

New Aspects of the Blood Coagulation Cascade, Anticoagulants and Vein Thrombosis in Asia

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Abstract

Purpose: This review describes recent views on blood coagulation and abnormalities of its physiological control that predispose to thrombosis, suggests that venous thrombosis and pulmonary embolism are more prevalent in Asia than was previously thought, and examines recent trials of novel anticoagulants for thrombosis prevention. **Sources:** 'Medline' was used to search for publications in English or with English language abstracts. **Content and Conclusions:** The study of blood coagulation is basic to understanding clotting and bleeding disorders, their prevention and treatment. Tissue factor, factor Xa, and thrombin are pivotal; together with physiological controls (positive and negative feedback loops, and natural anticoagulants) that first enhance thrombin generation but then preserve vessel patency by limiting haemostatic plug formation to areas of injury. Abnormalities in these mechanisms can increase thrombosis risk (thrombophilia). The traditional impression that venous thromboembolism is rare in Asia has been reinforced by the rarity of thrombophilic genetic polymorphisms outside of European populations. Nevertheless, there is increasing evidence for an increasing prevalence of symptomatic vein thrombosis and pulmonary embolism in Asia, and that thrombosis rates in 'high risk' clinical settings among elderly patients (as after major joint surgery or a stroke) now approach levels reported from the West. This indicates the need for greater clinical awareness of these conditions. Drugs now used routinely for thrombosis prevention in the West (especially low molecular weight heparins) are effective and relatively safe. New anticoagulants were even more effective in recent trials. There is urgent need for studies in Asia that define the locally relevant benefits and hazards of the increasing range of agents now available.

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Haemostasis and its Control Mechanisms

Injury to blood vessels triggers haemostasis, a process that has evolved to achieve two superficially incompatible outcomes: arresting blood loss while protecting vessel patency and blood flow to distal organs. Contributors to haemostasis include subendothelial tissues and endothelial cells, blood platelets, tissue factor, plasma clotting factors and their physiological inhibitors, and fibrinolytic enzymes.

Almost all bleeding disorders are caused by deficiency or dysfunction, inherited or acquired, of blood clotting factors or platelets. Inherited disorders are uncommon but require life-long care. Their study has led to detailed understanding of the genetics, amino acid sequence, tertiary structure, and function of the plasma blood clotting factors¹: well-known examples include the haemophilias (caused by factor VIII

or factor IX deficiency) and von Willebrand's disease. Two rare inherited platelet function disorders (Bernard-Soulier disease and Thrombasthenia) triggered research that defined platelet surface receptors responsible for binding collagen, fibrinogen, and von Willebrand factor during platelet adhesion and activation (GPIb/IX/V, GPIIb/IIIa and others). Acquired defects caused by liver failure, vitamin K deficiency, septic shock, obstetric complications or disseminated cancer are however, far more frequent and are therefore more important to the generalist.

A classic model of the blood clotting cascade gave equal importance to an 'intrinsic' pathway triggered by exposing 'contact factors' (XII and XI) to negatively charged subendothelial surfaces and an 'extrinsic' pathway initiated by tissue factor, where each converged on factor X (Fig. 1a). The presently favoured model (Fig. 1b) emphasises

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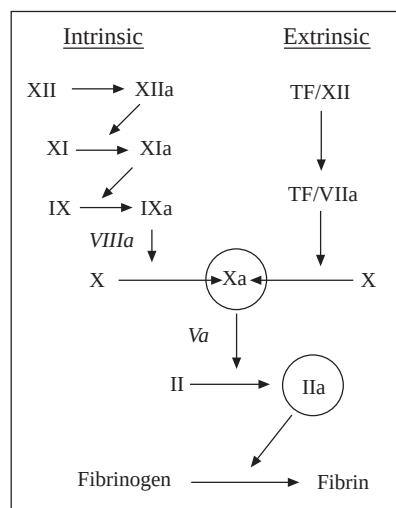


Fig. 1a. The classical description of distinct 'Intrinsic' contact activated and 'Extrinsic' tissue factor initiated clotting pathways, both of which converge at factor Xa.

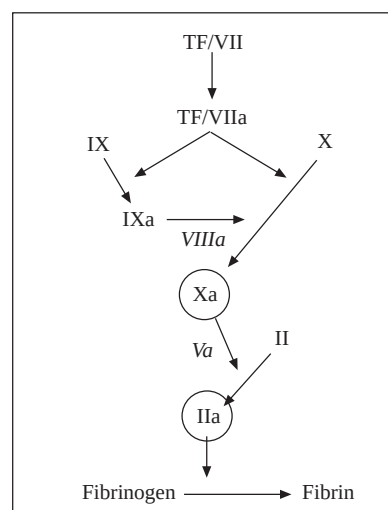


Fig. 1b. The presently favoured model where the tissue factor - factor VIIa complex activates factor X directly or by converting factor IX to IXa, and where 'Intrinsic' contact activation is considered to be relatively unimportant.

cells and cell surface-associated processes and the dominant influence of tissue factor.

Initiating Haemostasis

Platelets

Following vessel injury, platelets adhere to exposed subendothelial tissues, become stimulated, and undergo release and aggregation. Platelet activating stimuli include adherence, trace amounts of thrombin, platelet metabolites (thromboxane A₂), and released platelet products (adenosine diphosphate, serotonin).

Cells, Tissue Factor and Blood Coagulation

Tissue factor is a glycoprotein tightly associated with phospholipid within the membrane of cells in the vessel adventitia that become exposed to flowing blood only after vessel injury strips away their protecting layer of endothelium.¹ It can also be induced in vascular endothelial cells and blood monocytes by endotoxin and other stimulants.¹ The complex of tissue factor with factor VII/VIIa can initiate blood coagulation by activating factor X directly or indirectly, after converting factor IX to factor IXa. These and other linked interactions that convert previously inactive plasma proteins (pro-enzymes) to active enzymes (activated clotting factors) require cofactors (blood clotting factors V and VIII), ionised calcium, and an active phospholipid surface provided by activated platelets (Fig. 1b). In the end, prothrombin is converted to thrombin, soluble fibrinogen becomes insoluble fibrin, and a fibrin network enmeshes platelet aggregates with red blood cells and white blood cells to form a haemostatic plug that seals the area of blood vessel injury.

Control Mechanisms

These ensure the haemostatic system remains inactive at rest but responds quickly to vessel injury, and that haemostatic plugs do not progress to vessel occlusion but are restricted to areas of injury. Control is applied through positive and negative feedback loops that modulate the rate and duration of thrombin generation, by mechanisms that neutralise activated blood clotting factors, and by thrombolysis. The components include natural anticoagulants (protein C, protein S and antithrombin) and protective elements of the endothelial cell surface. Deficiency or dysfunction of control mechanisms may predispose to thrombosis (thrombophilia).

Positive Feedback Loops

Trace amounts of activated clotting factor X (factor Xa) and thrombin (factor IIa) greatly accelerate further thrombin generation by converting factor VII to VIIa (either free or bound to tissue factor) and through proteolytic activation of two large cofactors (factor VIII to VIIIa and factor V to Va) (Fig. 2). Thrombin also triggers further platelet activation, release and aggregation.

Negative Feedback Loops and the Endothelium

The most important negative feedback mechanism involves thrombomodulin (an endothelial cell surface receptor), thrombin, and two vitamin K dependent plasma proteins: protein C and protein S (Fig. 3).² Complex formation between thrombin and thrombomodulin has two outcomes³: thrombin becomes inactive towards platelets or fibrinogen, and the thrombin-thrombomodulin complex rapidly activates protein C to generate an enzyme

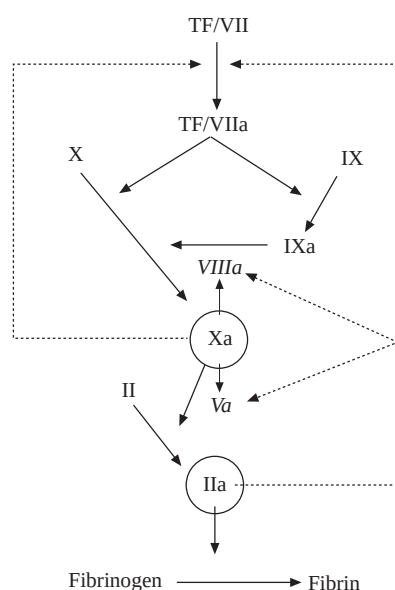


Fig. 2. Positive feedback loops where factor Xa and trace amounts of thrombin greatly increase the capacity for further thrombin generation. Dotted arrows indicate the activation pathways.

(activated protein C) which requires protein S as its cofactor to cleave susceptible sites on factor VIIIa and factor Va and curtail further generation of factors Xa and IIa.

Blood Clotting Factor Inhibition and Endothelial Cells

Antithrombin (previously called antithrombin III), a circulating general purpose serine protease inhibitor with a molecular weight of 58 kilodalton and plasma concentration of about 140 µg/mL, forms covalent complexes with clotting factors XIa, IXa, Xa and IIa (all are enzymes from the serine protease family) that are inactive and cleared by the liver. Complex formation is greatly accelerated by heparan sulphates on the endothelial cell surface. These heavily sulphated heparin-like polysaccharide chains induce a conformational change in antithrombin that greatly increases its affinity for serine proteases.⁴

Other Endothelial Cell Defences

Endothelial cells have at least two other defences to restrict extension of haemostatic plugs onto undamaged areas of vessel wall. Stimuli that cause platelets to generate and release thromboxane A₂ (a powerful vasoconstrictor and platelet pro-aggregant) also cause endothelial cells to generate prostacyclin (another prostaglandin derivative that is a powerful vasodilator and anti-aggregant). And local hypoxia from overlying thrombus deposition causes endothelial cells to release tissue plasminogen activator and initiate physiological fibrinolysis.

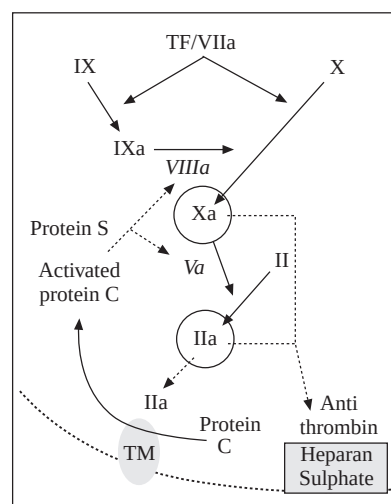


Fig. 3. Natural anticoagulants and haemostasis. Complex formation between thrombin and thrombomodulin, an endothelial cell surface protein, neutralises thrombin and activates protein C. Activated protein C (with protein S as cofactor) proteolytically degrades factors Va and VIIIa to reduce thrombin generation. The endothelial cell surface (coarse dotted line) also carries heparan sulphate, a heparin-like material that greatly accelerates factor Xa and thrombin inhibition by plasma antithrombin.

Inherited Abnormalities of Control Mechanisms

Important inherited abnormalities include deficiency or dysfunction of antithrombin, protein C, and protein S—all of which have a worldwide distribution and are associated with familial venous thrombosis and pulmonary embolism, idiopathic or recurrent venous thromboembolism at an early age, and vein thrombosis in unusual locations (mesenteric, axillary, cerebral). These deficiencies and polymorphisms (with rarely reported exceptions) do not predispose to artery occlusion.⁵ Inheritance is autosomal recessive for protein C and dominant for protein S and antithrombin abnormalities.⁶

Two thrombogenic genetic polymorphisms that affect factor V and factor II are common in European and related populations but are rare or absent elsewhere.⁶ In factor V Leiden, a point mutation (G1691A) found in 4% to 7% of Europeans substitutes Arg506 for Gln at the cleavage site for activated protein C. Thrombin generation is greater and lasts longer than usual because the abnormal factor V resists degradation by activated protein C (APC resistance). A prothrombin mutation (G20210A) affects 1% to 3% of European populations and causes a roughly 20% increase in the circulating level of plasma prothrombin. These polymorphisms are weak predispositions for venous thromboembolism when they act alone but gain importance when other risk factors are co-inherited or superimposed (including treatment with oestrogen-containing oral contraceptives).⁷ Their prevalence can reach 30% to 60% in Europeans with otherwise idiopathic or recurrent venous thrombosis.

Other Thrombophilias

Hyperhomocysteinaemia – or elevated levels of homocysteine, an endothelial poison – is increasingly recognised as risk factor for both venous and artery thrombosis.^{8,9} Hyperhomocysteinaemia can result from various genetic disorders which affect the trans-sulphuration or remethylation pathways of homocysteine metabolism e.g. cystathione beta synthase deficiency, methylene-tetrahydrofolate reductase (MTHFR) deficiency and a thermolabile variant of MTHFR. Acquired causes of hyperhomocysteinaemia include folate or vitamin B12 deficiency, renal failure, hypothyroidism and drugs such as methotrexate and phenytoin.

Antiphospholipid antibodies (anticardiolipin antibody and the ‘lupus anticoagulant’) are associated with an increased risk of venous or artery occlusion in systemic lupus erythematosus, and the antiphospholipid antibody syndrome.

Case control studies suggest that several other blood coagulation changes are also associated with an increased risk of developing venous thromboembolism. These include sustained elevation of factor VIII or IX coagulant activity,^{10,11} factor XI antigen¹² and the thrombin activable fibrinolysis inhibitor (TAFI).¹³ The clinical utility of these observations remains uncertain.

The present recommendation is to restrict screening for thrombophilia to young people with unprovoked or recurrent venous thromboembolism, or when there is vein thrombosis in unusual territories (mesenteric or cerebral).

Thrombophilias and Adverse Pregnancy Outcomes

The association between adverse pregnancy outcomes and the presence of lupus and the lupus anticoagulant is well recognised. There has also been much interest of late in observations that pregnancy loss (especially repeated pregnancy loss) and other adverse pregnancy outcomes may be associated with a high prevalence of inherited thrombophilia (including hyperhomocysteinaemia, activated protein C resistance, factor V or prothrombin mutation, protein C or S, and antithrombin deficiency) and may be preventable with anticoagulant prophylaxis. Studies to date have been relatively small and of highly selected patient populations. Systematic reviews indicate it is too early to judge the contribution of thrombophilia to adverse outcomes, and that routine screening for thrombophilias in pregnancy is not indicated.^{14–17} Large recent case control studies from Scotland and Canada have found no evidence of an excess pregnancy risk attached to factor V, prothrombin or methyltetrahydrofolate reductase polymorphisms in mothers or their newborn.^{18,19}

Thrombosis in Asia

The annual community prevalence of symptomatic deep

venous thrombosis and/or pulmonary embolism is about 1 to 2 per thousand in Europe and North America. It is probably less among emigrant Asian populations, since hospital discharge information from California suggests that people registered with Asian or Pacific Island ethnicity have an annual incidence of venous thromboembolism that is about 20% to 25% of that recorded among ‘whites’ or African Americans.^{20,21} Differences may be due to lifestyle and genetic predisposition, including the low prevalence of inherited thrombogenic polymorphisms outside people of European stock.²² The extremely low prevalence of factor V Leiden and the G20210A prothrombin mutation in Chinese and other Asian ethnic populations^{23–25} has contributed to the relative neglect of venous thromboembolism in Asia.

There is a long-standing belief that venous thromboembolism in Asia is extremely rare and clinically insignificant, but recent surveys suggest that this may not now be true and that in Asia the incidence of venous thrombosis and pulmonary embolism in some ‘high risk’ clinical settings is increasing and may approach that seen in the West. If this is so, then there is a need in Asia for an increased diagnostic sensitivity to venous thrombosis and pulmonary embolism and to consider formal studies of risk factors and prevention in Asian populations. There is a suspicion that predisposing factors may differ in Asia and the West. For instance, there appears to be a higher prevalence of inherited antithrombin, protein C and protein S deficiency among Chinese patients presenting in Hong Kong or Taiwan with venous thromboembolism.^{23,26}

The true incidence of venous thromboembolism in Asian populations remains unknown. There is, however, a growing body of evidence from autopsy studies, audits of admission diagnoses to major referral hospitals in large cities, and prospective screening for subclinical deep vein thrombosis in ‘high risk’ settings like major joint surgery or stroke.

Autopsy Studies

Pulmonary embolism was unusual and fatal embolism was rare among adult coroner’s autopsies done in Singapore between 1952 and 1966 (1.6 per 1000 necropsies),²⁷ but prevalence had increased to 1.05% by 1989 to 1993.²⁸ Autopsy reports from Queen Mary Hospital in Hong Kong that span 30 years strongly suggest a rising prevalence of embolism which now approaches – at least in this urban Chinese population – the levels reported from Europe and North America (Table I). Comparison of autopsy data from Hong Kong and Wales during 1990 to 1994 suggests the prevalence of massive pulmonary embolism is not significantly lower in Hong Kong.²⁹ Even the earliest (1964 to 1974) Hong Kong report found small emboli in 27% of lungs that were systematically searched after

TABLE I: THE PREVALENCE OF PULMONARY EMBOLISM AT AUTOPSY DURING 30 YEARS IN HONG KONG

Reference	Years	Autopsies	Autopsy rate	PE at autopsy (%)
Chan (1980) ³⁰	1964-76	3876	25%	0.75%
Chau (1991) ³³	1975-79	3777	36%	1.08%
	1980-84	3392	30%	1.83%
	1985-89	3179	27%	2.8%
Chau (1997) ³¹	1990-94	2348	21%	4.7%

PE: pulmonary embolism

optimal lung and vessel fixation.³⁰ The most recent series find that embolism is strongly age-dependent, as in Western reports.^{28,31} Also as in the West, pulmonary embolism found at autopsy was frequently misdiagnosed during life.³² The causes of a rising prevalence of pulmonary embolism in urban Chinese may include an ageing population, changing life-styles and increasing surgical and medical interventions for the diseases of older age. Table I suggests that an apparent rarity of venous thromboembolism in many clinical reports from Asia may be due in large part to lack of diagnostic suspicion and under-diagnosis.

Clinically Diagnosed Venous Thromboembolism in Reports from Asia

The clinical presentation of deep leg vein thrombosis in Asia appears to be similar to that described elsewhere – with leg pain and swelling the predominant complaints. The same is true for pulmonary embolism.³⁴ A significant minority of patients with thrombosis (roughly 25%?) has no apparent predisposition.³⁵

The true incidence of deep vein thrombosis in Asian populations remains uncertain, but there is suggestive evidence of a rising prevalence. A 1988 paper from Hong Kong reported 2.7 cases per 10,000 admissions to hospital,³⁶ similar to the admission rate in 1990 from Kuala Lumpur (2.8 per 10,000 hospital admissions).³⁷ A 1992 report from Singapore indicated a prevalence of 7.9 per 10,000 admissions to the National University Hospital (although about half of these cases were identified on clinical grounds alone and only half had confirmatory tests).³⁸ A recent report from Singapore General Hospital identified 388 cases of symptomatic deep vein thrombosis (332 acute and 63 previous, all confirmed by ultrasound imaging) admitted between 1996 and 1997. Almost 10% also had symptoms and confirmation of pulmonary embolism.³⁹ The observed prevalence of 15.8 per 10,000 admissions for acute deep vein thrombosis is much higher than was previously reported, and represents a minimum since it records only

patients with objectively confirmed diagnoses. Even so, it remains considerably lower than the 0.9% of hospital admissions reported from Worcester, Massachusetts.⁴⁰ A rising prevalence of venous thromboembolism in Asia may be due to an ageing population, increasing numbers of patients having surgical procedures at an older age, and more intensive treatment for malignancy.

Several surveys of symptomatic and confirmed venous thromboembolism suggest that patients who would be considered to be at 'high risk' in the West are also at risk in Asia. Almost 2:1000 pregnancies and deliveries in Chinese women from Hong Kong were complicated by venous thrombosis or pulmonary embolism, mostly postpartum and after caesarean section.⁴¹ High rates of symptomatic thromboembolism in the absence of prophylaxis were reported after colorectal surgery in Singaporean Chinese (11.4% after rectal surgery and 4.7% after surgery for malignancy),⁴² hip replacement in Kuala Lumpur (0.9%)⁴³ and surgery for oesophageal cancer in Japan.⁴⁴

This impression from clinical surveys that thrombosis is not truly infrequent in Asia is confirmed by prospective studies where patients not given thrombosis prophylaxis were screened with sensitive diagnostic tests for subclinical deep leg vein thrombosis (Table II). Reports vary and comparisons with Western studies are only approximate, since results may be affected by interpretation of diagnostic screening test results – although study methodology was otherwise similar. Thrombosis rates observed in Asia after abdominal or gynaecological surgery, and after ischaemic stroke, tend to be lower than those observed in the West. Asian thrombosis rates after knee replacement or hip fracture, on the other hand, are very high and in the same range as elsewhere. Hip replacement in Korea and Japan was followed by thrombosis rates of 15% to 25% that are high but somewhat lower than the rates of 50% to 60% reported from Europe and North America.

Surveys from Asia therefore suggest that routine thrombosis prophylaxis is probably indicated after major joint surgery, but that further studies in Asia are needed to define the need for prophylaxis in other medical and surgical settings. In addition, since average body weight tends to differ between Western and many Asian populations, there is a need for Asian studies about the safety of anticoagulant dosing regimens.

New Antithrombotic Drugs and Haemostasis

The observations on thrombosis rates make it relevant to consider the mechanisms of action and clinical role of old and newer antithrombotic drugs used for thrombosis prevention and treatment.

Two major groups of anticoagulants are now in general

TABLE II: REPORTS FROM ASIA OF DEEP LEG VEIN THROMBOSIS PREVALENCE AFTER MAJOR ORTHOPAEDIC OR GENERAL SURGERY OR AFTER A STROKE, WITHOUT THROMBOSIS PROPHYLAXIS, WHEN PATIENTS WERE SCREENED FOR SUBCLINICAL THROMBOSIS USING ROUTINE VENOGRAPHY, ULTRASOUND IMAGING OR 125I-FIBRINOGEN LEG SCANNING. THE RESULTS REPORTED FROM WESTERN SURVEYS ARE DERIVED FROM A RECENT OVERVIEW BY GEERTS ET AL, 2001⁴⁵

Condition	Country	Screening	DVT	Reference	% DVT in the West (mean and 95% confidence interval)
Hip replacement	Korea	Venography	8/50 (16%)	Yoo et al, 1997 ⁴⁶	54 (50-58)% (venography)
	Korea	Venography	10/50 (20%)	Kim et al, 1998 ⁴⁷	
	Japan	Venography	37/164 (23%)	Fujita et al 2000 ⁴⁸	
Mixed joint surgery	Malaysia	Venography	55/88 (62.5%)	Dhillon et al 1996 ⁴⁹	
Knee replacement	Japan	Venography	67/138 (49%)	Fujita et al 2000 ⁴⁸	64 (57-71)% (venography)
	Taiwan	Venography	68/107 (64%)	Wang et al 2000 ⁵⁰	
	Singapore	Ultrasound	14/100 (14%)	Ruban et al 2000 ⁵¹	
Hip fracture	Hong Kong	Venography	28/53 (53%)	Mok et al 1979 ⁵²	48 (43-53)% (venography)
	Hong Kong	Ultrasound	29/78 (37%)	Kew et al 1999 ⁵³	
Spinal surgery	Korea	Ultrasound	4/313 (1.3%)	Lee et al 2000 ⁵⁴	Approximately 3% (ultrasound)
Major general abdominal surgery	Malaysia	Leg scan	5/68 (12%)	Cunningham et al 1974 ⁵⁵	25 (24-27)% (leg scan)
	Hong Kong	Leg scan	4/150 (2.6%)	Nandi et al 1980 ⁵⁶	
	Hong Kong	Ultrasound	20/48 (42%)	Lee et al 2001 ⁵⁷	
	Japan	Leg scan	49/256 (15%)	Inada et al 1983 ⁵⁸	
	Singapore	Ultrasound	5/169 (3%)	Ho et al 1999 ⁵⁹	
Major gynaecological surgery	Thailand	Leg scan	4/117 (2.4%)	Chumnijakarij et al 1975 ⁶⁰	16 (14-19)% (leg scan)
	Hong Kong	Leg scan	4/154 (2.6%)	Tso et al 1980 ⁶¹	
Stroke	Hong Kong	Leg scan	6/35 (17%)	Tso 1980 ⁶²	55 (49-60)% (leg scan)

DVT: deep vein thrombosis

use: one includes heparin and the low molecular weight heparins – both given by injection; the other consists of the oral vitamin K antagonists (warfarin and its analogues). Newer anticoagulants have earned a limited clinical niche but may become more widely accepted. These include a synthetic heparin pentasaccharide with anti-factor Xa but no antithrombin activity (fondaparinux), several direct and specific antithrombins (hirudin and its analogues, melagatran, ximelagatran, argatroban), and a factor VIIa inhibitor (NAPc-2). There is, in addition, a range of novel anti-platelet and thrombolytic drugs.

Heparin, the Low Molecular Weight Heparins, and Fondaparinux (A Synthetic Heparin Pentasaccharide)

To understand how the anticoagulant effects of these drugs differ requires a discussion of interactions between heparin, plasma antithrombin, and the activated blood clotting factors (especially Xa and IIa).

Standard (unfractionated) heparin consists of heavily sulphated polysaccharide chains that vary in length, molecular weight (about 3000 to 15,000, averaging 15,000 Da), affinity for antithrombin and anticoagulant effect.⁴ An arginine-reactive site in antithrombin binds and blocks the active centre of serine protease clotting factors, especially IIa and Xa. This process is much accelerated when a specific pentasaccharide sequence in heparin becomes

attached to a lysine residue on antithrombin,⁶³ and induces conformational change in antithrombin that greatly accelerates factor Xa inactivation.⁶⁴⁻⁶⁶ About $\frac{1}{3}$ of heparin chains contain the specific antithrombin binding sequence and enhance anti-Xa activity, regardless of their chain length, but not all heparin chains also accelerate anti-IIa activity. To express anti-thrombin activity, heparin chains must be more than 15 or 16 saccharide units in length (this corresponds to a MW of at least 5000 to 6000 Da) and contain a second domain that electrostatically attracts thrombin until it collides with the reactive site of AT.⁶⁴ Unfractionated heparin is standardised to have approximately equal amounts of anti-Xa and anti-IIa activity.

The low molecular weight heparins are derived from standard heparin by chemical or enzymatic cleavage followed by fractionation, to yield shorter chain lengths with a MW of 1000 to 10,000 Da (averaging 4000 to 6000 Da). Anti-Xa activity predominates but all low molecular weight heparins retain some longer heparin chains with anti-IIa activity. Subcutaneously, injected low molecular weight heparins have excellent bioavailability, a longer circulating half-life and a much more predictable anticoagulant effect and dose response than standard heparin. This makes them much easier to use than standard heparin, which is normally given by intravenous infusion

in a dose that is adjusted to prolong a laboratory test like the plasma activated partial thromboplastin time (APTT) into its 'therapeutic range'. Low molecular weight heparins do not stimulate platelets and are less likely than standard heparin to provoke antibody mediated 'heparin-induced thrombocytopenia' (HIT).⁶⁶ Randomised trials show that low molecular weight heparins are effective and safe for the routine prevention and treatment of venous thrombosis and in some cardiac indications, where they are progressively replacing unfractionated heparin in routine clinical use.

The synthetic pentasaccharide, fondaparinux, is the methyl glycoside analogue of the antithrombin-binding sequence in heparin, with MW 1728 Da and selective anti-Xa activity that circulates in man with a half-life of about 18 hours. By greatly increasing the rate of factor-Xa inhibition by antithrombin, fondaparinux causes dose dependent decrease of thrombin generation in platelet-poor or platelet-rich plasma.^{67,68} It has no anti-IIa activity except at extreme concentrations,⁶⁹ does not prolong the prothrombin time, and has little effect on the activated partial thromboplastin time. Fondaparinux does not interact with platelets or cross-react with anti-platelet antibodies from patients with HIT.⁶⁹⁻⁷³ Other, as yet less well evaluated, synthetic heparin analogues with clinically interesting properties include SANORG 34006 (its anti-Xa activity has a very long circulating half-life of 62 hours in baboons⁷⁴) and Org 36764 (where an extra carbohydrate domain adds anti-IIa to anti-Xa activity^{64,75}).

Direct Thrombin Inhibitors

Thrombin (α -thrombin) cleaves fibrinopeptides A and B from fibrinogen to yield fibrin monomers that are cross-linked by factor XIIIa (itself activated by thrombin) to form insoluble fibrin. As well as the active site for substrates like fibrinogen, factors VIII and V, and protein C, thrombin carries binding sites that determine its specificity for fibrinogen (exosite I), heparin or thrombomodulin (exosite II), and factors VIII and V (exosites I and II).⁷⁶

The first clinically evaluated direct thrombin inhibitor was a recombinant form of hirudin – an anticoagulant from the medicinal leech that blocks both the active site and exosite I. More recently developed direct antithrombins include hirudin analogues like bivalirudin (which blocks only the exosite I), and small active site inhibitor molecules like argatroban and melagatran. Melagatran is of special interest since the development of an oral pro-drug (ximelagatran or H376/95) that is predictably absorbed from the gut and is then converted to the active material, melagatran.⁷⁷

Other Novel Anticoagulants

These include natural anticoagulants (e.g. activated

protein C), NAPc2 (derived from a small protein originally isolated from a tapeworm) that inhibits factor VIIa within the VIIa/tissue factor complex, and direct factor Xa inhibitors.

Recently Introduced Antiplatelet Drugs

Newer antiplatelet drugs that have undergone extensive clinical evaluation include inhibitors of the platelet surface ADP receptor (ticlopidine and clopidogrel), and a series of glycoprotein IIb/IIIa inhibitors – starting with the humanised chimeric monoclonal antibody Abciximab and now including eptifibatide and tirofiban. These have value in peripheral vascular disease (clopidogrel), in acute coronary syndromes, and after coronary artery interventions (glycoprotein IIb/IIIa inhibitors).⁷⁸

Preventing and Treating Venous Thromboembolism (Are the Newer Anticoagulants Any Better?)

The high thrombosis rates still observed after major joint surgery (hip or knee replacement and hip fracture) despite prophylaxis are a challenge to the development of new methods of thrombosis prevention that are effective and affordable but do not provoke excessive wound bleeding.

Recent trials suggest that newer drugs can safely reduce thrombosis rates after orthopaedic surgery to levels that are significantly below those achieved with low molecular weight heparins, the present practice standard (Table III).

Both the direct thrombin inhibitor hirudin and the selective anti-factor Xa inhibitor fondaparinux have achieved significantly lower postoperative thrombosis rates after hip replacement than a low molecular weight heparin (enoxaparin). Fondaparinux was also more effective in people with hip fracture, or having a knee replacement (Table III). Surgical bleeding was not, apparently, a clinically important issue with hirudin or fondaparinux. The hirudin trials found no more bleeding than with standard low dose heparin or low molecular weight heparin prophylaxis. Results pooled from the four fondaparinux trials⁸⁵ show that more people treated with fondaparinux had a bleeding index of 2 or greater after surgery (the 'bleeding index' is the postoperative fall in haemoglobin corrected for blood transfused) but there was minimal or no increase in wound bleeding that required a reoperation (Table IV).

An observation from the fondaparinux trials that is of great clinical interest relates to the time relative to surgery when anticoagulant prophylaxis is safest and most effective. Fondaparinux in these studies was started 4 to 8 hours (average 6 hours) after wound closure. Post-hoc analysis of the pooled trial data finds the bleeding index was increased only when the first fondaparinux dose was given sooner than 6 hours after wound closure. There was no increase in

TABLE III: THROMBOSIS RATES OBSERVED AFTER MAJOR JOINT SURGERY IN RANDOMISED THROMBOSIS PREVENTION TRIALS THAT COMPARED A NEWER ANTICOAGULANT WITH A LOW DOSE OF STANDARD HEPARIN OR WITH A LOW MOLECULAR WEIGHT HEPARIN. THE PRIMARY ENDPOINT IN ALL STUDIES WAS VTE, CONSISTING OF SUBCLINICAL DVT DETECTED AT ROUTINE POSTOPERATIVE VENOGRAPHY AND/OR SYMPTOMATIC AND CONFIRMED DVT OR PULMONARY EMBOLISM THAT DEVELOPED DURING THE TREATMENT PERIOD. THIS TABLE QUOTES THE OVERALL VTE RATES OBSERVED IN THESE STUDIES ('ANY'), TOGETHER WITH THE RATES OF PROXIMAL DVT OBSERVED AT VENOGRAPHY ('PROXIMAL' OR 'PROX').

Surgery	Reference	Standard preventive therapy (Heparin or low molecular weight heparin)		Newer Anticoagulant		Risk reduction relative to standard prophylaxis
		Drug	VTE rate	Drug	VTE rate	
Hip replacement	Eriksson et al 1997 ⁷⁹	Heparin 5000 IU 8 hourly sc*	41/177 (23%) any 29 (16%) proximal	Hirudin 5000 IU 8 hourly sc*	13/174 (7%) any 6 (3%) prox	68% for any VTE (<i>P</i> <0.0001) 79% for prox DVT (<i>P</i> <0.0001)
	Eriksson et al 1997 ⁸⁰	Enoxaparin 40 mg per day sc*	196/785 (25.5%) any 59 (7.5%) proximal	Hirudin 15 mg 12 hourly sc*	142/802 (18.4%) any 36 (4.5%) prox	28% for any VTE (<i>P</i> <0.001) 40% for prox DVT (<i>P</i> <0.01)
	Lassen et al 2002 ⁸¹	Enoxaparin 40 mg per day sc*	85/919 (9%) any 23/927 (2.5%) proximal	Fondaparinux 2.5 mg sc daily**	37/908 (4%) any 6/922 (0.7%) prox	56% for any VTE (<i>P</i> <0.0001) 61% for prox DVT (<i>P</i> = 0.002)
	Turpie et al 2002 ⁸²	Enoxaparin 30 mg bid sc**	66/797 (8%) any 10/830 (1.2%) proximal	Fondaparinux 2.5 mg sc daily**	48/787 (6%) any 14/816 (1.7%) prox	26% for any VTE (<i>P</i> = 0.099) +42% for prox DVT (<i>P</i> = 0.42)
Hip fracture	Eriksson et al 2001 ⁸³	Enoxaparin 40 mg per day sc*	119/624 (19%) any 28/646 (4.3%) proximal	Fondaparinux 2.5 mg sc daily**	52/626 (8%) any 6/650 (0.9%) prox	56% for any VTE (<i>P</i> <0.001) 58% for prox DVT (<i>P</i> <0.001)
Knee replacement	Bauer et al 2001 ⁸⁴	Enoxaparin 30 mg bid sc**	101/363 (27.8%) any 20/372 (5.4%) proximal	Fondaparinux 2.5 mg sc daily**	45/361 (12.5%) any 9/368 (2.4%) prox	55% for any VTE (<i>P</i> <0.001) 55% for prox DVT (<i>P</i> = 0.06)

DVT: deep vein thrombosis; VTE: venous thromboembolism

* Preventive treatment started before surgery.

** Preventive treatment started soon after surgery.

TABLE IV: RATES OF MAJOR BLEEDING AFTER MAJOR JOINT SURGERY OBSERVED IN THROMBOSIS PREVENTION TRIALS USING NEW ANTICOAGULANTS

Surgery	Reference	Standard preventive therapy (Heparin or low molecular weight heparin)		Newer anticoagulant		Bleeding rate relative to standard prophylaxis
		Drug	Wound complications	Drug	Wound complications	
Hip replacement	Eriksson et al 1997 ⁷⁹	Heparin 5000 IU 8 hourly sc*	Haematoma = 2% Swelling, haematoma, infection or dehiscence = 5%	Hirudin 5,000 IU 8 hourly sc*	Haematoma = 2% Swelling, haematoma, infection or dehiscence = 6%	
		Enoxaparin 40 mg per day sc*	Haematoma = 7.9% Deep infection = 0.2% Dehiscence = 0.5% Serious bleeding = 2.0%	Hirudin 15 mg 12 hourly sc*	Haematoma = 8.3% Deep infection = 0.2% Dehiscence = 0.6% Serious bleeding = 1.9%	
	Lassen et al 2002 ⁸¹	Enoxaparin 40 mg per day sc*	Major bleeding*** = 2.8% Reoperation = 0.26%	Fondaparinux 2.5 mg sc daily**	Major bleeding = 4.1% Reoperation = 0.44%	
Hip fracture	Turpie et al 2001 ⁸²	Enoxaparin 30 mg bid sc**	Major bleeding*** = 2.3% Reoperation = 0.2%	Fondaparinux 2.5 mg sc daily**	Major bleeding = 2.2% Reoperation = 0.2%	
		Enoxaparin 40 mg per day sc*	Major bleeding*** = 2.3% Reoperation = 0.2%	Fondaparinux 2.5 mg sc daily**	Major bleeding*** = 2.2% Reoperation = 0.4%	
	Eriksson et al 2001 ⁸³	Enoxaparin 30 mg bid sc**	Major bleeding*** = 0.2% Reoperation = 0.2%	Fondaparinux 2.5 mg sc daily**	Major bleeding*** = 2.1% Reoperation = 0.4%	
Knee replacement	Bauer et al 2001 ⁸⁴	Enoxaparin 30 mg bid sc**	Major bleeding*** = 0.2% Reoperation = 0.2%	Fondaparinux 2.5 mg sc daily**	Major bleeding*** = 2.1% Reoperation = 0.4%	P = 0.006

* Preventive treatment started before surgery.

** Preventive treatment started soon after surgery.

*** Major bleeding was defined as overt bleeding with a bleeding index of 2 or more (decrease in haemoglobin concentration corrected for blood transfusion), and/or bleeding that lead to reoperation, occurred into an internal organ, or was fatal.

bleeding index when the drug was started 6 to 8 hours after surgery, and no loss of prophylactic effectiveness. It is likely therefore, that strict attention to timing can avoid any small excess of bleeding risk attached to this drug regimen.

Efficacy, Safety and the Timing of Anticoagulant Prophylaxis Around the Time of Surgery

Until now, it was uncertain if a preoperative dose was needed to achieve an optimal outcome from surgical thrombosis prophylaxis. Two recent meta-analyses suggest that in hip surgery, efficacy is preserved when low molecular weight heparin prophylaxis is begun soon after surgery and the preoperative dose is omitted, but that low molecular weight heparin started just before or soon after surgery carries an increased bleeding risk.^{86,87} These conclusions are consistent with observations from the fondaparinux trials that suggest it is effective and safe to start prophylaxis after major joint surgery. Omitting the preoperative dose would greatly increase the confidence of surgeons and anaesthetists that surgical anticoagulant prophylaxis is safe. There is no data, however, on whether it is effective to abandon a preoperative dose of prophylactic low dose standard (unfractionated) heparin in general surgery.

What Do New Anticoagulants Tell Us About the Coagulation Cascade?

It appears that either selective thrombin inhibition (with hirudin) or selective factor Xa inhibition (with fondaparinux) can safely prevent venous thrombosis after high risk surgery. Phase III trials with results available later this year will tell if selective factor Xa inhibition after deep vein thrombosis and pulmonary embolism can also prevent the propagation of established thrombosis. If so, then that will reinforce the understanding that thrombus propagation relies very much on the recruitment of further thrombin generated through the positive feedback loops that can be interrupted by factor Xa inhibition.

REFERENCES

- Colman R W, Hirsh J, Marder V J, Clowes A W. Blood coagulation factors: their complementary DNA's, genes and expressions. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams and Wilkins, 2001:17-57.
- Esmon C T. Protein C, protein S, and thrombomodulin. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:335-53.
- Hirsh J, Colman R W, Marder V J, George J N, Clowes A W. Overview of thrombosis and its treatment. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1071-84.
- Rosenberg R D, Edelberg J M, Zhang L. The heparin/antithrombin system: a natural anticoagulant mechanism. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:711-31.
- Reiner A P, Siscovick D S, Rosendaal F R. Hemostatic risk factors and arterial thrombotic disease. *Thromb Haemostas* 2001; 85:584-95.
- Marder V J, Matei D E. Hereditary and acquired thrombophilic syndromes. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1243-75.
- Emmerich J, Rosendaal F R, Cattaneo M, Margaglione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism-pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. *Thromb Haemost* 2001; 86:809-16.
- Townend J, O'Sullivan J, Wilde J T. Hyperhomocysteinemia and vascular disease. *Blood Rev* 1998; 12:23-34.
- Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. *Thromb Haemost* 1999; 81:165-76.
- Kyrle P A, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 2000; 343:462.
- van Hylckama Vlieg A, van der Linden I K, Bertina R M, Rosendaal F R. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000; 95:3678-82.
- Meijers J C M, Tekelenburg W L H, Bouma B N, Bertina R M, Rosendaal F R. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000; 342:696-701.
- van Tilburg N H, Rosendaal F R, Bertina R M. Thrombin activable fibrinolysis inhibitor and the risk of deep vein thrombosis. *Blood* 2000; 95:2855-9.
- Walker I D. Thrombophilia in pregnancy. *J Clin Pathol* 2000; 53: 573-80.
- Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2002; 101:6-14.
- Roberts D, Schwartz R S. Clotting and hemorrhage in the placenta—a delicate balance. *N Engl J Med* 2002; 347:57-9.
- Walker I D. Prothrombotic genotypes and pre-eclampsia. *Thromb Haemost* 2002; 87:777-8.
- Morrison E R, Miedzybrodzka Z H, Campbell D M, Haite N E, Wilson B J, Watson M S, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: Results from a large population-based study and systematic review. *Thromb Haemost* 2002; 87:779-85.
- Infante-Rivard C, Rivard G-E, Yotov W V, Glenin E, Guiguet M, Weinberg C, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med* 2002; 347:19-25.
- White R H, Zhou H, Romano P S. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. *Ann Intern Med* 1998; 128:737-40.
- Klatsky A L, Armstrong M A, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol* 2000; 85:1334-7.
- Rees D C, Chapman N H, Webster M T, Guerreiro J F, Rochette J, Clegg J B. Born to clot: the European burden. *Br J Haematol* 1999; 105:564-6.
- Shen M-C, Lin J-S, Tsay W. High prevalence of antithrombin III, protein C and protein S deficiency, but no factor V Leiden mutation in

- venous thrombophilic Chinese patients in Taiwan. *Thromb Res* 1997; 87:377-85.
24. Lin J S, Shen M C, Tsay W. The mutation at position 20210 in the 3'-untranslated region of the prothrombin gene is extremely rare in Taiwanese Chinese patients with venous thrombosis. *Thromb Haemost* 1998; 80:343.
 25. Lim L C, Tan H H, Lee L H, Tien S L, Abdul Ghafar A. Activated protein C resistance: A study among 60 thromboembolic patients in the Singapore population. *Ann Acad Med Singapore* 1999; 28:252-5.
 26. Liu H W, Kwong Y L, Bourke C, Lam C K, Lie A K W, Wei D, et al. High incidence of thrombophilia detected in Chinese patients with venous thrombosis. *Thromb Haemost* 1994; 71:416-9.
 27. Hwang W S. The rarity of pulmonary thromboembolism in Asians. *Singapore Med J* 1968; 9:276-9.
 28. Lau G. Pulmonary thromboembolism is not uncommon—results and implications of a five-year study of 116 necropsies. *Ann Acad Med Singapore* 1995; 24:356-65.
 29. Dickens P, Knight B H, Ip P, Fung W S. Fatal pulmonary embolism: a comparative study of autopsy incidence in Hong Kong and Cardiff, Wales. *Forensic Sci Int* 1997; 90:171-4.
 30. Chan C W, Hoaglund F T. Pulmonary thromboembolism and venous thrombosis in the Chinese. *Clin Orthop Rel Res* 1980; 150:253-60.
 31. Chau K Y, Yuen S T, Wong M P. Clinicopathological pattern of pulmonary thromboembolism in Chinese autopsy patients: comparison with Caucasian series. *Pathology* 1997; 29:263-6.
 32. Teo C E S. A study of coroner's cases from hospitals: a comparison of autopsy and clinical diagnosis. *Ann Acad Med Singapore* 1993; 22:3-7.
 33. Chau K Y, Yuen S T, Ng T H K, Ng W F. An autopsy study of pulmonary thromboembolism in Hong Kong Chinese. *Pathology* 1991; 23:181-4.
 34. Nakamura M, Fujioka H, Yamada N, Sakuma M, Okada O, Nakanishi N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. *Clin Cardiol* 2001; 24:132-8.
 35. Peng Y Y, Jeng J S, Shen M-C, Tsay W, Wang B-S, Lin W-H, et al. Aetiologies and prognosis of Chinese patients with deep vein thrombosis of the lower extremities. *Q J Med* 1998; 91:681-6.
 36. Woo K S, Mak G Y K, Sun J J, Woo J L F, Metreweli C, Vallance-Owen J. The incidence and clinical pattern of deep vein thrombosis in the Chinese in Hong Kong. *Singapore Med J* 1988; 29:357-9.
 37. Liam C K, Ng S C. A review of patients with deep vein thrombosis diagnosed at University Hospital, Kuala Lumpur. *Ann Acad Med Singapore* 1990; 19:837-40.
 38. Kueh Y K, Wang T L, Teo C P, Tan Y O. Acute deep vein thrombosis in hospital practice. *Ann Acad Med Singapore* 1992; 21:345-8.
 39. Lee L H, Gu K, Heng D. Deep vein thrombosis is not rare in Asia—the Singapore General Hospital experience. *Ann Acad Med Singapore* 2002; 31:???
 40. Anderson F A, Wheeler B, Goldberg R J, Hosmer D W, Patwardhan N A, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991; 151:933-8.
 41. Chan L Y, Tan W H, Lau T K. Venous thromboembolism in pregnant Chinese women. *Obstet Gynecol* 2001; 98:471-5.
 42. Kum C K, Sim E K, Ngoi S S. Deep vein thrombosis complicating colorectal surgery in the Chinese in Singapore. *Ann Acad Med Singapore* 1993; 22:895-7.
 43. Tay B H, Masbah O, Razak M, Ruslan G N. Total hip arthroplasty in Malaysia – the Universiti Kebangsaan Malaysia and Hospital Kuala Lumpur experience. *Med J Malaysia* 2000; 55:74-85.
 44. Tsutsumi K, Udagawa H, Kajiyama Y, Kinoshita Y, Ueno M, Nakamura T, et al. Pulmonary thromboembolism after surgery for esophageal cancer: its features and prophylaxis. *Surg Today* 2000; 30:416-20.
 45. Geerts W H, Heit J A, Clagett G P, Pineo G F, Colwell C W, Anderson F A, et al. Prevention of venous thromboembolism. *Chest* 2001; 119:132S-75S.
 46. Yoo M C, Kang C S, Kim Y H, Kim S K. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *Int Orthop* 1997; 21:399-402.
 47. Kim Y H, Choi I Y, Park M R, Park T S, Cho J L. Prophylaxis for deep vein thrombosis with aspirin or low molecular weight dextran in Korean patients undergoing total hip replacement. A randomized controlled trial. *Int Orthop* 1998; 22:6-10.
 48. Fujita S, Hirota S, Oda T, Kato Y, Tsukamoto Y, Fuji T. Deep venous thrombosis after total hip or total knee arthroplasty in Japan. *Clin Orthop Rel Res* 2000; 375:168-74.
 49. Dhillon K S, Askander A, Doraismy S. Postoperative deep-vein thrombosis in Asian patients is not a rarity: a prospective study of 88 patients with no prophylaxis. *J Bone Joint Surg* 1996; 78-B:427-30.
 50. Wang C J, Wang J W, Chen L M, Chen H S, Yang B Y, Cheng S M. Deep vein thrombosis after total knee arthroplasty. *J Formos Med Assoc* 2000; 99:848-53.
 51. Ruban P, Yeo S J, Seow K H, Tan S K, Ng S C K. Deep vein thrombosis after total knee replacement. *Ann Acad Med Singapore* 2000; 29:428-33.
 52. Mok C K, Hoaglund F T, Rogoff S M, Chow S P, Ma A, Yau A C M C. The incidence of deep vein thrombosis in Hong Kong Chinese after hip surgery for fracture of the proximal femur. *Br J Surg* 1979; 66:640-2.
 53. Kew J, Lee Y L, Davey I C, Ho S Y, Fung K C, Metreweli C. Deep vein thrombosis in elderly Hong Kong Chinese with hip fractures detected with compression ultrasound and Doppler imaging: incidence and effects of low molecular weight heparin. *Arch Orthop Trauma Surg* 1999; 119:156-8.
 54. Lee H M, Suk K S, Moon S H, Kim D J, Wang J M, Kim N H. Deep vein thrombosis after major spinal surgery: incidence in an East Asian population. *Spine* 2000; 25:1827-30.
 55. Cunningham I G E, Yong N K. The incidence of postoperative deep vein thrombosis in Malaysia. *Br J Surg* 1974; 61:482-3.
 56. Nandi P, Wong K P, Wei W I, Ngan H, Ong G B. Incidence of postoperative deep vein thrombosis in Hong Kong Chinese. *Br J Surg* 1980; 67:251-3.
 57. Lee F Y, Chu W, Chan R, Leung Y F, Ng S M, Lai P B, et al. Incidence of deep vein thrombosis after colorectal surgery in a Chinese population. *Aust N Z J Surg* 2001; 71:637-40.
 58. Inada K, Shirai N, Matsumoto K, Hirose M. Postoperative deep vein thrombosis in Japan. *Am J Surg* 1983; 145:775-9.
 59. Ho Y H, Seow-Choen F, Leong A, Eu K W, Nyam D, Teoh M K. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Dis Colon Rectum* 1999; 42:196-202.
 60. Chumnijarakij T, Poshychinda V. Postoperative thrombosis in Thai women. *Lancet* 1975; 1:1357-8.
 61. Tso S C, Wong V, Chan V, Chan T K, Chan H K, Ma H K, et al. Deep vein thrombosis and changes in coagulation and fibrinolysis after gynecological operations in Chinese: effect of oral contraceptives and malignant disease. *Br J Haematol* 1980; 46:603-12.
 62. Tso S C. Deep vein thrombosis after strokes in Chinese. *Aust N Z J Med* 1980; 10:513-4.
 63. Arocas V, Bock S C, Raja S, Olson S T, Bjork I. Lysine 114 of antithrombin is of crucial importance for the affinity and kinetics of heparin pentasaccharide binding. *J Biol Chem* 2001; 276:43809-17.
 64. Petitou M, Herault J P, Bernat A, Driiguez P-A, Duchaussoy P, Lormeau J-C, et al. Synthesis of thrombin-inhibiting heparin mimetics without

- side effects. *Nature* 1999; 398:417-22.
65. Whisstock J C, Pike R N, Jin L, Skinner R, Pei X Y, Carrell R W, et al. Conformational changes in serpins: II. The mechanism of activation of antithrombin by heparindaggar. *J Mol Biol* 2000; 301:1287-305.
 66. Hirsh J, Warkentin T, Shoughnessy S G, Anand S S, Halperin J S, Raschke R, et al. Heparin and low molecular weight heparins. Mechanism of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; 119(Suppl):64S-94S.
 67. Walenga J M, Bara L, Petitou M, Samama M M, Fareed J, Choay J. The inhibition of the generation of thrombin and the antithrombotic activity of a pentasaccharide with sole anti-factor Xa activity. *Thromb Res* 1988; 51:23-33.
 68. Beguin S, Choay J, Hemker H C. The action of a synthetic pentasaccharide on thrombin generation in whole plasma. *Thromb Haemost* 1989; 61:397-401.
 69. Herbert J M, Petitou M, Lormeau J C, Cariou R, Necciari J, Magnani H N, et al. SR 90107A/Org 31540, a novel anti-factor Xa antithrombotic agent. *Cardiovasc Drug Rev* 1997; 15:1-26.
 70. Elalamy I, Lecrubier C, Potevin F, Abdelouahed M, Bara L, Marie J P, et al. Absence of in vitro cross-reaction of pentasaccharide with the plasma heparin-dependent factor of twenty-five patients with heparin-associated thrombocytopenia. *Thromb Haemost* 1995; 74:1385-6.
 71. Amiral J, Lormeau J C, Marfaing-Kolka A, Vissac A M, Wolf M, Boyer-Neumann C, et al. Absence of cross-reactivity of SR 90107A/ORG 31540 pentasaccharide with antibodies to heparin-PF4 complexes developed in heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis* 1997; 8:114-7.
 72. Walenga J M, Jeske W P, Bara L, Samama M M, Fareed J. Biochemical and pharmacological rationale for the development of a synthetic heparin pentasaccharide. *Thromb Res* 1997; 86:1-36.
 73. Ahmad S, Jeske W P, Walenga J M, Hoppensteadt D A, Wood J J, Herbert J M, et al. Synthetic pentasaccharides do not cause platelet activation by antiheparin-platelet factor 4 antibodies. *Clin Appl Thromb Hemost* 1999; 5:259-66.
 74. Herbert J M, Herault J P, Bernat A, van Amsterdam R G, Lormeau J C, Petitou M, et al. Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting synthetic pentasaccharide. *Blood* 1998; 91:4179-205.
 75. Petitou M, van Boeckel C. Heparin: from the original "soup" to well-designed heparin mimetics. *Pure Appl Chem* 1997; 69:1839-46.
 76. Jenny N S, Mann K G. Thrombin. In: Colman R W, Hirsh J, Marder V J, Clowes A W, George J N, editors. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:171-89.
 77. Weitz G, Hirsh J. New anticoagulant drugs. *Chest* 2001; 119(Suppl):95S-107S.
 78. Cairns J A, Theroux P, Lewis H D, Ezekowitz M, Meade T W. Antithrombotic agents in coronary artery disease. *Chest* 2001; 119(Suppl):228S-52S.
 79. Eriksson B I, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C, et al. Prevention of thromboembolism with use of recombinant hirudin. Result of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg* 1997; 79-A:326-33.
 80. Eriksson B I, Wille-Jorgensen P, Kalebo P, Mouret P, Rosenscher N, Bosch P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997; 337:1329-35.
 81. Lassen M R, Bauer K A, Eriksson B I, Turpie A G G. Postoperative fondaparinux versus preoperative enoxaparin for the prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002; 359:1721-6.
 82. Turpie A G G, Bauer K A, Eriksson B I, Lassen M R. Postoperative fondaparinux versus postoperative enoxaparin for the prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002; 359:1721-6.
 83. Eriksson B I, Bauer K A, Lassen M R, Turpie A G G. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001; 345:1298-304.
 84. Bauer K A, Eriksson B I, Lassen M R, Turpie A G G. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001; 345:1305-10.
 85. Bounameaux H, Perneger T. Fondaparinux: a new synthetic pentasaccharide for thrombosis prevention. *Lancet* 2002; 359:1710-11.
 86. Hull R D, Pineo G F, Stein P D, Mah A, MacIsaac S M, Dahl O E, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: A systematic review. *Arch Intern Med* 2001; 161:1952-60.
 87. Strebel N, Prins M, Agnelli G, Buller H R. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002; 162:1451-6.