Fondaparinux: Pharmacology and Clinical Experience in Cardiovascular Medicine

V. Toschi* and M. Lettino

Department of Hematology and Transfusion Medicine, Ospedale San Carlo Borromeo, Milano, and Department of Cardiology, Fondazione Policlinico San Matteo - IRCCS, Pavia, Italy

Abstract: Fondaparinux is a synthetic, five-saccharide chain, AT-dependent, anti-FXa agent. Studies showed that fondaparinux acts in prevention and treatment of venous thromboembolism and in ischemic heart disease, without significant bleeding risk. The drug inhibits thrombin generation, has long half-life and can be administered once-daily without laboratory monitoring. It may be used in HIT treatment.

Key Words: Antithrombotic, factor Xa inhibitor, heparin, low molecular weight heparin, fondaparinux.

INTRODUCTION: MECHANISM OF ACTION OF HEPARIN

Heparin is a highly-sulfated glycosaminoglycan composed of alternating uronic acid and glucosamine units [1]. Since it was introduced in the clinical practice in 1937, however, it was demonstrated that heparin is not a chemically defined substance but it is a complex mixture of molecules differing in their chain length and in the fine structure of its monosaccharide units [2,3]. It was later clarified that heparin is an indirect anticoagulant which is able to inhibit the coagulation cascade by binding to the endogenous serine protease inhibitor antithrombin (AT) [3]. The binding of heparin to AT induces a conformational change in AT molecule which increases its inhibitory efficiency of a number of activated coagulation enzymes including factors Xa (FXa), IXa, XIa, and XIIa [4]. After the formation of the binding between the active coagulation enzyme and AT-heparin complex, heparin is immediately released thus allowing its binding to another AT molecule. It was subsequently demonstrated that binding of AT to its activated target factor is mediated by an AT-binding pentasaccharide present in heparin molecule, and that only 30-50% of heparin preparations, the so-called 'high affinity material', have this property [5]. Among activated coagulation factors, thrombin and FXa are the most responsive to inhibition by AT-heparin complex, thrombin being about 10-fold more sensitive than FXa [6,7], and FXa and thrombin inactivation is considered as the most important for the antithrombotic activity of heparin. Besides these mechanisms, heparin has other AT-independent antithrombotic actions such as thrombin inhibition by heparin's cofactor II (HCII) [8] and release of endogenous tissue factor pathway inhibitor (TFPI) from endothelial cells [9]. Heparin's biological actions other than those directly related to antithrombotic properties have also been described. Heparin may contribute to maintain vascular patency (profibrinolytic activity), to prevent atherosclerotic lesion development, to reduce tumor growth and dissemination (antiproliferative and antimetastatic action) and to inhibit inflammatory response (anti-inflammatory and antiadhesive properties) thus extending its therapeutic benefits to several areas of medicine [10].

LIMITATIONS OF UNFRACTIONATED HEPARIN (UFH)

Heparin is the cornerstone of anti-thrombotic treatment and it has been largely used in the therapy of both arterial and venous thromboembolism. However this agent has important limitations. It binds to several plasma proteins such as histidin-rich glycoprotein, vitronectin and fibronectin which are acute phase reactants and therefore exhibit important variations in their levels from one individual to another [11]. Heparin may also bind to platelet factor 4 (PF4) and von Willebrand factor released by platelets activated by thrombin and to high multimers of von Willebrand factor released by endothelial cells upon thrombin stimulation. For these reasons heparin activity may be significantly reduced at site of vascular injury in proximity of a fresh platelet-rich thrombus [12]. Heparin also binds to endothelial sites thus contributing to its poor bioavailability and to a rather unpredictable effect. The non-linear dose-response curve of UFH is the result of its nonspecific binding and of dose-dependent renal excretion: low doses are rapidly cleared while higher doses are cleared more slowly with large individual variations in response to a certain dose [13]. This implies that both its efficacy and safety are not considered optimal, and laboratory monitoring, by activated partial thromboplastin time (APTT), is still necessary to assess its anticoagulant efficacy and prevent bleeding complications. The poor bioavailability and the short half-life of UFH also have important consequences on the route of administration of the drug. Specifically, for treatment of venous thromboembolism (VTE) the drug must be administered by continuous intravenous infusion or twice or thrice daily sc injection. Binding of this polyanionic molecule to proteins and cells is also the cause of some important side effects of UFH. Binding of UFH to PF4 may generate a neoepitope which forms immune complexes with its specific antibodies. This immune mediated mechanism is the cause of heparin induced throm-

*Address correspondence to this author at the Department of Hematology, and Blood Transfusion, Ospedale San Carlo Borromeo, *Via* Pio II, 3 – 20153 Milano, Italy; Tel: +39 02 4022 2430; Fax: +39 02 7381216;
E-mail: vincenzo.toschi1@virgilio.it

1389-5575/07 $50.00+.00

bocytopenia (HIT), which is frequently complicated by severe venous and/or arterial thrombosis [14].

RELATIVE ADVANTAGES OF LOW MOLECULAR WEIGHT HEPARINS (LMWHs)

On the other hand, low-molecular-weight heparins (LMWH) have a less variable anticoagulant response due to their lower affinity to plasma proteins and consequently they do not necessitate laboratory monitoring to ensure their effectiveness [14]. Additionally, it was demonstrated that the shortening of heparin polysaccharide chain and the purification of low molecular weight heparin fractions were associated with reduced anti-IIa activity but unaltered anti-Xa action, did not prolong APTT and caused less bleeding tendency [15]. The reduced anti-IIa activity of LMWHs is the result of a different mechanism of action displayed by these molecules and is shown in Fig. (**1**). AT-mediated inactivation of FXa only requires binding of a short heparin residue containing a short pentasaccharide chain to AT, whereas for thrombin inhibition both binding to AT and to thrombin is necessary [16], which is only possible with molecules of a MW > 5.4 kDa, consisting of more than 17 monosaccharide units. LMWHs are presently produced by chemical means such as acid hydrolysis, radical oxidation or basic β-elimination or enzyme degradation of UFH by the different manufacturers. LMWH must have a MW < 8.0 kDa but a large heterogeneity in MW and chemical changes, such as different terminal residues of the molecules, desulfation and deacetylation, is present among the different preparations available for clinical use [17]. Each LMWH is therefore a distinct drug with specific biochemical and pharmacological properties [18] and therefore the different LMWHs cannot be used interchangeably, though the real existence of relevant therapeutic differences from one preparation to another is not yet known. However, LMWHs share many advantages over UFH: they have less nonspecific bindings [19], they less significantly interact with PF4 and therefore are less frequently associated with HIT [20], their bioavailability is almost complete after sc injection with a longer and dose-dependent half life, and their elimination is mainly due to renal excretion [20]. For all these reasons LMWHs have a more predictable dose-response relationship and once a day administration is sufficient for VTE prophylaxis. They are also recommended and extensively used in the therapy of deep vein thrombosis (DVT) and pulmonary embolism (PE).

LIMITATIONS OF UFH AND LMWH

Despite many pharmacological advantages of LMWHs some unsolved problems still exist with this class of drugs. In fact both UFH and LMWHs are natural substance from animal origin. Therefore any potential contamination with pathogens such as prions or porcine viruses cannot be ruled out. Specifically, the problem of spongiform encephalopathy (BSE) discouraged the use of bovine heparin in Europe and porcine heparin completely replaced the substance from bovine origin with possible future shortage in the supply of the material for UFH and LMWH production. Moreover, like all products from natural origin, a wide variation in the composition of the starting heparin material exist with difficulties in the standardization of the product for clinical use. Finally, heparin has important side effects such as HIT which is associated with severe thrombotic complications and is not completely abolished by the extensive introduction of LMWHs [14]. The limitations of this family of substances prompted in the last few years an intense research work on several classes of new antithrombotic agents, acting at different levels of thrombin-mediated thrombus formation, and many of them have been developed and already tested in phase II and III clinical trials.

THE DEVELOPMENT OF FONDAPARINUX AND ITS CLINICAL APPLICATIONS

The first step in fondaparinux development was the synthesis by Choay and coworkers in 1983 of the AT-binding pentasaccharide sequence present in the native heparin molecule [21]. Other oligosaccharides were subsequently synthe-

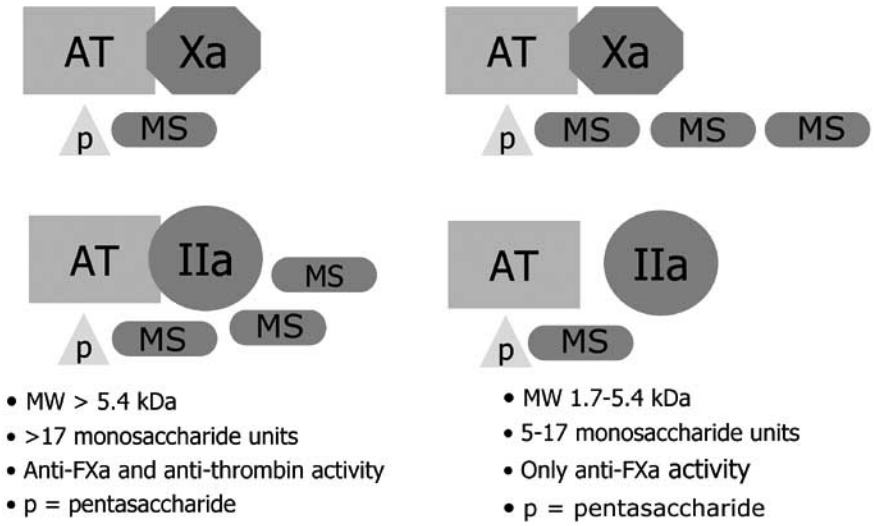

Fig. (1). Differences between the mechanism of AT-mediated inhibition of FXa and that of thrombin by heparins. Inactivation of FXa only requires binding of a short heparin residue containing a pentasaccharide chain to AT, whereas for thrombin inhibition both binding to AT and to thrombin is necessary, which is only possible with molecules of a MW > 5.4 kDa and consisting or more than 17 monosaccharide units.

sized and tested for their biological activity *in vitro* and finally the pentasaccharide SR90107A, later named fondaparinux, was produced in significant amount in 1988, Fig. (**2**). *In vivo* studies carried out in 1990s demonstrated that the drug was superior to UFH and LMWH in a rat model [22] both in term of high antithrombotic efficacy and low bleeding tendency. These preliminary results forced investigators to test the drug in phase II clinical trials [23] and later on in a large scale phase III program [24-28]. Large scale phase III clinical trials were started to evaluate the efficacy and safety of fondaparinux in high-risk orthopedic surgery in > 7,300 patients [24-28]. Specifically, these studies tested the drug in hip replacement surgery, hip fracture and major knee surgery and unequivocally demonstrated that fondaparinux was superior to LMWHs in the prevention of VTE in these settings. Moreover, recent large scale, prospective, randomized experience indicates that the selective factor Xa inhibitor fondaparinux, administered 6 to 8 hours after surgery, does not increase the risk of epidural hematoma in orthopedic surgery when used in combination with neuroaxial anesthesia [29,30] thus suggesting that fondaparinux may be the drug of choice in these patients. After publication of the results of these studies the drug was approved by FDA in 2001 and by EMEA in 2002 for the prevention of VTE in patients undergoing major orthopedic surgery of the lower limbs. The effectiveness of fondaparinux for the prevention of VTE in high-risk abdominal surgery and in older acute medical patients was subsequently assessed in the PEGASUS and ARTEMIS studies respectively. In PEGASUS study postoperative fondaparinux proved at least as effective as perioperative dalteparin in the prevention of VTE [31], whereas data from ARTEMIS clearly demonstrated that fondaparinux significantly reduced the risk of symptomatic and asymptomatic VTE in older patients with a series of acute medical conditions including congestive heart failure, acute respiratory illness in the presence of chronic lung disease and other acute infections or inflammatory diseases, compared to placebo [32]. The incidence of major bleeding was also similar in the two groups. Two large scale, randomized, phase III studies on fondaparinux in the treatment of VTE were carried out in the MATISSE studies in patients with symptomatic DVT and in patients with symptomatic, hemodynamically stable acute PE respectively. Of 1098 patients with DVT randomly assigned to fondaparinux, 3.9% had recurrent thromboembolic events compared with 4.1% of 1107 assigned to enoxaparin [33]. Similarly, of 1103 patients with PE randomly assigned to fondaparinux 3.8% had recurrent VTE as compared to 5.0% of the 1110 assigned to receive UFH [34]. No differences in major bleeding were observed in the two groups, thus demonstrating that once daily fondaparinux was as effective and safe than twice daily, body weight-adjusted enoxaparin or continuous intravenous infusion UFH in the treatment of subjects with symptomatic VTE. Fondaparinux was also tested in acute coronary syndromes (ACS). In the PENTUA study the rate of composite endpoint of death, myocardial infarction (MI) and recurrent ischemia was significantly lower in patients with unstable angina (UA) or non-Q wave MI assigned to fondaparinux 2.5 mg once daily than in those treated with enoxaparin or higher fondaparinux doses, without any difference in bleeding complications [35]. A recently published international, randomized, double blind trial comparing the efficacy and safety of fondaparinux *vs*. enoxaparin in > 20,000 patient with UA or non-ST segment elevation MI (STEMI) (OASIS-5) demonstrated that fondaparinux is equally effective as enoxaparin in reducing the risk of ischemic events at nine days but was associated with less major bleeding and improves long term mortality [36]. Fondaparinux was also well tolerated and as effective as UFH in maintaining arterial patency in the dose-ranging PENTALYSE study carried out in patients with STEMI treated with altplase [37]. Finally, OASIS-6 study showed that fondaparinux reduces mortality and reinfarction without increasing bleeding and stroke compared with UFH in > 12,000 patients with STEMI [38]. These results suggest that fondaparinux may be at least as effective as heparin in prevention and treatment of both venous and arterial thrombosis and may improve and simplify antithrombotic therapy of a broad range of medical and surgical conditions.

FONDAPARINUX: MECHANISM OF ACTION

Fondaparinux is the first of a new class of synthetic antithrombotic agents inhibiting FXa. It is a fully synthetically produced pentasaccharide, which specifically binds to AT with high affinity and by this mechanism specifically inhibits FXa [39]. Fondaparinux non-covalently binds to a specific arginine-rich domain of AT thus inducing a conformational change in the serpin molecule. This results in about 340-fold acceleration of complex formation with FXa. After covalent binding formation of AT with FXa, fondaparinux is released

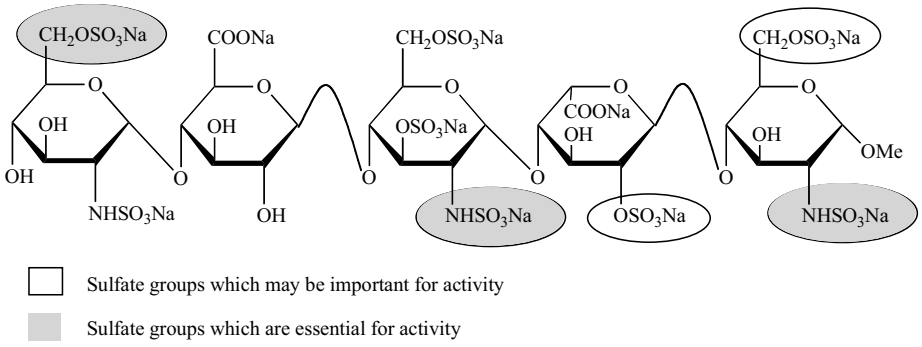

Fig. (2). Chemical structure of fondaparinux. Sulfate groups are essential or important for activity (adapted from Alban S. [39]).

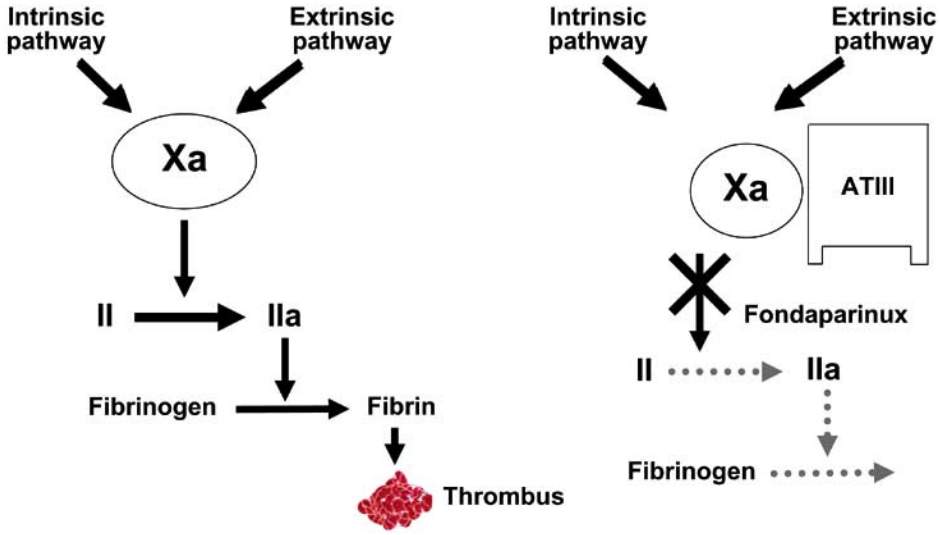

Fig. (3). Mechanism of action of fondaparinux in inhibiting thrombin formation. Fondaparinux non-covalently binds to a specific arginine-rich domain of AT thus inducing a conformational change in the serpin molecule. This results in an about 340-fold acceleration in complex formation with FXa. Inhibition of FXa, which is the first factor involved in the so called 'common pathway' of activation of the coagulation cascade both through the 'extrinsic' and 'intrinsic' pathways, effectively reduces thrombin generation without direct affecting thrombin function.

and therefore it is available for catalyzing further AT-FXa complex formation. Inhibition of FXa, which is the first factor involved in the so-called 'common pathway' of activation of the coagulation cascade both through the 'extrinsic' and 'intrinsic' pathways, effectively reduces thrombin generation without directly affecting thrombin function [40], Fig. (**3**).

PHARMACOKINETICS OF FONDAPARINUX

The drug administered subcutaneously is completely, rapidly and dose-independently absorbed, with a $C_{max}/2$ reached in 25 min and a C_{max} after 2 hrs, whereas LMWHs need about twice as long. The rapid rise in plasma levels is subsequently followed by a slow reduction with a half-life of approximately 17 hrs, in contrast to LMWHs which exhibit a half-life of about 3-5 hrs. These features allow once-a-day administration, rapid onset of action, predictable duration of activity and have no need of dose adjustment or laboratory monitoring. At once daily administration of 2.5 mg, peak steady-state plasma levels of 0.39-0.50 μg/mL are reached after 3-4 days. Experimental studies demonstrate a linear dose-dependent inhibition in thrombin generation and thrombus growth in human platelet-depleted plasma *ex-vivo* [40]. Fondaparinux does not significantly bind to plasma proteins and therefore its interaction with other drugs through competing protein binding is negligible. The drug has no influence on CY450 enzymes and therefore another possible mechanism of drug interaction is not clinically relevant. Fondaparinux is mostly eliminated by the kidney as an unchanged molecule and therefore it has to be considered that in patients with renal insufficiency, and in patients aged > 75 years the half-life increases to about 21 h. In patient with severe renal impairment (creatinine clearance 20-30 mL/min) a reduced dose of 1.5 mg is recommended, whereas for values < 20 mL/min the use of fondaparinux is contraindicated [41]. However, altogether the drug shows linear pharmacokinetic profile with little inter- and intrasubject variability. It can be safely used once-daily, as fixed dose sc administration in all the indications mentioned in previous chapters, without need of routine laboratory monitoring.

CONCLUSIONS

Fondaparinux is the first of a new class of synthetic antithrombotic agents inhibiting FXa. The drug exhibits several important advantages over both unfractionated and low molecular weight heparins (LMWHs) and it is functionally more potent than its native pentasaccharide counterpart. Fondaparinux is a fully synthetically produced substance and thanks to this feature it does not have any potential risk of contamination and batch-to-batch variability. Moreover, it is a structurally defined chemical entity and does not have the problem of standardization of anti-Xa activity which is found in LMWHs and may cause the need of dose adjustment. Finally, fondaparinux does not interact with acute phase or other plasma proteins, and does not form neoepitopes with PF4. Consequently, fondaparinux does not cross-react with antibodies associated to heparin-induced thrombocytopenia (HIT) [42]. Preliminary data support the use of fondaparinux for thromboembolic treatment or prophylaxis in patients with antibody assay-confirmed HIT who do not have a contraindication for fondaparinux use [43]. However, randomized controlled trials are needed to elucidate the efficacy, safety, optimal doses, treatment duration, and incidence of thromboembolic events when fondaparinux is used in this setting.

REFERENCES

[1] Jorpes, E. *Biochem. J.,* **1935***, 29,* 1817.
[2] Crafoord, C. *Acta Chir. Scand*., **1937***, 79,* 407.
[3] Rosemberg, R.D.; Damus, P.S. *J. Biol. Chem.,* **1937***, 24,* 6490.
[4] Björk, I.; Olson S.T.; Shore, J.D. In *Heparin, Chemical and Biological Properties; Clinical Applications,* Lane, D.A.; Lindahl, U. Eds.; CRC Press: Boca Raton, Fl, **1989**; pp. 229-56.
[5] Beguin, S.; Welzel, D.; Al Dieri, R.; Hemker, H.C. *Haemostasis* **1999***, 29,* 170.
[6] Rosemberg, R.D.; Bauer, K.A. In *Hemostasis and Thrombosis: Basic Principle and Clinical Practice;* Colman, R.W.; Hirsh, J.;

Marder, V.J.; Salzman E.W. Eds.; J.B. Lippincott: Philadelphia, PA, **1994**; pp. 837-60.
[7] Ofosu, F.A. In *Heparin, Chemical and Biological Properties: Clinical Applications;* Lane, D.A.; Lindahl, U. Eds.; CRC Press: Boca Raton, Fl, **1989**; pp. 433-54.
[8] Tollefsen, D.M.; Majerus, D.W., Blank, M.K. *J. Biol. Chem.,* **1982**, *257,* 2162.
[9] Abildgaard, U. *Haemostasis,* **1999**, *23*(Suppl. 1),103.
[10] Linhardt, R.J.; Toida, T. In *Carbohydrates in Drug Design*; Witczak, Z.J.; Nieforth, K.A. Eds.; Marcel Dekker: New York, **1997**; pp. 277-341.
[11] Hirsh, J.; Warkentin, T.E.; Shaughnessy, S.G.; Anand, S.S.; Halperin, J.L.; Raschke, R.; Granger, C.; Ohman, E.M.; Dalen, J.E. *Chest,* **2001**, *119*(Suppl. 1), 64S.
[12] Weitz, J.; Crowther, M. *Thromb. Res.,* **2002**, *106,* V275.
[13] Boneu, B. *Thromb. Res.,* **2000**, *100,* V113.
[14] Lettino, M.; Toschi, V. *Curr. Med. Chem.,* **2004**, *2,* 267.
[15] Andersson, L.O.; Barrowcliffe, T.W.; Holmer, E.; Johnson, E.A.; Sims, G.E. *Thromb. Res.,* **1976**, *9,* 575.
[16] Olson; S.T.; Björk, I.; Sheffer, R.; Craig, P.A.; Shore, J.D.; Choay, J. *J. Biol. Chem.,* **1992**, *276,* 12528.
[17] Alban, S. In *Carbohydrates in Drug Design*; Witczak, Z.J.; Nieforth, K.A. Eds.; Marcel Dekker: New York, **1997**; pp. 209-76.
[18] Alban, S.; Gastpar, R. *Thromb. Haemost*., **2001**, *85,* 824.
[19] Weitz, J.L. *N. Engl. J. Med.,* **1997**, *337,* 688.
[20] Warkentin, T.E.; Levine, M.N.; Hirsh, J.; Horsewood, P.; Roberts, R.S.; Gent, M.; Kelton J.G. *N. Engl. J. Med.,* **1995**, *332,* 1330.
[21] Choay, J.; Petitou, M.; Lormeau, J.C.; Sinay, P.; Casu, B.; Gatti, G. *Biochem. Biophys. Res. Commun.,* **1983**, *116,* 492.
[22] Garon, J.E. *Clin. Leadersh. Manag. Rev.,* **2003**, *17,* 47.
[23] Turpie, A.G.; Gallus, A.S.; Hoek, J.A. *N. Engl. J. Med.,* **2001**, *345,* 1298.
[24] Eriksson, B.I.; Bauer, K.A.; Lassen, M.R.; Turpie, A.G. *N. Engl. J. Med.,* **2001**, *345,* 1298.
[25] Bauer, K.A.; Eriksson, B.I.; Lassen, M.R.; Turpie, A.G. *N. Engl. J. Med.,* **2001**, *345,* 1305.
[26] Lassen, M.R.; Bauer, K.A.; Eriksson, B.I.; Turpie, A.G. *Lancet,* **2002**, *359,* 1715.
[27] Turpie, A.G.; Bauer, K.A.; Eriksson, B.I.; Lassen, M.R. *Lancet,* **2002**, *359,* 1721.
[28] Turpie, A.G.; Bauer, K.A.; Eriksson, B.I.; Lassen, M.R. *Arch. Intern. Med.,* **2002**, *162,* 1833.
[29] Agnelli, G.; Bergqvist, D.: Cohen, A.T.; Gallus, A.S.; Gent, M. PEGASUS Investigators. *Br. J. Surg.,* **2005**, *92,* 1212.
[30] Cohen, A.T.; Davidson, B.L.; Gallus, A.S.; Lassen, M.R.; Prins, M.H.; Tomkowski, W.; Turpie, A.G.; Eqberts, J.F.; Lensing, A.W. ARTEMIS Investigators. *BMJ,* **2006**, *332,* 325.
[31] Buller, H.R.; Davidson, B.L.; Decousus, H.; Gallus, A.; Gent, M.; Piovella, F.; Prins, M.H.; Raskob, G.; Segers, A.E.; Cariou, R.; Leeuwenkamp, O.; Lensing, A.W. Matisse Investigators. *Ann. Inter. Med.,* **2004**, *140,* 867.
[32] Buller, H.R.; Davidson, B.L.; Decousus, H.; Gallus, A.; Gent, M.; Piovella, F.; Prins, M.H.; Raskob, G.; van den Berg-Segers, A.E.; Cariou, R.; Leeuwenkamp, O.; Lensing, A.W. Matisse Investigators. *N. Engl. J. Med.,* **2003**, *349,* 1695.
[33] Simoons, M.L.; Bobbink, I.W.; Boland, J.; Gardien, M.; Klootwijk, P.; Lensing, A.W.; Luzyllo, W.; Umans, V.A.W.M.; Vahanian, A.; Van De Werf, F.; Zeymer, U. PENTUA Investigators. *J. Am. Coll. Cardiol.,* **2004**, *43,* 2183.
[34] Cannavo, D. *Am. J. Orthop.,* **2002**, *31*(Suppl. 11), 21.
[35] Colwell, C.W. Jr; Kwong, L.M.; Turpie, A.G.; Davidson, B.L. *J. Arthroplasty,* **2006**, *21,* 36.
[36] Yusuf, S.; Metha, S.R.; Chrolavicius, S.; Afzal, R.; Pogue, J.; Granger, C.B.; Budaj, A.; Peters, R.J.G.; Bassand, J.-P.; Wallentin, L.; Joyner, C.; Fox, K.A.A. Fifth Organization to Assess Strategies in Acute Ischemic Syndrome Investigators. *N. Engl. J. Med.,* **2006**, *354,* 1524.
[37] Coussement, P.K.; Bassand, J.P.; Convens, C.; Vrolix, M.; Boland, J.; Grollier, G.; Michels, R.; Vahanian, A.; Vanderheyden, M.; Rupprecht, H.-J.; Van De Werf, F. PENTALYSE Investigators. *Eur. Heart. J.,* **2001**, *22,* 1716.
[38] Yusuf, S.; Metha, S.R.; Chrolavicius, S.; Afzal, R.; Pogue, J.; Granger, C.B.; Budaj, A.; Peters, R.J.G.; Bassand, J.-P.; Wallentin, L.; Joyner, C.; Fox, K.A.A. OASIS-6 Trial Group. *JAMA,* **2006**, *295,* 1519.
[39] Bauer, K.A.; Hawkins, D.W.; Peters, P.C.; Petitou, M.; Herbert, J.M.; Van Boeckel, C.A.; Meuleman, D.G. *Cardiovasc. Drug. Rev.,* **2002**, *20,* 37.
[40] Lormeau, J.C.; Herault, J.P. *Thromb. Haemost.,* **1995**, *74,* 1474.
[41] Alban, S. *Eur. J. Clin. Invest.,* **2005**, *35*(Suppl. 1), 12.
[42] Amiral, J.; Lormeau, J.C.; Marfaing-Koka, A.; Vissac, A.M.; Wolf, M.; Boyer-Neumann, C.; Tardy, B.; Herbert, J.M.; Meyer, D. *Blood Coagul. Fibrinolysis,* **1997**, *8,* 114.
[43] Efird, L.E.; Kockler, D.R. *Ann. Pharmacother.,* **2006**, *40,*1383.

Received: 04 July, 2006 **Revised: 07 August, 2006** **Accepted: 08 August, 2006**