



Antithrombotic Therapy During and After Acute Coronary Syndromes

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ABSTRACT

Antithrombotic treatment of acute coronary syndrome consists of aspirin and (low-molecular weight) heparin, whereas glycoprotein IIb/IIIa receptor antagonists and fibrinolytic therapy are only given when indicated. Long-term protection also consists of antiplatelet therapy and, if indicated, by anticoagulant therapy, either given as low-molecular weight heparin or as oral anticoagulants.

Antithrombotic therapy of acute coronary syndrome potentially consists of anticoagulant therapy (heparin, hirudin, coumadin), fibrinolytic therapy and antiplatelet therapy and is aimed at inhibition of clot formation and propagation and at lysis.

ACUTE TREATMENT

Anticoagulants

The anticoagulant used most in acute coronary syndrome is heparin. Heparin exerts its antithrombotic effect through its stimulating effect of antithrombin-III. Therefore, it is an indirect thrombin inhibitor. Hirudin is a direct thrombin inhibitor and does not need antithrombin-III for its effects. Intravenous heparin rapidly decreases thrombin activity in the plasma, but it has a large intra- en interindividual variability in dose response. The effect of heparin is usually measured with the prolongation of the activated partial thromboplastin time (aPTT). The therapeutic range is thought to be an aPTT between 60 and 90 seconds. Unfractionated heparin has been tested in acute coronary syndrome in 6 randomized controlled trials of moderate size and found to be marginally effective¹ over antiplatelet therapy alone (aspirin, see below) with an acceptable risk of major bleeding (1.5% versus 0.4% for aspirin alone). A rebound phenomenon is observed after unfractionated heparin is discontinued, against which aspirin is partially effective.² Low-molecular weight heparin consists of the smaller molecules of the compounds of which heparin is a mixture. The pharmacological response (anti-Xa activity) is more predictable and does not need aPTT monitoring. Furthermore, the agent can be given subcutaneously, which makes ambulatory use possible. Low-molecular weight heparin together with aspirin is considerable more effective than aspirin alone³ and is at least as effective as unfractionated heparin.⁴⁻⁷ Through its ease of administration and lack of need for monitoring it has become the

preferred anticoagulant treatment in acute coronary syndrome. Hirudin has also a well predictable dose response. A rebound is also possible with hirudin.⁸ Large clinical trials do not show a significant benefit over unfractionated heparin.^{9,10} Due to the high cost hirudin is not a useful anticoagulant in acute coronary syndrome. Oral anticoagulants inhibit indirectly thrombin activity by inhibition of the formation of several clotting factors, one of which is prothrombin. They are not commonly used in the early management of acute coronary syndrome, since large trials showing efficacy are not available.

Fibrinolysis

Fibrinolytic therapy is aimed at plasminogen activation at the site of the thrombotic occlusion during the early hours of acute transmural myocardial infarction. Besides lysis of fibrinogen, plasmin also splits several important clotting factors like prothrombin. When prothrombin is split, thrombin generation occurs and this has strong procoagulant effects. Although the procoagulant effect of fibrinolysis can be diminished by concomitant heparin therapy, the nature of heparin therapy with its unpredictable efficacy and bleeding risk makes complete abolishment of the procoagulant effect of fibrinolytic therapy unsure. Since most patients with ST-elevation acute coronary syndrome have acutely occluded vessels, fibrinolytic therapy is indicated in most cases, if primary balloon angioplasty can not be applied within 90 minutes of first medical contact. Only few patients with acute coronary syndrome without ST-elevation have a total thrombotic coronary occlusion. Therefore, in those patients reperfusion therapy is not indicated and may be even harmful through its procoagulant effect. In several trials on fibrinolytic therapy in acute coronary syndrome bleeding and thrombotic complications have made this therapy unpopular.¹¹

Antiplatelet therapy

The most effective treatment strategy in acute coronary syndrome is antiplatelet therapy. Platelet inhibitors affect the properties of blood platelets to aggregate. Aspirin (acetylsalicylic acid) inhibits the activity of cyclooxygenase in all body cells. Since platelets do not have a nucleus, cyclooxygenase can not be formed after the platelets have been in contact with aspirin and the platelets are not able to produce thromboxane A₂, the proaggregatory platelet-specific prostaglandin, during its life span (median 8 days), while the other body cells rapidly pick up cyclooxygenase production after contact with aspirin. There is no tolerance with aspirin and there is no rebound effect observed in patients who are on chronic aspirin therapy.¹² Spontaneous life-threatening bleeding with aspirin is rare. Five important trials performed in the seventies and the eighties showed in patients with acute coronary syndrome a reduction of myocardial infarction and death of up to 70%.¹³⁻¹⁷ Since aspirin is inexpensive, it is very cost-effective.

The second generation platelet inhibitors are the thienopyridines ticlopidine and clopidogrel. Ticlopidine inhibits the ADP receptor on the platelet surface and does not interfere with the cyclooxygenase pathway inhibition by aspirin. Ticlopidine prolongs bleeding time beyond that of aspirin. In contrary to aspirin the effect of ticlopidine takes several days to develop. It takes also several days to disappear after ticlopidine discontinuation. Ticlopidine is indicated in patients, who have undergone coronary stenting and there has been one larger study performed with ticlopidine in unstable angina.¹⁸ Rebound effect of ticlopidine has not been observed. Due to the sometimes severe hematologic and dermatologic side-effects of ticlopidine the agent has been replaced by clopidogrel. Clopidogrel on top of aspirin reduces death and (recurrent) myocardial infarction in the largest trial ever in acute coronary syndromes (CURE¹⁹). These results have been confirmed in the CREDO trial.²⁰ The third generation platelet inhibitors are the glycoprotein IIb/IIIa receptor antagonists. They specifically inhibit the fibrinogen receptor on the platelet, which is the instrument of the final common pathway of platelet aggregation. Both monoclonal antibodies (abciximab) and non-anti-body compounds (tirofiban, eptifibatid and lamifiban) may achieve this inhibition. The agents severely prolong bleeding time. The monoclonal antibody achieves an irreversible binding to the receptor and the non-anti-body compounds a competitive one. After discontinuation of these intra-venous drugs the effects on platelets disappear within hours. They are indicated in interventional cardiology. In acute coronary syndrome without ST-elevation they show a reduction of myocardial infarction and death up to 25% compared to aspirin and heparin alone.²¹ Their beneficial effects are seen in both patients undergoing coronary interventions and in those without interventions. Also patients with acute coronary syndrome with ST-elevation undergoing primary balloon angioplasty benefit from routine abciximab.²² The rate of severe bleeding is acceptable. The agents are expensive (up to \$ 1,000 per treatment), which is prohibitive for routine use, and their cost-effectiveness over aspirin and heparin is not established yet. Oral glycoprotein IIb/IIIa blockers have a longer plasma half-life, but the results are disappointing with regard to efficacy and safety.²³

LONG-TERM TREATMENT

Antiplatelet therapy

Antiplatelet therapy in the form of aspirin should be continued forever. Whether clopidogrel on top of aspirin should be continued as well, depends on the results of more studies.

Anticoagulation

Continuation of low-molecular weight heparin after the acute phase has recently been studied in the large FRISC-2 trial and was found to be effective in the first 45 days. Thereafter the benefit seems to dissipate.²⁴ This strategy could be especially effective in patients awaiting revascularisation. Oral anticoagulation after acute coronary syndromes has begun to make a come-back. Combination with low-dose aspirin consistently results to better outcome provided the International Normalized Ratio (INR) is kept above 2.0.²⁵⁻³²

CONCLUSIONS

Antithrombotic treatment of acute coronary syndrome consists of aspirin, (low-molecular weight) heparin and clopidogrel. Intravenous, but not oral glycoprotein IIb/IIIa blockers on top of this may be used in high-risk individuals, especially when they undergo angioplasty. Fibrinolytic therapy is only indicated in acute coronary syndrome with ST-elevation, if primary angioplasty is not within short reach. Long-term protection consists of aspirin, possibly clopidogrel, as well anticoagulants, either given subcutaneously for a medium term or orally for the long-term.

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