EDITORIALS

Present and Future of Antithrombotic Therapy in Acute Coronary Syndromes

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Antithrombotic therapy in the management of an acute coronary syndrome is designed to inhibit both the coagulation cascade and platelet activation, thus preventing the development of the pathophysiological consequences of these processes. The main therapeutic approaches used for this purpose are unfractionated heparin, low-molecular-weight heparins, or direct antithrombins, all of them being molecules that interfere with the formation of a thrombin clot. Numerous clinical studies have investigated the advantages and disadvantages of each of these strategies and the benefits and risks of combined therapy with these drugs or their association with platelet inhibitors. The difficulty of establishing the relative benefits of different therapeutic approaches is due in part to the enormous number of possible combinations and the different clinical situations in which they can be used. In addition, the need for antithrombotic agents with a more specific inhibitor activity and a broader therapeutic range is motivating active investigation in laboratories worldwide. This has lead to the design of recombinant molecules and monoclonal antibodies that interrupt the activation of the coagulation cascade in several strategically important points. The relation between the clinical benefits obtained from this new generation of molecules and the increased health care costs generated by their design and development remains to be seen.

Key words: *Unfractionated heparin. Low-molecular-weight heparin. Antithrombins. IIb/IIIa inhibitors. Platelets. Tissue factor.*

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Presente y futuro del tratamiento antitrombótico en el síndrome coronario agudo

La terapia antitrombótica en el tratamiento del síndrome coronario agudo está dirigida a inhibir tanto la cascada de coagulación como la activación plaquetaria, y evitar de este modo el desarrollo de las consecuencias fisiopatológicas que se derivan de estos procesos. Los principales enfoques terapéuticos que se utilizan para este fin incluyen el uso de heparina no fraccionada, heparinas de bajo peso molecular o antitrombinas directas, moléculas todas ellas que interfieren en la formación del coágulo de trombina. Numerosos estudios clínicos han investigado las ventajas e inconvenientes de cada una de estas estrategias, así como los beneficios y riesgos que puede tener la terapia combinada de estos fármacos o su asociación con inhibidores plaquetarios. La dificultad para establecer los beneficios relativos de las diferentes aproximaciones terapéuticas se debe, en parte, al enorme número de combinaciones posibles y a las distintas situaciones clínicas en las que pueden utilizarse. Además, la necesidad de encontrar agentes antitrombóticos con una actividad inhibidora más específica y un rango terapéutico más amplio está promoviendo el desarrollo de una investigación activa en diversos laboratorios de todo el mundo, que ha conducido al diseño de moléculas recombinantes y anticuerpos monoclonales dirigidos a interrumpir la activación de la cascada de coagulación en diversos puntos estratégicos. Queda por probar cuál será la relación entre el beneficio clínico de las moléculas de nueva generación y el coste económico añadido a los gastos de atención sanitaria que se destine a su diseño y desarrollo.

Palabras clave: *Heparina no fraccionada. Heparina de bajo peso molecular. Antitrombinas. Inhibidores IIb/IIIa. Plaquetas. Factor tisular.*

INTRODUCTION

In acute coronary syndromes, monocyte tissue factor is exposed after rupture of a vulnerable plaque. This phenomenon activates the cascade of coagulation factors, which leads to the production of hundreds of thrombin molecules. Thrombin production has important pathophysiological consequences, not only because it participates in the formation of the fibrin clot but also
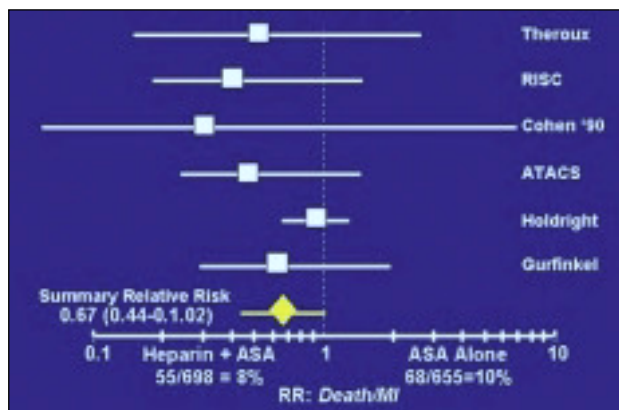
Fig. 1. Reduction of the main composite endpoint consisting of death/acute myocardial infarction in association with treatment with unfractionated heparin and aspirin, according to the results of various clinical trials. The overall reduction in relative risk found in a meta-analysis of the results of several studies is shown in yellow. (Taken from Oler A.[4])

because of its potent platelet-activation agonist effect. Activated platelets express the glycoprotein IIb/IIIa receptor on their surface and can form connections mediated by circulating fibrinogen molecules with other platelets. Antithrombotic therapy centers around interventions that inhibit both the coagulation cascade and activated and aggregated platelets. Evidence from the analysis of antithrombotic treatment in more than 200 000 patients has shown that, regardless of which antithrombotic therapy proves suitable for the management of acute coronary syndrome, aspirin must be a fundamental component of antithrombotic treatment.[1]

Four different approaches to the specific inhibition of the coagulation cascade have been developed: unfractionated heparin, low-molecular-weight heparins, direct antithrombins, and inhibitors of factor Xa. Unfractionated heparin acts as a scaffold that facilitates contact between the antithrombin molecule and the catalytic center of thrombin or factor IIa through a pentasaccharide sequence. This mechanism allows unfractionated heparin to increase the capacity of antithrombin to block the catalytic center of thrombin 700 to 1000-fold. Another therapeutic approach has been to develop a low-molecular-weight heparin by the digestion of glycosaminoglycans in the molecule. Low-molecular-weight heparins contain the pentasaccharide sequence but not the thirteen additional sugar residues needed to reach the binding domain of heparin. Consequently, low-molecular-weight heparins do not inhibit thrombin but they do inhibit factor IIa and are described in terms of their anti-Xa/anti-IIa ratio. Other approaches have inhibited more specific targets in the coagulation cascade. Thus, direct antithrombins bind simultaneously to the catalytic center and to the substrate recognition,

directly inhibiting thrombin. In addition, the pentasaccharide sequence has been shown to specifically inhibit factor Xa.

UNFRACTIONATED HEPARIN OR LOW-MOLECULAR-WEIGHT HEPARIN?

The use of unfractionated heparin has been investigated in several studies. Recently, the results of this therapy in several randomized trials[2] have been reported. In these trials, patients received unfractionated heparin in the context of acute myocardial infarction with elevation of the ST segment, both with and without aspirin administration. Unfractionated heparin significantly reduced the death rate, but this effect was attenuated, but still significant, when unfractionated heparin was given with aspirin. Unfractionated heparin also reduced the rate of re-infarction, although this effect was associated with a greater risk of hemorrhage. Unfractionated heparin has become a mainstay in the therapy of patients with acute myocardial infarction with ST-segment elevation. Due to the massive use of this drug, and to the administration of high doses, in 1999 the American College of Cardiology, American Heart Association, and European Society of Cardiology officially recommended the use of a lower dose of unfractionated heparin and consideration of the use of a dose adjusted to the patient´s weight. According to these recommendations, the initial bolus should be 60 U/kg and the initial infusion, 12 U/kg/h. A maximum bolus dose of 4000 U and infusion dose of 1000 U was recommended. These recommendations were based initially on observations and small studies. However, comparison of the results of the ASSENT-2 and ASSENT-3 studies in terms of the frequency of major in-hospital hemorrhage associated to treatment with the new thrombolytic agent TNK has confirmed the advantages of using lower doses of unfractionated heparin.[3]

The available evidence for recommending the use of unfractionated heparin in patients without ST-segment elevation is limited. At present, its use probably would not be approved if it were subject to the same requisites as those placed on new-generation molecules. In a meta-analysis in which the combination of unfractionated heparin with aspirin was investigated, a reduction of about 33% in the 30-day risk of death or myocardial infarction was demonstrated[4] (Figure 1). Therefore, it is recommended that an antithrombotic be administered in association with aspirin therapy in these patients.

Low-molecular-weight heparins have some advantages over unfractionated heparins. They have a greater ratio of anti-Xa/anti IIa activity, more bioavailability (thus allowing subcutaneous administration), a more reliable anticoagulant effect (which eliminates the need to measure aPTT), and they are not inhibited by

substances released by activated platelets, such as platelet factor 4. The low-molecular-weight heparins have been studied in many clinical trials that have included patients with acute myocardial infarction and ST-segment elevation. In these trials they have been used in two different ways: *a)* as a coadjuvant to the use of fibrinolytic agents; *b)* as stand-alone treatment without fibrinolytic agents. In general, what these studies have demonstrated is that low-molecular-weight heparins produce the same type of early angiographic patency as unfractionated heparin in angiography performed at 60 minutes or 90 minutes. Nevertheless, the probability that the artery involved in the infarction will be patent in 5 to 8 days is much greater if the patient is treated with a low-molecular-weight heparin than with an unfractionated heparin. In addition, the possibility of achieving resolution of the ST-segment deviation in the electrocardiogram is also greater with low-molecular-weight heparin.

The main evidence of these important advantages of low-molecular-weight heparin comes from the AS-SENT-3 trial, whose primary study endpoints were the incidence of death, re-infarction in the hospital, and refractory ischemia.[3] Patients were randomized to receive TNK in association with unfractionated heparin (group control) or TNK in association with either a low-molecular-weight heparin (enoxaparin) or abciximab. The patients in the control group had a significantly worse outcome than the other two groups. The results of this study are shown in Figure 2. It should be noted that one of the main problems of therapy with abciximab associated with a fibrinolytic agent is that, although lower doses of the fibrinolytic are used, there is a serious increase in the risk of hemorrhage, particularly in older patients.

We are currently conducting a major clinical trial, ExTRACT TIMI-25, in which approximately 21 000 patients with acute myocardial infarction and ST-segment elevation will be recruited worldwide. Persons seen in the first 6 hours after the appearance of symptoms will be candidates for treatment with fibrinolytic agents. The physician will be asked to select one of the following treatments: TNK, tPA, rPA, or SK. The patient will always receive aspirin and antithrombotic therapy (enoxaparin or an unfractionated heparin). The main study endpoints will be death and acute myocardial infarction in the first 30 days. It is expected that the results of this study will clarify whether or not enoxaparin should replace unfractionated heparin as antithrombotic therapy in patients undergoing fibrinolysis.

Four studies have analyzed the use of low-molecular-weight heparin in patients who do not present ST-segment elevation (Figure 3). The findings of these studies have shown no significant differences between treatment with dalteparin or nadroparin and unfractionated heparin. On the contrary, two different studies
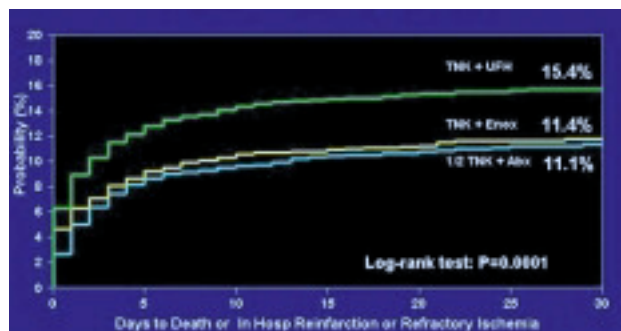

Fig. 2. Incidence of death, in-hospital re-infarction, or refractory ischemia in patients who received TNK associated with unfractionated heparin, enoxaparin, or abciximab, according to the findings of the AS-SENT-3 study. The worst outcome was observed in the group of patients treated with unfractionated heparin. (Taken from The Lancet.[3])
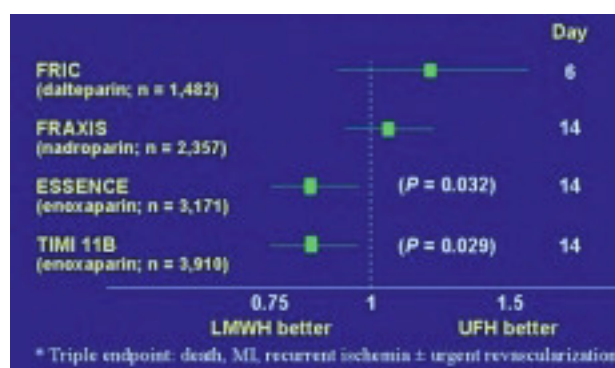

Fig. 3. Comparison of the protective effect associated with low-molecular-weight heparin versus unfractionated heparin treatment in four independent studies.

(the ESSENCE and TIMI-11B studies) have demonstrated that treatment with enoxaparin significantly reduces mortality, myocardial infarction, and recurrent ischemia in comparison with unfractionated heparin. Considered overall, these studies constitute a database of 7000 patients and solid evidence that enoxaparin treatment is associated with a 20% reduction in the risk of death or myocardial infarction.

After reviewing these results, the question that arises is what happens in the long-term follow-up of patients receiving enoxaparin compared to patients receiving unfractionated heparin? According to our results, the early benefit obtained with enoxaparin is maintained for up to 1 year.[5] The rates of death, acute myocardial infarction, and emergency revascularization were significantly lower in patients who had been previously treated with enoxaparin, and there was no loss of the benefit over time.

One of the main obstacles encountered when using low-molecular-weight heparins in the treatment of patients with acute coronary syndrome is the lack of knowledge about its use in the catheterization laboratory. In the NICE-1 study, intravenous enoxaparin was used in patients who did not receive glycoprotein

IIb/IIIa inhibitors. In the NICE-4 study, a lower dose of enoxaparin was given to patients who received abciximab in the catheterization laboratory. Finally, the NICE-3 study included patients who received one of the three glycoprotein IIb/IIIa inhibitors intravenously with enoxaparin subcutaneously. In every case, hemorrhage rates have been low. Therefore, the use of enoxaparin in the catheterization laboratory is a safe practice. In any case, definitive proof of the advantages of replacing unfractionated heparin with low-molecular-weight heparin in the catheterization laboratory will come from the results of the SYNERGY study, a controlled, randomized trial including about 8000 patients with unstable angina. A comparison will be made of the effect on the incidence of death or acute myocardial infarction in the first 30 days of treatment based on either unfractionated heparin or enoxaparin.

ADVANTAGES AND DISADVANTAGES OF DIRECT ANTITHROMBINS

A different concept in the clinical management of thrombolysis is based on the use of direct antithrombins, a therapeutic strategy that derives from elegant theoretical reasoning: these drugs have the potential to inhibit simultaneously both fibrin-bound thrombin and freely circulating thrombin. Although it is true that the direct antithrombins can exert their blocking action more effectively than the unfractionated heparins, these drugs have a very narrow therapeutic window and their use puts patients at a high risk for hemorrhage. The benefit of using a direct antithrombin administered in a single dose does not entail a major risk of hemorrhage, as shown by the meta-analysis made by the Direct Thrombin Inhibitors Trialist Group,[6] which compared therapy with direct antithrombins to unfractionated heparin. According to the results of this meta-analysis, there are no differences in the mortality rate, but there are when a composite endpoint consisting of death and myocardial infarction is considered. At the end of treatment (usually 3 days), a reduction of about 15% in the probability of death or myocardial infarction was observed in patients treated with direct antithrombin. Nevertheless, one of the most surprising findings associated with this therapy was a rebound effect that appeared as the blood concentration of direct antithrombin decreased, probably due to activation of the part of the coagulation cascade that was not inhibited. This rebound effect gives rise to thrombin formation. Therefore, direct antithrombins are valuable anticoagulants with a short-term benefit, but the effect of treatment tends to disappear with time.

The benefit of therapy with bivalirudin, a direct antithrombin, in patients with acute myocardial infarction and ST-segment elevation receiving streptokinase has been investigated in the HERO-2 trial.[7] The results of the study demonstrated that there were no differen-
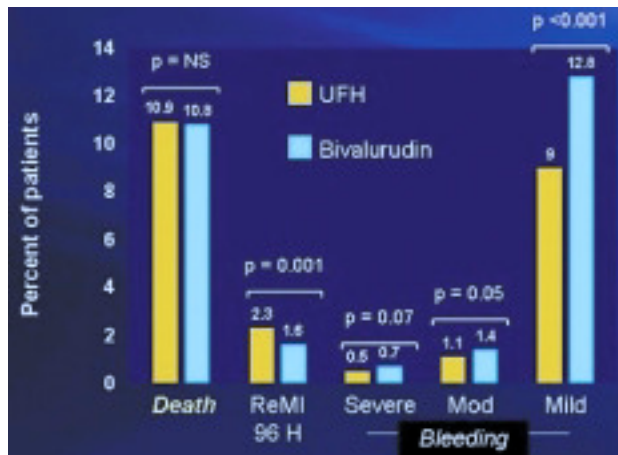

Fig. 4. Therapy with bivalirudin or unfractionated heparin in patients with acute myocardial infarction and elevation of the ST segment who received streptokinase. Although the mortality rate was the same in both groups, treatment with bivalirudin significantly reduced the incidence of recurrent infarction. (Taken from White H.[7])

ces in mortality when bivalirudin was compared with unfractionated heparin, but there was a significant reduction in recurrent myocardial infarction in the first 96 hours. A summary of these results is shown in Figure 4. It should be noted that the benefit was achieved at the expense of an increased risk of moderate and mild hemorrhage.

There is an interesting observation with respect to the use of bivalirudin in patients who undergo percutaneous coronary intervention. When the effect of this direct antithrombin is compared with that of heparin, a lower risk of hemorrhage associated with the intervention is observed, probably due to the short duration of the biological effect of this drug. The results of the REPLACE-2 study will tell us if bivalirudin should be used in percutaneous coronary interventions instead of glycoprotein IIb/IIIa inhibitors, or if the two drugs should be used in combination.

A summary of the advantages and disadvantages of each of the therapies discussed above is presented in the table, together with currently available evidence. In this context it should be emphasized that some aspects of antithrombotic therapy are still little known. For example, it is often overlooked that protamine can be used to neutralize low-molecular-weight heparin in exactly the same way that it is used for unfractionated heparin. Protamine neutralizes 100% of the anti-IIa activity and approximately a 60% of the anti-Xa activity of low-molecular-weight heparin. In contrast, there is no antidote for direct antithrombin, and the only way to counteract its effect is to interrupt the infusion and facilitate drug elimination.

NEW ANTITHROMBOTIC THERAPIES

Various pharmaceutical laboratories are developing

new molecules to inhibit coagulation more safely and effectively. For example, a company in Cambridge (Massachusetts) is attempting to separate the glycosaminoglycan sequences from unfractionated heparin and from the various fractions of low-molecular-weight heparin to isolate the specific sequences responsible for anti-IIa activity and anti-Xa activity and improve the molecular profile of the drugs of the heparin family.

Another approach has been to attack the tissue factor. There is a recombinant form available of the anticoagulant protein of a nematode, NAPc2, which directly inhibits the interaction between the tissue factor and factor VII-a, thus preventing the later activation of the lower part of the coagulation cascade.[8] Clinical trials have recently begun with NAPc2 to determine if it an attractive anticoagulant capable of replacing unfractionated heparin.

Other experimental approaches in the area of investigation into new antithrombotic molecules are being tested. Thus, for example, various pharmaceutical laboratories have worked to develop monoclonal antibodies designed specifically to block the tissue factor. The anti-tissue factor antibody acts by inhibiting the interaction of tissue factor with factor Xa of the coagulation cascade and impeding the activation of the rest of the factors involved in the chain of reactions that finally lead to clot formation. Some clinical trials are beginning to test the effectiveness of this experimental approach.

A different approach with an interesting clinical applicability is to interrupt the interaction between leukocytes and the endothelium through the CD11 and CD18 receptors. The blockade of the CD11 and CD18 receptors inhibits leukocyte migration through the arterial wall. However, contrary to expectations, the clinical data available to date have not demonstrated that this effect is beneficial in reducing infarction size in patients with ST-segment elevation. It remains to be seen if this therapeutic strategy can protect patients who do not have ST-segment elevation.

Warfarin is a molecule that has generated expectations due to its capacity to block different points in the coagulation cascade. Nevertheless, its long-term administration has drawbacks because it produces unpredictable rises and falls in the international normalized ratio. In order to resolve this limitation, an oral anticoagulant has been developed, ximelagratan, which is converted to its active form, melagratan, and acts as a direct antithrombin. A clinical study is being made to determine if this drug could be an alternative to warfarin.

The development of new molecules capable of inhibiting the coagulation cascade is linked to impressive advances in antiplatelet therapy. In this sense, the clinical studies that have investigated the protective role of clopidogrel in ischemic heart disease should be mentioned. The capacity of clopidogrel to inhibit the appearance of high-risk vascular episodes is small compared with aspirin (CAPRIE study[9]). However, the association of clopidogrel with aspirin in patients without ST-segment elevation (CURE study) produced a 20% reduction in the relative risk of the main composite endpoint of cardiovascular death, acute myocardial infarction, and cerebrovascular accident.[10] In addition, the PCI-CURE substudy demonstrated that the benefit of clopidogrel treatment is also observed in patients undergoing percutaneous coronary intervention who received the drug before intervention and continued the treatment in an open regimen.[11]

Figure 5 shows a diagram of the different therapeutic possibilities available for blocking the coagulation cascade. To these maneuvers must be added strategies that are being developed to inhibit platelet activation, which range from blocking cyclo-oxygenase with aspirin to blocking ADP receptors with clopidogrel or the specific inhibition of membrane glycoprotein IIb/IIIa. We still do not know which strategy is best or how the different possibilities should be combined. The design of clinical studies to analyze all the available options would involve more than fourteen factorial combinations. This is one of the main reasons why it is so difficult to establish the relative benefits of the association of antithrombotic drugs. In addition, it is

Table 1. **Advantages and disadvantages of treatment with unfractionated heparin, low-molecular-weight heparin, and direct antithrombins.**

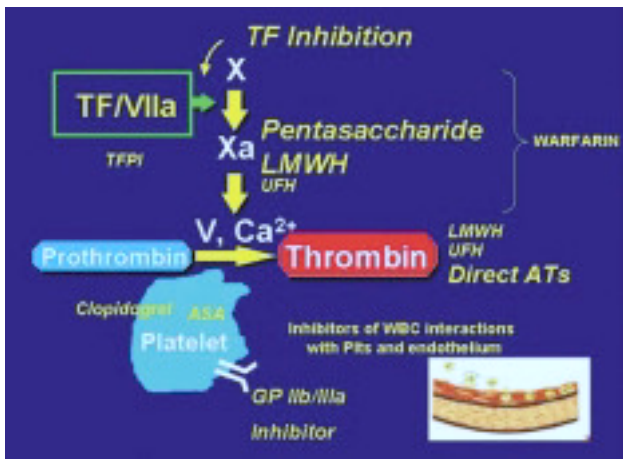|	UFH	LMWH	Direct AT
Administer Rx	IV	SC	IV
Check aPTT?	Yes	No	Yes
Convenient	No	Yes	No
Efficacy ws. UFH		> UFH*	Short term
Use with IIb/IIIa	Yes	Pending	Pending
Use in PCI	Yes	Pending	Limited data
Use in CABG	Yes	No data	Limited (HIT)
Use with lytic	Yes	Pending	Caution
Antidote	Yes	Partial	None

*In the case of enoxaparin.

Fig. 5. Diagram of various therapeutic options available for blocking the coagulation cascade or platelet activation.

necessary to consider that the design of new, more specific and safer recombinant molecules involves major expenses in addition to other health-care costs. The important advances that could derive from developing these molecules are a challenge to society, which must decide whether to increase even more its expenditures for health care in this important area of research.

REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
2. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997;336:847-60.
3. The Assessment of the safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605-13.
4. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996;276:811-5.
5. Antman EM, Cohen M, McCabe C, Goodman SG, Murphy SA, Braunwald E. Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE. Eur Heart J 2002;23:308-14.
6. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. Lancet 2002;359:294-302.
7. White H. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet 2001;358:1855-63.
8. Bergum PW, Cruikshank A, Maki SL, Kelly CR, Ruf W, Vlasuk GP. Role of zymogen and activated factor X as scaffolds for the inhibition of the blood coagulation factor VIIa-tissue factor complex by recombinant nematode anticoagulant protein c2. J Biol Chem 2001;276:10063-71.
9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.
10. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
11. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.