients scheduled to undergo these coronary interventions, its effect on platelet function is unselective and relatively weak. Many new, more potent, antiplatelet agents such as thromboxane synthase inhibitors, antagonists of the serotonin, endoperoxide and glycoprotein (GP) IIb/IIIa-receptors are now available for clinical evaluation in patients with coronary artery disease. The latter platelet membrane receptor belongs to the integrin family and binds fibrinogen and other adhesive proteins to form cross-bridges between adjacent platelets. These molecular interactions constitute the final common pathway of platelet aggregation, irrespective of the stimulus. In recent years antagonists of the GPIIb/IIIa-receptor have been evaluated in patients undergoing PTCA and other coronary interventions. Recently, two large studies with c7E3, a chimeric monoclonal antibody Fab fragment directed against the GPIIb/IIIa-receptor, now called abciximab, have been prematurely stopped because of a highly significant reduction in the primary endpoint of the trial in the group receiving abciximab. It is unusual in the field of acute coronary syndromes and coronary interventions that a trial is stopped prematurely because of clinical efficacy.

In the EPILOG (Evaluation of PTCA to improve Long-Term Outcome by cF7E3 Glycoprotein Receptor Blockade) trial a total of 2980 patients undergoing elective PTCA were to be randomized between standard therapy with placebo, abciximab with low dose heparin and abciximab with standard dose heparin. After the first interim analysis in 1500 patients a highly significant reduction in the primary, composite endpoint (incidence of death and myocardial infarction) was observed in patients receiving abciximab: 2.6% in patients randomized to abciximab plus low dose heparin and 3.6% in those given abciximab plus standard heparin vs 8.1% in control patients. An excess of major bleeding complications was found in the abciximab groups with the excess being smaller in the abciximab plus low dose heparin group. In the CAPTURE trial (a phase III randomized, placebo-controlled multicentre trial of c7E3 in patients scheduled for urgent PTCA due to refractory unstable angina) 1400 patients with refractory unstable angina were to be randomized between placebo or abciximab (on top of standard treatment) during 16 to 24 h preceding PTCA and continuing 1 h following the completion of the procedure. The interim analysis in 1050 patients showed a highly significant reduction in the composite endpoint of death, myocardial infarction or need for urgent intervention in the abciximab group: 10.8% vs 16.4% in the control group. A non-significant increase in major bleeding complications with abciximab was also observed in this trial. In both cases the Data Monitoring and Safety Board recommended to stop further enrollment of patients. The results of EPILOG and CAPTURE are in full agreement with those of EPIC, the first large trial with abciximab in patients undergoing PTCA, and clearly indicate that antagonists of the GPIIb/IIIa-receptor are able to reduce the risk of thrombotic/ischaemic complications following coronary interventions, but with an increased risk of bleeding. It is possible that this increased risk is partly due to the concomitant administration of heparin. EPILOG suggests that reducing the dose of heparin may also reduce the excess of bleeding complications with abciximab.

Besides the problem of concomitant heparin administration, there are still many other unresolved issues with the use of GPIIb/IIIa-receptor antagonists in patients undergoing PTCA. We do not know whether GPIIb/IIIa-receptor antagonists are beneficial for all patients scheduled to undergo PTCA and whether these agents are equally effective for all
types of coronary interventions. Clearly, in EPIC and CAPTURE a patient group at increased risk of ischaemic complications was selected. The comparative efficacy and safety of various GPIIb/IIIa antagonists is also unknown. For example, the less impressive results obtained with integrin in the IMPACT II trial (4010 patients undergoing coronary interventions), presented at the ECC meeting in Amsterdam in August 1995, may be due to the different pharmacological profile of integrin, to the selection of a different study population (at lower risk of ischaemic complications) or to the more frequent performance of directional atherectomy in this study.

Summarizing, all the available clinical data suggest that platelet GPIIb/IIIa-receptor blockade with abciximab is highly effective in reducing ischaemic and thrombotic complications in patients undergoing coronary interventions, particularly high-risk patients, with an acceptable excess of bleeding complications. The complete data of EPILOG, CAPTURE, IMPACT II and of other ongoing trials testing other GPIIb/IIIa-receptor antagonists in the setting of coronary interventions like RESTORE (tirofiban) and FRASCATI (fradafiban), are eagerly awaited.

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References