quality. Most patients receive reperfusion therapy, oral antiplatelet agents, and anticoagulant therapy as appropriate. However, intravenous therapy with glycoprotein IIb/IIIa receptor blockers as well as \( \beta \)-blockers, statins and probably ACE inhibitors are underused. Furthermore, the coronary revascularization procedures are not used as often as recommended in recent guidelines. In particular, access to such procedures should be improved for patients initially treated in hospitals without facilities for invasive investigation and therapy.

Repeated surveys and ongoing registries indicate that adherence to guidelines does improve over time, and that this is associated with improved patient outcome (Fig. 1). Continuing surveys and registries are essential to reassess the quality of care at regular intervals. This may be greatly facilitated by integration of clinical data registration systems and data collection for national and international registries and surveys[3].

At this moment, the financial support for these surveys and registries comes from the European Society of Cardiology, a few national heart foundations and pharmaceutical and medical device industries. We should be grateful for this industrial support. But, this carries the risk that these studies may be limited to areas of significant industrial financial interest, including acute coronary syndromes, heart failure and preventive therapy. Independent support through health care providers, national health authorities and/or the European Union would be appropriate to ensure ongoing assessment of the quality of care in cardiology.

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References


Thrombin inhibitors in acute coronary artery disease

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Ischaemic heart disease is the most common cause of death worldwide. Following disruption of an atherosclerotic plaque, the de-endothelialized vascular surface is exposed to flowing blood. The coagulation system is activated, leading to thrombin generation. Thrombin generation is a powerful platelet agonist that contributes to platelet activation and recruitment, and catalyzes the formation of fibrin. This dynamic process of platelet–fibrin thrombus underlies the pathogenesis of the acute coronary syndromes. Therapies designed to interrupt this thrombotic process include antiplatelet and anticoagulant agents.

Unfractionated heparin remains a widely used anticoagulant, and is endorsed by the major treatment guidelines published on both sides of the Atlantic[1,2]. However, the antithrombin effects of unfractionated heparin are limited for numerous reasons: heparin inhibits thrombin indirectly (requiring an interaction with antithrombin III); unfractionated heparin is bound by circulating plasma proteins, resulting in unpredictable bioavailability and difficulties in maintenance of a stable therapeutic range; the residual thrombus contains active thrombin bound to fibrin, which is stoichiometrically poorly accessible to the large heparin–antithrombin III complex; the platelet rich arterial thrombus releases large amounts of platelet factor 4, which inhibits heparin; fibrin II monomer formed by the action of thrombin on fibrinogen may inhibit thrombin; heparin may cause immunologically mediated thrombocytopenia. Numerous clinical studies have described an increase in thrombotic events and coagulation markers following cessation of heparin infusion (‘rebound’). It is not altogether surprising therefore that the available (but underpowered) clinical trial data fail to provide conclusive evidence demonstrating benefit from the addition of unfractionated heparin in addition to aspirin.
Low molecular weight heparins offer a more specific anti-Xa effect (due to higher antifactor Xa activity/antifactor IIa activity ratio), decreased sensitivity to platelet factor 4, a more predictable anticoagulant response without the need for continuous monitoring, and less thrombocytopenia compared to unfractionated heparin\[3\]. Although all clinical trials evaluating low molecular weight heparins for treatment of acute coronary syndrome have shown equivalent or superior efficacy compared with unfractionated heparin, the low molecular weight heparins share some characteristics of unfractionated heparin: low molecular weight heparin depend on an interaction with antithrombin III, and are thus fundamentally still indirect thrombin inhibitors, and rebound following treatment cessation has been observed.

Direct thrombin inhibitors, such as hirudin, do not require a cofactor such as antithrombin III, inhibit clot bound thrombin, are not bound by plasma proteins and are not inhibited by platelet factor 4. Mega trials evaluating hirudin in patients with acute coronary syndrome have demonstrated dramatic short-term benefits compared to unfractionated heparin, but the benefit observed was not sustained over time. This consistent finding from the clinical trials was especially disappointing in lieu of the aforementioned theoretical advantages of hirudin over unfractionated heparin, and ex vivo data showing enhanced thrombus dissolution with hirudin, even when compared with very high doses of unfractionated heparin\[4\]. When the results of GUSTO IIb and TIMI 9B trials failed to show statistically significant difference between hirudin and heparin, the validity of the ‘thrombin hypothesis’ (stating that specific thrombin inhibition in patients with acute coronary syndromes would result in superior clinical outcomes) was challenged\[5\].

Several potential explanations have been suggested to account for the lack of superiority of hirudin compared with unfractionated heparin. In a substudy of GUSTO IIb, Kottke-Marchant and colleagues measured haemostatic markers during and after treatment with hirudin and heparin\[6\]. During drug treatment, hirudin was modestly more effective than unfractionated heparin in inhibiting thrombin activity, but neither heparin nor hirudin prevented thrombin generation. Following discontinuation of therapy with either agent, both thrombin generation and activity increased; however, treatment with hirudin resulted in slower increases in thrombin formation. Increases in thrombotic markers after drug discontinuation correlated to 30-day death and reinfarction. These findings are consistent with previous observations comparing the haemostatic effects of hirudin and heparin. Other potential explanations noted that the ability of hirudin to inhibit clot-bound thrombin is only 50% as potent as its ability to inhibit fluid-phase thrombin, which minimizes its potential advantage over unfractionated heparin. In addition, unfractionated heparin is a catalytic inhibitor of thrombin capable of dissociating from the antithrombin:thrombin complex, enabling a single molecule of unfractionated heparin to catalyze the action of multiple molecules of antithrombin. In contrast, hirudin binds tightly in a 1:1 stoichiometric fashion to thrombin in both the fluid phase and the clot-bound phase. It is potentially possible to ‘exhaust’ the supply of hirudin, permitting thrombin molecules to remain enzymatically active. However, increasing the concentration of hirudin to inhibit more thrombin appears to be associated with unacceptable bleeding rates.

Re-elevation of thrombotic markers after cessation of intravenous antithrombin therapy, as observed in this study, suggest an ongoing and clinically relevant prothrombotic state. Are these observations still relevant in the new millennium? Since GUSTO IIb was conducted in the mid 1990s, treatment of acute coronary syndrome has become more aggressive\[7\]. Restoration of brisk coronary artery blood flow, such as may be accomplished by intracoronary stent implantation, may alter the local rheology at the site of the disrupted plaque, and diminish the clinical consequences of haemostatic marker reactivation. The routine use of new pharmacologic agents in the management of patients with acute coronary syndrome may also blunt the clinical impact of the re-activation of the haemostatic markers. For example, in the GUSTO IIb substudy of Kottke-Marchant, platelet activation (as measured by platelet factor 4 levels) increased in both treatment groups after drug termination. In fact, PF-4 levels exceeded baseline levels (at least for unfractionated heparin-treated patients) by 24 h after treatment. However, more powerful inhibitors of platelets, such as platelet glycoprotein [GP] IIb/IIIa inhibitors administered during the acute hospital phase of acute coronary syndrome and during percutaneous coronary intervention\[8\], and adenosine diphosphate antagonists\[9\] administered during the chronic phase may also reduce the clinical consequences of re-elevation of the thrombotic markers. Ironically, although the direct antithrombins have never been shown to inhibit thrombin generation, GP IIb/IIIa antagonists, by interfering with the exposure of procoagulant phospholipids by the platelets, appear to inhibit thrombin generation\[10\].

Lepirudin (r-hirudin) is approved for use in patients with heparin induced thrombocytopenia, and bivalirudin has been approved for high risk coronary angioplasty patients. None of the direct thrombin inhibitors is currently indicated for routine use in acute coronary syndrome. However, recent publications demonstrating modest benefits of hirudin in the setting.
of percutaneous coronary intervention\cite{11}, and as an adjunct to fibrinolysis (with streptokinase only)\cite{12} validate continued interest in pursuing better thrombin inhibitors. Low molecular weight, active site thrombin inhibitors, (argatroban and melagotran) are currently approved (for HIT) or are in late stage clinical trials. In addition, new parenteral agents which block the coagulation cascade upstream of thrombin, by targeting Factor VII/tissue factor (tissue factor pathway inhibitor), Factor X (pentasaccharide and DX-9065a), or enhancing the Protein C pathway, all offer potential improvements in the therapeutic options for thrombin inhibition for patients with acute coronary disease. If clinical trials evaluate these novel compounds in conjunction with conventional treatments such as percutaneous coronary intervention, GP IIb/IIIa inhibitors and fibrinolytics, clinicians will be able to integrate these agents into current clinical practice. It is important to note that while clinical trials of the available antithrombins have thus far demonstrated important effects during the period of drug infusion, these effects are not consistently maintained following cessation of drug administration. The availability of an oral direct antithrombin permitting long-term antithrombin treatment would be of great benefit to the clinical cardiovascular community. Hence, the results of ongoing late-stage clinical trials studying the safety and efficacy of several oral antithrombins in a variety of clinical indications are awaited. Oral formulations may yield realistic opportunities for safe, chronic anticoagulation without the need for regular laboratory monitoring in patients at highest risk. Optimally, observations such as those in the study by Kottke-Marchant et al. will guide the clinical development of better thrombin inhibitors that will finally consign unfractionated heparin to the retirement it so richly deserves.

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\section*{References}
\begin{enumerate}
\item Antman EM. The search for replacements for unfractionated heparin. Circulation 2001; 103: 2310.
\end{enumerate}

\textbf{European Heart Journal} (2002) \textbf{23}, 1144–1146
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\textbf{Low molecular weight heparin: a bridge over troubled water}

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Coronary artery thrombosis plays a major role in the development and complications of coronary atheroma aggravated by plaque rupture. Patients presenting with ST-segment elevation have a markedly improved coronary artery patency, reduced infarct size and, thereby, early and long-term mortality\cite{11}. In patients without ST-segment elevation, antithrombotic therapy

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