Measurement of thrombosis and its prevention

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Introduction

Thrombosis remains the commonest cause of death (including premature death) in developed countries, and is a growing epidemic in developing countries because of increasing prevalence of smoking, obesity, hypertension and type 2 diabetes.

Primary and secondary prevention of thrombosis is therefore an important part of public health, and primary and secondary healthcare. In addition to public and individual education (and management) of smoking, exercise, obesity, hypertension, diabetes and hypercholesterolaemia) antithrombotic drugs have an important role. In recent years, many randomized controlled trials have not only clarified the antithrombotic benefits (and bleeding risks) of traditional antiplatelets (aspirin), anticoagulants (unfractionated heparin, warfarin) and thrombolytics (streptokinase) but have also investigated the role of newer antithrombotics. Evidence-based guidelines on antithrombotic therapy are now reviewed every few years, to keep pace with advances in knowledge from new trials, and epidemiological studies [1–3]. This review considers the nature of thrombosis, antithrombotic therapies, the endpoints used in such studies, and the potential use of blood thrombotic markers in predicting persons at increased thrombotic risk.

Thrombosis: haemostasis in the wrong place

There is increasing evidence that thrombosis is 'haemostasis in the wrong place' (Table 1). Haemostasis is the continuous process through which bleeding following injury to small blood vessels (e.g. mechanical stresses of daily life, trauma, surgical and medical procedures) is arrested. Vascular injury exposes flowing blood to subendothelial collagen and to substances released from

damaged cells such as adenosine diphosphate (ADP). These activate circulating platelets, which adhere to the injured vessel wall and aggregate forming an initial, platelet-rich haemostatic plug which arrests bleeding within a few minutes (primary haemostasis). Simultaneously, blood coagulation factors are activated, primarily through exposure of flowing blood to tissue factor, which activates coagulation factor VII. Coagulation factors interact on platelet and other cell surfaces, generating thrombin from prothrombin. Thrombin converts circulating fibrinogen to fibrin, which stabilizes the initial platelet plug and prevents secondary haemorrhage (secondary haemostasis). Thrombin also activates platelets; generates further coagulation by activating factors V and VIII; activates factor XIII which cross-links fibrin, which increases its resistance to lysis by the endogenous fibrinolytic system; and inhibits fibrinolysis through the thrombin activated fibrinolytic inhibitor (TAFI). The fibrinolytic system digests the fibrin haemostatic plug over several days, in parallel with tissue repair. Tissue-type plasminogen activator activates plasminogen to plasmin, which degrades fibrin to fibrin degradation products (FDP), such as fibrin D-Dimer.

Excessive generalized bleeding can arise from fragile blood vessels (e.g. scurvy), low platelet count, low concentrations of platelet cofactors (most commonly von Willebrand's disease in which plasma von Willebrand factor (vWF) levels are low, reducing platelet adhesion and aggregation), low concentrations of coagulation factors (e.g. factor VIII in classical haemophilia), or occasionally high concentrations of t-PA (e.g. produced by some cancers) (Table 1).

Thrombosis can be viewed as a large, occlusive platelet-fibrin haemostatic plug in a vein, artery, or within the heart. It develops in veins as a result of venous trauma (e.g. central venous catheters, intravenous pacemakers) or venous stasis in leg veins (e.g. after major trauma, surgery or medical illness; puerperium; long-distance travel). In arteries, thrombosis usually occurs following rupture of an atheromatous plaque, exposing blood to the thrombogenic plaque contents.

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Table 1 Thrombosis is haemostasis in the wrong place.

	<i>Haemostasis</i>	<i>Thrombosis</i>
Vessel wall	Small vessels – injury	Veins – stasis Arteries – rupture
Platelets	Low count Low vWF	Antiplatelets
Coagulation	Low VIII	Anticoagulants
Fibrinolysis	High t-PA	Fibrinolytics

Antithrombotic drugs

Antiplatelet and anticoagulant drugs reduce formation of the platelet and fibrin components of thrombi, respectively. At the same time they reduce the platelet or fibrin components of haemostatic plugs. Fibrinolytic agents such as streptokinase or recombinant t-PA (alteplase) lyse not only thrombi, but also haemostatic plugs. Hence with all antithrombotic drugs, their therapeutic benefits (reduction of clinical morbidity and mortality from thrombosis) must be balanced against their adverse effects (especially, increased risk of bleeding) [1–3] (Table 1).

Antiplatelet drugs

Aspirin is the most commonly used antiplatelet drug, and has the largest evidence base in meta-analyses of randomized controlled trials [4–6]. It reduces the risk of both arterial [4] and venous [5] thromboembolic events by about 25%, at the cost of a 75% increased risk of bleeding. Because aspirin reduces prostaglandin synthesis in the gastrointestinal tract as well as in platelets, its adverse effects include nausea, dyspepsia, constipation and bleeding. The absolute annual risk of excessive major gastrointestinal bleeding is about 1 per 200 patients; the absolute annual risk of intracranial haemorrhage is about 1 in 2000 patients [6]. While the risk–benefit equation is therefore generally favourable for aspirin in secondary prevention of arterial thrombosis in patients with clinical arterial disease (annual risk about 5%), and in prophylaxis of venous thromboembolism after major surgery (risk of clinical DVT about 2% in first 35 days) [5], careful consideration should be given to its use in primary prevention of arterial thrombosis (risk: benefit favourable when annual risk of myocardial infarction is 1.5–2%) [6, 7].

The thiopyridenes (ticlopidine, clopidogrel) are antagonists of the platelet ADP receptor. They are slightly more effective than aspirin in secondary prevention of arterial thrombosis [8], and do not increase the risk of dyspepsia or gastrointestinal bleeding [9]. They are more expensive than aspirin and therefore used mostly in patients in whom

aspirin is contra-indicated or not tolerated [1]. Clopidogrel is preferred to ticlopidine because the latter may cause neutropenia and requires initial monitoring of blood cell counts. The combination of clopidogrel with aspirin is more effective than aspirin alone in reducing thrombosis within coronary stents [10] and in acute coronary syndromes [11].

The IIb/IIIa platelet receptor blockers are also more effective (when added to aspirin) than aspirin alone, when given intravenously in acute coronary syndromes [4]. In contrast, oral IIb/IIIa platelet receptor blockers were not more effective than aspirin in secondary prevention of arterial thrombosis, and increased the risks of bleeding, thrombocytopenia and death [12].

Anticoagulants

Subcutaneous heparins (unfractionated or low molecular weight) are effective at low doses in prophylaxis of venous thromboembolism [2, 3] and at higher doses in initial treatment of venous thromboembolism [3]. Low molecular weight heparins are more expensive, but have the advantages of once-daily administration (facilitating out-patient prophylaxis or treatment) and possibly lower risks of bleeding and of heparin associated thrombocytopenia. Low molecular weight heparins are more effective than unfractionated heparin in acute coronary syndromes [3]. Newer parenteral anticoagulants include hirudins and pentasaccharides [3].

Warfarin is the oral anticoagulant used most commonly, and is effective in secondary prevention of venous thromboembolism as well as prevention of cardiac thromboembolism in high-risk patients with atrial fibrillation and/or heart valve disease or prostheses. Its major disadvantages include high inter- and intraindividual variability in effect (partly as a result of influences of diet, drugs and alcohol), a narrow therapeutic range, and the need for regular monitoring of the INR. The annual risk of major bleeding is 1–5%. Newer oral anticoagulants include antithrombins and factor Xa inhibitors, which may have more predictable effects, and therefore may not require monitoring and may have a lower risk of bleeding [3].

Thrombolytics

Thrombolytics (streptokinase, t-PA) has an established place in treatment of acute myocardial infarction [3]. Their use in acute stroke [13] and acute venous thromboembolism [14, 15] remains controversial, because of the uncertain balance of bleeding risk and benefit.

Venous thromboembolism

Primary prophylaxis

Early studies of primary prophylaxis of venous thromboembolism in high-risk surgical and medical groups of hospitalized patients used mainly radiolabelled fibrinogen leg scans, which are sensitive to deep vein thrombosis (DVT) especially in the calf veins. In the 1980s such screening was abandoned because of the potential risk of viral transmission by human fibrinogen. Routine venography is invasive, but more specific and sensitive for detection of DVT in proximal veins, which are common after lower limb trauma and orthopaedic surgery. The majority of such thrombi are asymptomatic, but a minority cause symptomatic venous thromboembolism (DVT or pulmonary embolism), in 1–5% of patients following major trauma or major orthopaedic or general surgery, in the absence of specific prophylaxis [2, 3]. The risk of fatal PE is 0.1–1%. About 1–5% of such patients also experience excessive bleeding (e.g. wound haematomas) in the absence of specific prophylaxis.

Clinical endpoints in trials of primary prophylaxis include asymptomatic DVT at routine venography (usually performed 10–14 days after surgery/hospitalization, or earlier if DVT is suspected clinically). The frequency of asymptomatic DVT in the absence of specific prophylaxis is about 40–50% after elective total hip or knee replacement or hip fracture; and about 20–25% after major general surgery or medical illness; about one-third of thrombi are in proximal veins (popliteal or above) [2, 3]. Asymptomatic DVT has been the primary endpoint in recent trials, because trials of several hundred patients are powered to detect reductions in risk compared to the comparator group. However, this endpoint has recently been criticised especially by UK orthopaedic surgeons, because only a minority of such patients experience clinical events; and because if venography is performed 4–5 weeks after elective hip or knee replacement (and 2–3 weeks after heparin prophylaxis is stopped) the incidence of DVT approaches 40% (i.e. heparin prophylaxis only postpones DVT development) [2].

A recent meta-analysis of randomized controlled trials of antiplatelet agents (usually aspirin) including the large PEP trial, observed that aspirin reduced the risks of asymptomatic DVT, symptomatic DVT, and clinical PE, each by about one-third [5]. This benefit was not outweighed by the increased risk of major bleeding (about 1 in 1000 in the absence of concomitant heparin prophylaxis). The large (17 000 patient) PEP trial did not perform screening for DVT, and was designed to detect reductions in clinical DVT and PE.

Pooled analyses of low-dose heparin or unfractionated heparin prophylaxis indicate that they reduce the

incidence of asymptomatic DVT by about two-thirds in general surgical and general medical patients, and also reduce the incidence of PE by about 50% [2, 3]. A key question in orthopaedic surgery is whether or not extended heparin prophylaxis (or warfarin in some North American centres) is more beneficial than routine prophylaxis with spinal/epidural anaesthesia, mechanical prophylaxis (e.g. compression stockings) and aspirin for 5 weeks; given the increased risk of bleeding on heparin or warfarin [2].

Treatment

Routine treatment of acute venous thromboembolism (DVT or PE) is with heparin for a few days and warfarin for 3–6 months. Endpoints in studies include recurrent symptomatic DVT (confirmed by a new or extended thrombus at ultrasound examination or venography) or symptomatic PE (confirmed by a new or extended thrombus/perfusion defect at isotope lung scanning, spiral CT scanning, pulmonary angiography, or echocardiography) [2, 3].

Arterial thromboembolism

In secondary prevention of arterial thrombosis, the usual composite efficacy endpoint is myocardial infarction (MI), stroke, or vascular death (e.g. in meta-analyses by the Antiplatelet Trialists' Collaboration, now the Antithrombotic Trialists' Collaboration) [4]. Vascular death includes fatal MI, fatal stroke, sudden cardiac death, and death resulting from other vascular occlusive events such as mesenteric or limb infarction: all of these clinical events usually have a thrombotic basis. New stable angina or claudication is 'vascular', but not necessarily 'thrombotic': for example it can occur following unusual exercise. On the other hand, new unstable angina or critical limb ischaemia requiring acute hospital admission is more likely to be 'thrombotic'. Coronary, peripheral or cerebral arterial interventions (angiography, angioplasty, bypass grafting, carotid endarterectomy) are certainly costly occurrences; however, there is wide international variation in their incidences, resulting in uncertain generalisability of these endpoints.

About 85% of strokes are thromboembolic (because of cardiac, aortic, carotid or vertebrobasilar thromboembolism; or lacunar infarction), while about 15% are haemorrhagic. It is clearly desirable to try to establish through early investigations whether strokes occurring during trials of antithrombotic agents are thromboembolic or haemorrhagic, for explanatory analysis and discussion. However, to the patient a stroke is a stroke, hence it is pragmatic to include all strokes in the primary composite

endpoint, because the clinical effect of antithrombotic drug administration is on the total stroke rate.

While the WHO definition of stroke has been used for many years, it was recently suggested that the WHO definition of myocardial infarction be replaced by a new definition, based primarily on a serial rise and fall in recently introduced sensitive measures of myocardial necrosis (troponin or creatinine kinase MB fraction) [16]. Such a finding should be accompanied by symptoms of ischaemia, ECG Q-wave or ST segment elevation or depression, or coronary intervention. Pathological findings of acute or healed MI are also included. This proposed redefinition has been criticised [17]. It moves from a primarily clinical diagnosis, supported by investigations (as for stroke and other vascular events), to a primarily biochemical diagnosis, which requires patients to survive long enough to be admitted to one of the minority of hospitals in the world which performs such investigations routinely, and to stay alive for sufficient days for the results of their blood tests to go up and down (or for a coronary intervention – as noted above, the wide international variation in intervention rates makes such definitions poorly generalisable). Because most patients with acute MI die before hospital admission, are admitted to hospitals which do not perform routine troponin or CK-MB assays, or die before the results of such assays can go up and down; and because autopsies are not routinely performed, it is clear that only a minority of patients with MI will be detected by the new definitions; while those with fatal MI will be virtually ignored [17]. The new definition will pick up many trivial cases of 'troponin blips' which leads to inappropriate 'labelling', with adverse consequences for patients. It is *not* a true consensus statement applicable to epidemiological and healthcare monitoring studies of MI and it is to be hoped that the WHO will not approve it. It would be a dangerous precedent, for 'new definitions' of stroke and peripheral ischaemia could also become defined primarily by blood measures of release products from damaged organs, of doubtful clinical significance.

Definitions of bleeding

Robust, clinically meaningful and truly consensual definitions are required, not only for the thrombotic events which antithrombotic drugs may prevent, but also for the bleeding events which they may produce. This is clearly important if practitioners are to use evidence from trials and observational studies to judge the balance of risks and benefits for their individual patients. Estimates such as numbers needed to treat (NNT) and to harm (NHH) require such definitions of thrombotic and bleeding events.

Consensus is approaching that *major bleeding* includes:

- Substantial fall in haemoglobin concentration ($\geq 4 \text{ g dl}^{-1}$) without other explanation
- Need for hospital admission and/or blood/red cell transfusion
- Fatal or disabling bleeding (e.g. intracranial, intraspinal, retroperitoneal, intraocular)

Can we predict thrombotic events?

At present, prediction of risk of arterial thrombotic events (MI and other CHD events, and stroke) is calculated from charts of equations using data on age, sex, and classical risk factors including smoking, diabetes, arterial pressure, and cholesterol (usually, ratio of total: HDL cholesterol) from prospective studies such as Framingham [18]. Such charts should be used to calculate absolute risk of CHD when considering primary prophylaxis with aspirin [6, 7]. These charts can also be used to illustrate (to patients as well as healthcare professionals) the cardiovascular risk benefits of reducing smoking, arterial pressure, and cholesterol concentrations [18]. However, it remains a paradox that we give smoking advice and/or drugs to smokers; blood pressure advice and/or drugs to those with high blood pressure; and cholesterol-lowering drugs to those with high cholesterol; but we give antithrombotics without measuring thrombotic tendency. It is therefore worth assessing whether blood tests of thrombotic tendency are useful in predicting groups of patients at high risk of arterial thrombosis, over and above the risk predicted by classical CHD risk predictors.

While several phenotypic or genetic tests have been evaluated, to date meta-analyses of prospective studies show that plasma fibrinogen [19], viscosity [20], von Willebrand factor [21], t-PA antigen [22], and fibrin D-dimer [23] are independent risk predictors for coronary heart disease. There is some evidence that these variables are also predictors of stroke, although further studies are required. In particular, D-dimer (a global marker of activation of coagulation forming cross-linked fibrin, followed by endogenous fibrinolysis) may be of interest, because high plasma levels can be reduced by warfarin but not by aspirin [24]. In theory therefore, high D-dimer concentrations in persons might predict subsets of the population who might benefit more from longterm anticoagulant prophylaxis, rather than longterm antiplatelet prophylaxis. This hypothesis requires testing in prospective studies.

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