Thrombosis & Platelets

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Thrombosis in coronary artery disease: its pathophysiology and control

Pierre Theroux, MD

From the Department of Medicine - Montreal Heart Institute - and University of Montreal - Montreal - CANADA

Over the last two decades, converging observations on the close interactions between platelets and the coagulation system, and on the biology of the vessel wall, atherosclerosis, and inflammation, have established the role of intravascular thrombus formation as the immediate trigger for acute coronary syndromes. This progress in the understanding of the pathophysiological processes has been matched by the incremental success of treatment achieved by the introduction of aspirin and heparin, new antiplatelet agents (adenosine diphosphate [ADP] and GP IIb/IIIa [GP, glycoprotein] receptor antagonists), and new anticoagulants (low-molecular-weight heparins and direct thrombin inhibitors), and the judicious use of combined antiplatelet therapy and combined antiplatelet and anticoagulant therapy. This article reviews the mechanisms of thrombus formation, the current antithrombotic therapy, and the new antithrombotic therapy that is emerging at an accelerated pace, and the rationale for their use.

A cute coronary syndromes (ACS) are the consequence of a buildup of pathophysiological events that culminate in myocardial ischemia, myocardial infarction (MI), and death. The immediate precipitating cause is intravascular thrombus formation. The thrombus can be totally or severely obstructive, or be the source of distal embolization of thrombotic material plugging the microcirculation. Thus, intramyocardial platelet aggregates are found in association with nonocclusive thrombi at pathology in approximately half of the patients with unstable angina dying suddenly. Myocardial cell ischemia rapidly progresses to cell necrosis in the absence of reperfusion, due to the lack of aerobic reserve of the myocytes.

Although a systemic thrombogenic state can be contributive in some patients, intracoronary thrombus formation is first and foremost a local physiological response of the platelets and of the coagulation system to thrombogenic material exposed to the circulation following endothelial disruption. The underlying cause of endothelial disruption is atherosclerosis and, more precisely, an atherosclerotic plaque rendered friable by intense inflammation and tissue degradation and prone to rupture under the hemodynamic stress.

Given the high prevalence of coronary artery disease and acute coronary syndromes, one can suspect that there is a large number of individuals at risk due to the presence of unstable plaques at subclinical stages of evolution (Figure 1, see page 5). Thus, plaque disruption is found at pathology in 10% of individuals with atherosclerosis dying of noncardiac reasons and, conversely, small thrombi are frequently observed at sites other than those of the major culprit lesion in patients dying of acute coronary syndromes. Multiple focal complex plaques with thrombus, ulceration, plaque irregularity, and impaired flow in locations remote from the culprit lesion have been described in 40% of patients with an acute MI undergoing early angiography.
The florid pathophysiologic mechanisms that cascade to cell death lend themselves to multiple opportunities for interrupting the process at various stages, by acting on: (i) the development and progression of atherosclerosis; (ii) the mechanisms leading to inflammation, plaque degradation, and thrombus formation; and, (iii) the progression of ischemia to cell death (Figure 1). This article focuses primarily on the triggers and mechanisms of thrombus formation that are relevant for practitioners.

Markers of Disease

Markers of atherosclerosis and inflammatory plaque, of activation of platelets and the coagulation cascade, and of cell ischemia and necrosis are numerous. The most useful in clinical practice are summarized in Figure 1. Fibrinogen, C-reactive protein, white cell count, and amyloid-A protein are acute phase reactants associated with inflammation. Interleukin-6 is a proinflammatory cytokine, and neopterin, associated with cell-mediated immunity, is a marker of macrophage activation. The diagnostic and prognostic value of the highly-sensitive C-reactive protein test has been particularly well validated in patients with an ACS or stable angina, and in individuals at risk with no known disease, as well as the benefit of drug therapy with aspirin and with a statin when C-reactive protein values are elevated. Small elevations of troponin T or I values are diagnostic of myocardial cell suffering and necrosis induced by an ongoing thrombotic process and indicate a risk of further distal embolization and/or thrombotic occlusion; antithrombotic therapy is highly effective in these patients. Small elevations of troponin T or I values are diagnostic of myocardial cell suffering and necrosis induced by an ongoing thrombotic process and indicate a risk of further distal embolization and/or thrombotic occlusion; antithrombotic therapy is highly effective in these patients. D-dimers generated by endogenous fibrinolysis are sensitive markers of thrombus formation. Others markers of a thrombotic state are the prothrombin fragment F1+2, released when thrombin is generated, and the thrombin-anti-
thrombin complex marking the presence of thrombin. ST-segment shifts reflect regional ischemia in relation with severe coronary artery obstruction of a dynamic or fixed nature. Brain natriuretic factor can also be useful in patients with an ACS as an indicator of the severity of left ventricular dysfunction associated with the ischemia.

THROMBUS FORMATION

Platelets and coagulation factors are the main players in intracoronary thrombus formation and act in close intimacy (Figure 2). Thrombin is the most powerful platelet agonist in vivo, whereas platelets provide a membrane surface for the assembly of the coagulation system and acceleration of the enzymatic reactions by outside translocation of the inner acidic membrane phospholipid layer early during activation. Furthermore, activated platelets secrete numerous coagulation proteins, such as fibrinogen and factors V, XI, and XIII. The basis for thrombus formation is a segment of endothelium that has lost its integrity and thereby its anticoagulant, antiplatelet, and fibrinolytic properties; white cells contribute to the process as active spectators.

Platelet function

Platelets circulate freely in the blood stream in an inactive state, but are geared toward prompt reaction and adhere to the damaged endothelium. Adhesion triggers a series of internal events in platelets that result in thrombus formation and can also contribute to progression of atherosclerosis. Platelets cannot renew themselves, since they have no nucleus. Their half-life is 7 to 10 days, therefore, 10% of the platelet pool is replenished every day by shedding from megakaryocytes. Platelet function is classically divided into adhesion, activation, secretion, and aggregation (Figure 3, see next page).

![Figure 2](image_url)

**Figure 2.** Close and reciprocal interactions between platelets and coagulation factors in thrombus formation. The membrane of activated platelets provides the surface for assembly of the coagulation factors; thrombin is the most potent platelet agonist.

**Figure 1.** Summary of the cascade of events associated with the development of acute coronary syndromes. There is a broad base of patients and of individuals at risk; only proportions progress to more advanced stages of the disease. Mechanisms involved are indicated (left) as well as clinically useful markers (right).

**Abbreviations:** CK-MB, creatine kinase, myocardial band; hs, high sensitivity.
Weibel-Palade bodies, and GP Ia/IIa (α2β1) binds collagen present in the deeper vessel wall. Other glycoproteins play a supportive role.

**Activation and secretion**

Adhesion, like agonist stimulation, induces intracellular signaling via the messenger G proteins, leading to an increase in intracellular calcium content via modulation of the activity of adenylate cyclase (AC) and guanylate cyclase (GC) and activation of phospholipase C (PLC) and phospholipase A2 (PLA2). AC and GC raise cyclic adenosine monophosphate (cAMP) and guanosine-3',5'-monophosphate (cGMP) levels, respectively, thereby promoting calcium uptake into the sarcoplasmic reticulum and reducing platelet activation. PLC activates platelets by mobilizing calcium from the dense tubular granules, and PLA2 liberates arachidonic acid from the cell membrane, which acts as an agonist for PLC. Strong platelet agonists stimulate both PLC and PLA2, whereas weak agonists mainly stimulate PLA2. The increase in Ca2+ concentration is central to further platelet activation. It leads to polarization of the membrane phospholipids, cytoskeleton contraction, platelet shape changes, release, and surface expression from the intracellular granules of a host of active products promoting aggregation and activation, further platelet recruitment, vasoconstriction, mitogenesis, and cell proliferation. Dense granules mainly secrete coagulation and growth factors, while α-granules secrete platelet agonists. Conformational changes and clustering of the GP Ia/IIa complexes occur during platelet activation, making them competent to bind fibrinogen and various other ligands.

The most important endogenous platelet agonists are thromboxane A2 (TXA2) and adenosine diphosphate (ADP), secreted by activated platelets, and thrombin, generated at the platelet surface by the coagulation process.

**The cyclooxygenase pathway and thromboxane A2**

Arachidonic acid released from membrane phospholipids is converted into leukotrienes by lipoxigenase and into intermediate prostaglandin endoperoxides by cyclooxygenase (COX), and is subsequently transformed into prostacyclin (PGI2) and TXA2. TXA2 is a potent vasoconstrictor and platelet aggregant, whereas PGI2 is a potent vasodilator and antiaggregant. COX occurs as two isozymes. The COX-1 isozyme is constitutive in platelets and most tissues. The COX-2 isozyme, 60% homologous with COX-1, but produced by a different gene, is readily inducible in smooth muscle, endothel...
ial cells, and monocytes/macrophages by cytokines and growth factor stimulation. Arachidonic acid can also be nonenzymatically converted through lipid peroxidation by oxygen free radicals and low-density lipoprotein (LDL) particles into a series of compounds named isoprostanes. Some of these, like 8-iso-PGF$_{2a}$, induce vasoconstriction and amplify the response of human platelets to other agonists.

**ADP and the purinergic receptors**
ADP is released from the platelet granules and from nonplatelet sources like damaged red cells. It plays numerous roles in platelet functions like mediation of thrombin-induced binding of vWF to GPIb/IX, activation of PLC, inhibition of AC activity, and mobilization and clustering of the GP Ib/IIa complexes. The effects of ADP are enhanced in situations of high shear stress, whereas the ADPase activity of the vessel wall is reduced with endothelial injury. ADP purinergic receptors (P$_{2x}$) are classified into three varieties: (i) P$_{2x}$, which are ion-gated channels responsible for early calcium entry into the cell; (ii) P$_{2y}$, coupled with activation of PLC to mobilize calcium and produce early changes in shape and initiation of aggregation; and (iii) P$_{2y3}$, coupled with amplification of AC secretion and aggregation.$^8$

**Thrombin**
Thrombin cleaves the protease-activated receptors PAR-1 and PAR-4 to generate a new amino-terminal that becomes a ligand activating its substrate. Thrombin therefore has a chain effect, one molecule of thrombin having the potential to cleave numerous receptors.

**Aggregation**
Platelet bridging and aggregation to form the three-dimensional platelet clot is mediated by the binding of one fibrinogen molecule to several GP Ib/IIa receptors. Other molecules containing an Arg-Gly-Asp (RGD) sequence, such as vWF, fibronectin, vitronectin, and thrombospondin, are also recognized by the receptor. Fibrinogen, however, is the main ligand by a mass effect because of high plasma concentrations. Fibrinogen is a symmetrical molecule with six binding sites for the receptor, two RGD sequences on each α chain, and one dodecapeptide (KQAGDV) chain on each γ chain. The integrin GP Ib/IIa is specific to platelets and is the most abundant glycoprotein, with 40 000 to 80 000 copies per platelet and an additional 30 000 expressed from an internal pool upon platelet activation. The integrin requires conformational changes to become competent to bind fibrinogen; this is achieved by inside-to-outside signaling. Alternatively, the receptor can be stimulated by an outside-to-inside signaling when occupied with immobilized fibrinogen or other ligands and chemicals, including drugs.$^9$ This results in expression of new ligand-induced binding sites (LIBS) and stimulation of many platelet functions. This outside-to-inside signaling may vary in intensity with different compounds and different sites occupied on the receptor.

**Heterotypic aggregation**
The interactions between platelets and leukocytes are particularly critical for linking inflammation and thrombosis. Platelet-neutrophil and platelet-macrophage co-aggregates are formed through the binding of P-selectin expressed on activated platelets with P-selectin ligand-1 (PSLG1) on myeloid cells, and through fibrinogen cross-linking the β3 chains common to integrin GP IIb/IIIa and integrin MAC-1 (CD11b/CD18) on white cells. The CD40 ligand expressed by activated platelets interacts with CD40 receptors present on endothelial cells, smooth muscle cells, macrophages, and T-cells, to promote expression of adhesive molecules, inflammatory cytokines, and tissue factor, enhancing the inflammatory and thrombotic activity of the active plaque.

**The coagulation system**
Four critical pivotal steps exist in the coagulation cascade: formation of the tissue factor–factor VIIa complex (TF–FVIIa), factor Xa, thrombin, and fibrin (Figure 4). Tissue factor is a membrane glycoprotein normally present in the adventitia of vessel wall and not exposed to the circulation. It is overexpressed in the atherosclerotic plaques, mainly in the inflamed plaque, by monocytes/macrophages and smooth muscle cells surrounding the lipid core. When exposed to the circulation, it binds factor VIIa. The complex triggers both the extrinsic and intrinsic pathways of coagulation by activation of factor X and factor IX, respectively. The two pathways converge to generate factor Xa within the tenase complex. Factor Xa is pivotal as it converts prothrombin to thrombin within the prothrombinase complex. Thrombin has multiple functions in addition to converting fibrinogen into fibrin: it contributes to the cross-linking of fibrin, amplifies its own reaction by stimulating factors V, VIII, and XI, and activates a number of cells, including platelets, white blood cells, endothelial cells, and smooth muscle cells.

**Natural anticoagulants**
Antithrombin (AT), tissue factor pathway inhibitor (TFPI), and activated protein C (APC) are natural anticoagulants. AT inhibits thrombin, factor Xa, and fac-
tors IXa, XIa, and XIIa. TFPI forms a complex with factor Xa, which inactivates factor Xa, and the TF-FVIIa complex. Thrombin forms a complex with thrombomodulin in the vessel wall to activate protein C, inhibiting the activation of factors Va and VIIIa. The complex also activates the thrombin-activatable fibrinolysis inhibitor (TAFI) to prevent the conversion of plasminogen into plasmin.

**ANTIPLATELET THERAPY**

Alongside aspirin, which has become the cornerstone of therapy for cardiovascular diseases, a number of new platelet-active agents have been developed, expanding the available options for antiplatelet therapy. The extensive meta-analysis by the Antiplatelet Trialists’ Collaboration, which included more than 100,000 individuals, delineated the benefit expected from antiplatelet therapy.10 All risk categories of patients combined, antiplatelet therapy reduces the risk of MI, stroke, or vascular death by 22% (P < 0.00001), death by 15%, (P < 0.00001), nonfatal MI by 35% (P < 0.00001), and nonfatal stroke by 25% (P < 0.00001).

In acute situations, the risk reductions were 11% in stroke, 30% in MI, and 46% in unstable angina. In secondary prevention trials in patients with prior stroke or transient ischemic attack, prior MI, or peripheral vascular disease, the risk reductions ranged from 20% to 25%. Aspirin reduces the risk associated with balloon angioplasty by 53%, preserves patency of venous grafts, and prevents shunt thrombosis in hemodialysis. Figure 3 gives a classification of antiplatelet agents according to their platelet effects. Thus, GP IIb/IIIa antagonists prevent aggregation, but do not inhibit activation, whereas aspirin blocks TXA2-induced activation and aggregation, but has little influence on aggregation induced by other agonists (Figure 5). As these drugs have relatively selective sites of action, additive benefit resulting from the combination of various drug is not surprising.

**Platelet adhesion**

Many drugs under development block the GP IIb/IIIa interaction, preventing platelet adhesion. This approach raises concerns about the risk of bleeding, since it interferes with the initial platelet response to tissue injury.

**Calcium mobilization**

Prostacyclin and prostacyclin analogs stimulate the activity of AC, and nitric oxide and organic nitrates stimulate the activity of GC, to produce cAMP and cGMP, respectively. Specific phosphodiesterase (PDE) inhibitors can prevent the degradation of these cyclic nucleotides and maintain intracellular calcium concentrations low and reduce platelet activation. The type III gene family is selective for cAMP-PDE and type V for
The use of PG\(_I\)\(_2\) and active analogs like iloprost did not show any benefit, nor did numerous trials performed with dipyridamole alone or in combination with aspirin. A modified sustained-release formulation of dipyridamole was recently successfully evaluated in a trial involving 6602 patients with prior stroke or transient ischemic attack\(^{11}\). The risk of stroke or death was reduced by 15% with dipyridamole 200 mg bid \((P=0.015)\), compared with placebo, by 13% \((P=0.016)\) with aspirin 25 mg bid, and by 24% \((P=0.0001)\) with the combination of both drugs. The combination therapy (Aggrenox\textsuperscript{TM}) now approved for the secondary prevention of stroke, has not yet been tested in other manifestations of cardiovascular disease. Cilostazol, a specific PDE3 inhibitor, has shown some success in preventing restenosis and stent thrombosis.

**Platelet agonist pathways**

Most antiplatelet drugs block relatively specific pathways of platelet aggregation. Heparins and the more potent direct thrombin inhibitors block the formation of the PAR-1–tethered ligand. Ketanserin blocks the serotonin receptor antagonist, and \(\beta\)-blockers inhibit the catecholamines’ effects on platelets. The main targets of current therapy are the cyclooxygenase pathway and the ADP receptor.

**The cyclooxygenase pathway and aspirin**

Aspirin acetylates serine residue 530 on COX-1, preventing conversion of arachidonic acid into TXA\(_2\). This inhibition is reversible in platelets because COX production is regulated by the cell nucleus. It is dose-related, cumulative, and completely obtained with a single dose of 300 mg or repeated low doses of 80 mg/day, which achieve peak blood concentrations of 0.02 mM. Intermediate doses of aspirin of 2 to 4 g/day (0.2 mM) inhibit COX-2, and high doses of 6 to 8 g/day (0.4 mM) possess analgesic and antipyretic effects. Very high doses of 16 g/day (5 mM) have anti-inflammatory, anticytokine, and anti–cell adhesion molecule effects. Inhibition of COX-1 is believed to fully account for the benefits of aspirin\(^{13}\). Some anti-inflammatory effects cannot, however, be excluded. In the Physicians’ Health Study (PHS), the risk of a first MI and the benefit of aspirin were both directly related to the baseline levels of C-reactive protein.
The benefits of aspirin are present in acute situations as well as in secondary prevention, and across the broad spectrum of manifestations of cardiovascular thrombotic disorders. Aspirin is also useful in primary prevention in selected individuals. In a meta-analysis of 4 trials including more than 51,000 subjects, aspirin reduced the risk of nonfatal MI by 32% (95% confidence interval [CI], 21%-41%) and the risk of important vascular events by 13% (95% CI, 5%-19%). There was no increase in risk of vascular disease–related death (+1%; 95% CI, -12% to 16%) and nonfatal stroke (+8%; 95% CI, -12% to 33%), but a 1.7-fold increase in risk of hemorrhagic stroke (95% CI, 6%-269%).

The adverse effects of aspirin are primarily related to bleeding, particularly gastrointestinal. The risk is reduced, but still present, with the low doses. Contraindications to aspirin are infrequent; these are intolerance and allergy, active bleeding, an active peptic ulcer or other serious source of bleeding. Gout may rarely be precipitated because of impaired urate excretion. The reduction of vasodilator effects of angiotensin-converting enzyme (ACE) inhibitors appears to be of little clinical significance.

The issue of aspirin nonresponders is clinically important and is discussed by C. Patrono in this issue of Dialogues.

**TXA2 synthetase and TXA2 receptor inhibitor**

Dazoxiben, a TXA2 synthetase inhibitor, failed to show any benefit in various clinical situations. Ridogrel, in addition to blocking the synthetase, is a weak antagonist of the TXA2 receptor (TP). The drug failed to show any advantage over aspirin as adjunctive treatment to streptokinase in acute MI. S 18886, a potent antagonist to the receptor with favorable pharmacodynamics, has been evaluated in pilot studies and is now in phase 3 investigation.

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**

NSAIDs reversibly inhibit the two COX isoforms. COX-2 possesses the same serine residue as COX-1 for acetylation, but is more accommodating and requires higher dose of aspirin for complete blockade. No clear benefit has been demonstrated with sulfipyrazone. Indobufen, a more potent inhibitor, was effective in preventing venous graft occlusion.

COX-2 inhibitors do not possess significant antiplatelet properties and may have some negative effects by blocking prostacyclin synthesis. A small excess of stroke and MI was reported with rofecoxib (0.8% versus 0.4%), but not with celecoxib. The differences between the two drugs could be explained by different study populations and different use of aspirin and naproxen, which have antiplatelet effects. The use of low-dose aspirin is recommended when a coxcib is prescribed in patients with a previous ischemic cardiovascular event.

**Other drugs**

Fish oils containing the omega-3 fatty acids substitute for arachidonic acid to produce biologically inactive thromboxane. Triflusal is a salicylic acid derivative that reversibly inhibits COX-1, with benefits in the same range as those of aspirin.

**ADP receptor antagonists**

The following looks only at the thienopyridines and P2Y12 purinergic antagonists; a special chapter is devoted to the GP IIb/IIIa antagonists.

**The thienopyridines**

Clopidogrel and ticlopidine share similar chemical structures and physiologic effects. They are prodrugs requiring liver transformation for pharmacological effect. Their metabolites, which are not well identified, inhibit the P2Y12 receptor by approximately 60%. Full biologic efficacy is reached after 3 to 5 days of administration or earlier, within a few hours, following a bolus administration. As for aspirin, the effects are irreversible and disappear approximately 5 to 7 days after discontinuation. Ticlopidine was shown to be effective in unstable angina, in the secondary prevention of stroke and MI, and in the prevention of coronary artery venous graft occlusion and of subacute stent thrombosis. It is slightly—but significantly—more effective than aspirin in preventing stroke. The side effects are gastrointestinal intolerance, neutropenia in approximately 2.4% of patients (severe in 0.8% of patients), and, rarely, thrombotic thrombocytopenic purpura. Neutropenia usually resolves within 1 to 3 weeks after discontinuing therapy, but may be fatal, as can be thrombocytopenic purpura. Monitoring of ticlopidine therapy includes a complete blood count and differential counts every 2 weeks during the first 3 months.

Clopidogrel has, in practice, replaced ticlopidine, based on similar properties, a safer side effect profile, and on the results of the Clopidogrel versus Aspirin in
Patients at Risk of Ischemic Events (CAPRIE)\textsuperscript{17} and Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trials.\textsuperscript{18} The CAPRIE trial randomized 19,185 patients with a recent ischemic stroke or MI, or with peripheral arterial disease, to clopidogrel (75 mg/day) or aspirin (325 mg/day). Clopidogrel reduced the annual risk of ischemic stroke, MI, or vascular death by 8.7% ($P=0.043$).

CURE compared the combination of aspirin (75-325 mg/day) with clopidogrel (300 mg loading dose followed by 75 mg/day) with aspirin plus placebo, in 12,562 patients. The study drugs were initiated within 24 hours of admission for an ACS and administered for a minimum of 3 months and up to 1 year. The primary end point of cardiovascular death, MI, or stroke was reduced by 20% with the combination (9.28% vs 11.47%, $P=0.00005$) (Figure 6). The results were very homogenous for all end points and subgroup analyses. The survival curves diverged within the first days, during the first 30 days, and again between 30 days and 1 year. The combination therapy increased the risk of major bleeding from 2.7% to 3.6% ($P=0.03$), that of minor bleeding from 8.6% to 15.3% ($P<0.0001$), and the need for transfusion from 2.2% to 2.8%, ($P=0.03$). The rate of bleeding with coronary artery bypass surgery performed within 5 days after stopping clopidogrel was 9.5%, compared with 4.4% with placebo, and 6.3% when the drug was discontinued for more than 5 days before surgery. There was no excess thrombocytopenia or neutropenia with clopidogrel compared with placebo. Bleeding following the administration of clopidogrel can be controlled by platelet transfusions.

**PY12 purinergic antagonists**

Selective specific inhibitors of the PY12 receptors with the potential to optimize the benefit of ADP receptor blockade are under development. These drugs inhibit the receptor directly, reversibly, and dose-dependently. They are active orally as well as intravenously and possess a short half-life.

**THE GP IIb/IIIa RECEPTOR ANTAGONISTS**

Experimental and clinical studies show that clinically significant benefit is obtained with GP IIb/IIIa receptor antagonists achieving 80% and more receptor occupancy, which results in approximately 80% inhibition of ADP-induced aggregation. Some agents possess strong affinity for the receptor, with platelet half-life outlasting plasma half-life. Other agents have no special affinity and platelet occupancy is in equilibrium with plasma levels. Abciximab is a Fab fragment of a chimeric antibody. Eptifibatide and tirofiban are small molecules that have been approved for clinical use. Eptifibatide tightly binds the RGD- and dodecapeptide-recognizing sequences of the receptor. Plasma half-life is approximately 10 minutes and biologic half-life 6 to 12 hours. Receptor occupancy persists weeks after drug exposure, although platelet aggregation progressively returns to normal within 12 to 24 hours. Abciximab is not specific for GP IIb/IIIa and also inhibits the vitronectin receptor ($\alpha_v\beta_3$) on the endothelium and smooth muscle cell and MAC-1 ($\alpha_m\beta_3$) integrin on neutrophils and monocytes. The clinical relevance of occupancy of these receptors involved in cell proliferation and leukocyte activation, respectively, is not well known.

Eptifibatide is a cyclic heptapeptide derived from the structure of barbourin occurring in the venom of a pigmy rattlesnake possessing a Lys-Gly-Asp (KGD) sequence able to bind fibrinogen. Tirofiban is a non-peptide mimetic of the RGD sequence. The half-life of the two compounds is approxi-
mately 2 hours, with 50% recovery of aggregation within 4 hours after drug discontinuation and nearly 100% within 8 hours.

Although most evidence points to a class effect of GP IIb/IIIa receptor antagonists, it is appropriate to consider the drugs according to clinical situations, as clinical trials have shown heterogeneous results that could be related to study designs, type of population enrolled, dose selections, drug properties, or other factors.

**Effects according to clinical situations**

**Coronary angioplasty and stent implantation**

Numerous clinical trials have documented the efficacy of abciximab in elective as well as in emergency procedures and with balloon angioplasty as well as with stent implantation; the reductions in risk of death, MI, or need for target revascularization reach 40%, and the benefits are sustained over the long term. Meta-analyses have also documented a reduction in death. The Evaluation of IIB/IIA platelet receptor antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial was the prototype of these trials and led to drug approval. The Chimeric 7E3 AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) trial enrolled patients with refractory unstable angina after the identification of a culprit lesion suitable for angioplasty, while the Evaluation of Platelet IIb/IIA Inhibitor for STENTing trial (EPISTENT) trial enrolled patients undergoing elective or emergency stenting.

One placebo-controlled trial with eptifibatide showed risk reductions within the range of those observed with abciximab after dose optimization and a double bolus injection. Only one trial directly compared the respective benefit of two different GP IIb/IIIa antagonists. This trial demonstrated the superiority of abciximab over tirofiban when used before stent implantation; the doses of tirofiban in the catheterization laboratory might have been inadequate. Based on these results, abciximab is recommended as the first-choice GP IIb/IIIa antagonist in the catheterization laboratory, particularly in high-risk patients, and eptifibatide as a valid second choice.

**Non–ST-segment elevation ACS**

Contrasting with the results observed in percutaneous procedures, abciximab showed no benefit in the medical management of patients with an ACS. The large Global Use of Streptokinase and Tissue plasminogen activator for Occluded arteries (GUSTO-IV) trial enrolled 7800 patients excluding those in whom percutaneous coronary intervention (PCI) or coronary artery bypass grafting was planned within 30 days. The primary end point of death or MI at 30 days occurred in 8.0% of patients administered placebo, 8.2% of patients randomized to a 24-hour infusion of abciximab, and 9.1% of patients randomized to 48-hour infusion of abciximab (NS). Patients with troponin elevation had impaired prognosis, but also fared worse with abciximab.

On the other hand, the combination of tirofiban and heparin in the Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) trial reduced the risk of death, MI, or refractory ischemia at 7 days (primary end point) by 32% (P = 0.004) and the risk of death/MI at 30 days by 30% (P = 0.03). Eptifibatide in the Platelet IIb/IIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial (PURSUIT) trial reduced the risk of death/MI at 30 days (primary end point) by 9% (P = 0.042). The benefit was optimized in the two trials in patients who underwent a revascularization procedure. Based on these results, the use of eptifibatide or of tirofiban is recommended in patients with a high-risk ACS, particularly when troponin T or I is elevated and an intervention planned, situations in which the benefit of treatment has been particularly well validated. In the Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival (TACTICS) trial, which randomized patients to an early invasive or noninvasive management strategy and showed superiority of the former.

**ST-segment elevation MI**

Based on favorable angiographic results, the Global Utilization of Strategies to open Occluded arteries in acute myocardial infarction (GUSTO-V) trial tested the hypothesis that the combination of half a dose of reteplase and a full dose of abciximab would improve mortality in ST-segment elevation MI, compared with full-dose reteplase. In the 16 588 patients randomized, mortality at 30 days was 5.6% with the combination and 5.9% with full-dose reteplase (P = 0.43). A secondary end point consisting of death, reinfarction, or emergency percutaneous revascularization was significantly reduced (16.2% versus 20.6, P = 0.0001). There was, however, excess bleeding with the combination and excess intracranial bleeding in patients older than 75 years (2.1% vs 1.1%, P = 0.03).

The ASsessment of the Safety and Efficacy of a New Thrombolytic agent (ASSENT-3) trial randomized 6095 patients to full-dose tenecteplase (TNKase) and
enoxaparin, half-dose TNKase with abciximab, or full-dose TNKase with weight-adjusted unfractionated heparin. The benefit of abciximab was similar to that in the GUSTO-V trial, but there was also excess bleeding, precluding the recommendation to use the drug in patients undergoing thrombolysis. The benefits with enoxaparin were, however, within the same magnitude as those observed with abciximab, with rates of death, myocardial infarction, or refractory ischemia significantly less frequent than with unfractionated heparin (11.4% vs 15.4%, relative risk [RR] 0.74, 95% CI 0.63-0.87, \( P=0.0002 \)). Major bleeding occurred more frequently with enoxaparin (4.8% vs 2.5%, NS), but there was no excess stroke or intracranial bleeding. The trial was not powered to show definitive results. Nevertheless, the favorable clinical experience gained with enoxaparin in ACS and the safety and efficacy data observed in pilot studies with the combination of enoxaparin and various thrombolytic agents support the clinical use of the enoxaparin-TNKase combination. A large ongoing trial is evaluating the value of enoxaparin as adjunctive therapy with various thrombolytic agents.

Abciximab is indicated when primary angioplasty or stenting is planned in patients with ST-segment elevation MI. One study showed that its prompt administration before planned angiography and stenting reduced the rate of death, reinfarction, or emergency revascularization at 30 days from 14.6% with placebo to 6.0% (\( P=0.01 \)) in association with better TIMI-3 flow before the procedure (16.8% vs 5.4%, \( P=0.01 \)), immediately afterward, and after 6 months, supporting the concept of facilitated PCI.

Complications of GP IIb/IIIa antagonists

The major complication of GP IIb/IIIa antagonists is bleeding. This typically occurs at vascular puncture sites or is mucocutaneous; it is severe enough to require blood transfusion in 1% to 2% of patients. More rarely, the bleeding is retroperitoneal, gastrointestinal, or genitourinary. The drugs do not cause intracranial bleeding. Management of severe bleeding requires discontinuation of antithrombotic drugs, transfusion of blood products, and time for the drug to be eliminated. Platelet transfusions (10 units) halt the bleeding caused by abciximab, since the drug is not present in plasma. Platelet transfusion is generally not required with epifibatide and tirofiban, since the high plasma concentrations of the drugs that are in the blood will saturate the new platelets transfused. Furthermore, these high blood concentrations will decline rapidly after discontinuation of the drugs. Emergency surgery can be performed following discontinuation of epifibatide and tirofiban. With abciximab, it may be necessary to decrease the dosage of heparin during surgery under close surveillance of activated clotting time (ACT), and administer platelet transfusions. Severe thrombocytopenia is an unusual complication that occurs in 0.2% of patients, more frequently with abciximab. Thrombocytopenia is believed to be immune-mediated and is not associated with thrombotic complications. Less severe thrombocytopenia with platelet counts below 100 000/mm^3 is more frequent.

Oral GP IIb/IIIa antagonists

Five large trials have shown excess bleeding and no benefit with four different GP IIb/IIIa antagonists, ximelofiban, orbofiban, sibrafiban, and latrofiban. A meta-analysis of four of these trials, totaling 33 326 patients, showed a consistent and statistically significant increase in mortality with therapy (odds ratio [OR], 1.37; \( P=0.001 \)) and trends toward more MI. The exact reasons for the apparent toxicity are not well known. They could be related to platelet activation induced by receptor occupancy through outside-to-inside signaling, resulting in a prothrombotic state or inadequate dosing of the drugs as an attempt to reduce the high rate of annoying bleeding associated with effective doses.

Combination antiplatelet therapy

The different mechanisms of drug effects provide opportunities for added benefit with combination therapies. The combination of aspirin and ticlopidine or clopidogrel is standard therapy for a duration of 3 to 4 weeks after stent implantation, and 6 to 12 months after brachytherapy. An intravenous GP IIb/IIIa antagonist is also currently used with aspirin and clopidogrel at the time of stent implantation.

Additive benefit of the aspirin/dipyridamole combination in the secondary prevention of ischemic cerebrovascular events has been demonstrated in one trial. The CURE trial has documented a clear benefit with the low-dose aspirin/clopidogrel combination in ACS, suggesting a new standard of efficacy of antiplatelet therapy.

ANTICOAGULANT THERAPY

The efficacy of anticoagulants has been well documented in ACS, with an incremental gain from unfractionated heparin (UH) to low-molecular-weight heparins (LMWHs) and direct thrombin inhibitors. A pentasac-
Charide is under investigation. Figure 4 lists the currently available anticoagulants as well as some new promising compounds undergoing clinical investigation.

**Drugs acting on the initiation of coagulation**

Thromboplastin (= tissue factor, TF) and factor VIIa can be inhibited separately, or the TF-VIIa complex can be inhibited as a whole. This latter approach is currently under investigation using a recombinant form of tissue factor pathway inhibitor (TFPI).

**Drugs acting on thrombin generation**

UH, LMWHs, and a pentasaccharide act by accelerating the physiologic effects of antithrombin. UH is a mixture of polysaccharides of various lengths with molecular weights ranging between 5000 and 30 000, which bind to a number of plasma proteins, blood cells, and endothelial cells, and are characterized by poor bioavailability and marked variability in anticoagulant response among patients. The anticoagulant effects need, therefore, to be closely monitored. Fixed doses lead to a substantial proportion of patients being under- or overanticoagulated. Weight-adjusted dosing is therefore recommended. Mild thrombocytopenia occurs in 10% to 20% of patients and more severe thrombocytopenia (platelet count <100 000) in 1% to 2% of patients. A rare (<0.2% incidence), but severe complication is autoimmune heparin-induced thrombocytopenia (HIT) with thrombosis. Serial platelet counts are necessary to monitor for heparin-induced thrombocytopenia.

LMWHs are obtained by depolymerization of the polysaccharide chains to provide chains with lower molecular weights, maintaining the pentasaccharide sequence necessary to bind antithrombin, but with fewer 16-saccharide chains to bind thrombin. Therefore, LMWHs are more selective in catalyzing the inhibition of factor Xa and less selective in inactivating thrombin. They possess distinct advantages over UH, which include less binding to other proteins, dose-independent clearance, and longer half-life, thus enabling reproducible and sustained anticoagulation with once- or twice-daily subcutaneous administration. There is usually no need to monitor the activity of these agents, and less platelet-agonist effects are observed with them. Thrombocytopenia is also less frequent. The pharmacodynamic and pharmacokinetic profiles of the various commercial LMWH preparations depend on their mean molecular weight, which ranges from 4200 to 6000. Accordingly, their anti-Xa-to–anti-IIa ratio also varies, from 1.9 to 3.8. As the short polysaccharide chains are renally excreted, dosage should be reduced or intervals between doses prolonged in patients with significant renal failure, and efficacy should be monitored by assessing anti-Xa activity.

Org31540/SR90107A is a new synthetic pentasaccharide which binds antithrombin with high affinity and highly selectively inhibits factor Xa. Phase 3 studies of prophylaxis of venous thrombosis have been successfully completed, and the pentasaccharide has been approved for this indication. Phase 2 trials in acute coronary syndromes (with and without ST-segment elevation) have been completed with promising results.

Recombinant activated protein C inhibits thrombin generation. The tick anticoagulant peptide (TAP) and antistatin are direct factor Xa inhibitors. Direct inhibitors inhibit thrombin selectively without the need for a cofactor. They act on clot-bound thrombin as well as circulating thrombin and have no known plasma inhibitors. Hirudin directly binds to the anion binding site and the catalytic site of thrombin. It is approved for the prophylaxis of vein thrombosis in hip and knee surgery and for the management of patients with HIT. Argatroban, an arginine derivative that binds thrombin at the apolar-binding site, is also approved for the latter indication. Bivalirudin, a small peptide modeled on the active sites of thrombin, is approved for use during percutaneous coronary angioplasty. A long-acting preparation of hirudin (pegylated hirudin, or PEG-hirudin) suitable for once-a-day subcutaneous administration is currently investigated. Orally active direct antithrombins are being intensively developed, one of them is melegatran, which is currently investigated in atrial fibrillation and in the secondary prevention of coronary ischemic events.

**Clinical use**

**Unfractionated heparin and LMWHs**

A recent meta-analysis of 12 trials including a total of 17 157 patients receiving aspirin and randomized to UH or to a LMWH showed a significant short-term reduction in the rates of death or MI (OR 0.53; CI 0.38-0.73, P=0.0001). The early gain was attenuated in some of the trials by a reactivation of the disease process following discontinuation of anticoagulant, and in one trial after dose reduction from twice-a-day to once-a-day. The meta-analysis further showed a modest advantage of LMWHs compared with UH (OR 0.88, P=0.80). Four comparison trials were included in the
analyses. Two of them showed a significant reduction in the composite end point of death, myocardial ischemia, or refractory ischemia,\(^39,40\) and two no benefit and even some negative trends.\(^41,42\) The two positive trials evaluated enoxaparin. A combined analysis of the 7081 patients enrolled in the two trials showed a significant reduction in MI or death rates with enoxaparin.\(^43\) Whether the heterogeneous results with the LMWHs can be explained by different population characteristics, study designs, different properties, or other reasons is undetermined.

In the trials, UH and LMWH were generally administered for periods of 2 to 5 days. Three trials looked at the potential benefit of longer-term administration, but showed excess bleeding without any additional gain. In one of these trials, the benefit in medically treated patients extended to 45 days.\(^43\) A recent meta-analysis of 15 044 patients from 5 randomized trials comparing the combination of an antivitamin K and aspirin with aspirin alone following an ACS, showed that the combination prevented 3 deaths or reinfarctions (15.3% vs 17.5%, \(P=0.002\)) at the cost of 1 major bleeding (2.4 vs 1.7% (\(P=0.003\)), with some reduction in ischemic stroke and no excess hemorrhagic stroke.\(^44\)

**Hirudin and other direct thrombin inhibitors**

Trials with direct thrombin inhibitors have generally yielded disappointing results despite the theoretical advantages of the drugs and some documentation of superiority over unfractionated heparin. Hirudin, the prototype of direct thrombin inhibitors, has been investigated in three major trials. Excess bleeding rates forced a dosage reduction in these trials. In the Global Use of Strategies To open Occluded arteries in acute coronary syndromes (GUSTO-IIb) trial, 12 142 patients stratified according to presence or absence of ST-segment elevation at admission were randomized to 72 hours of therapy with hirudin or heparin.\(^45\) The primary end point of death or nonfatal MI at 30 days occurred in 9.8% of the hirudin group and 8.9% of the hirudin group (OR 0.89, \(P=0.06\)). The Organization to Assess Strategies for Ischemic Syndromes–2 (OASIS-2) trial included 10 141 patients with an ACS randomized to hirudin or UH. The primary end point of cardiovascular death or new MI at 7 days occurred in 3.6% and 4.2% of patients, respectively (RR 0.84, 95% CI 0.69–1.01; \(P=0.064\)).\(^46\) A meta-analysis of the hirudin trials showed a statistically significant 10% risk reduction in death or MI at 35 days (\(P=0.015\)).\(^46\) Phase 2 trials with other direct thrombin inhibitors, such as argatroban, bivalirudin, and inogatran have not shown any clear benefit.\(^47\) Bivalirudin was effective in balloon angioplasty, with a favorable safety profile.\(^48\) A megatrial of bivalirudin as an adjunct to thrombolysis with streptokinase showed no benefit on the primary end point of death at 30 days and excess bleeding compared with unfractionated heparin.\(^49\)

**CONCLUSIONS**

Antithrombotic therapy is the cornerstone of therapy for acute coronary syndromes, which is consistent with the thrombotic etiology of the disease. Aspirin remains the gold standard and is indicated during the acute phase as well as for secondary prevention. Clopidogrel is indicated in patients intolerant to aspirin as well as in combination with aspirin in high-risk patients with an acute coronary syndrome. The combination therapy is applied for 1 month and up to 9 to 12 months. During the acute phase, combination therapy with unfractionated heparin or, preferably enoxaparin, is indicated. In hemodynamically unstable patients and in patients with elevated troponin T or I or with refractory ischemia, a GP IIb/IIIa antagonist is preferred. These patients are best promptly referred to invasive management. Tirofiban or eptifibatide is used “up-front” before referral to the catheterization laboratory and abciximab or eptifibatide is used in the catheterization laboratory. With this invasive approach, the administration of clopidogrel may be best delayed until the decision is made not to refer the patient to coronary artery bypass surgery. An alternative approach is to administer platelet transfusions if excess bleeding occurs perioperatively. In patients with ST-segment elevation, a combination of enoxaparin and TNKase appears to be the best thrombolytic strategy at the present time, and, when invasive management is selected, “up-front” abciximab to facilitate primary intervention. As the world of antithrombotic therapy is rapidly evolving, keeping constantly abreast of information concerning new and more efficacious treatment strategies is required.
THREE KEY QUESTIONS

Hitherto this issue of the *Dialogues* has focused on antithrombotic therapy as appreciated through drug effects on specific mechanisms of intravascular thrombus formation and clinical trial data. This leaves many practical questions unanswered and exciting opportunities unexplored. In the following section, our expert consultants address three major questions. First, Keith Fox fills the gaps that exist between the world of practice and that of clinical trials, by answering the question: "Thrombosis in coronary artery disease: what are clinical trial and registry data telling us?" The human genome has just been published. So what comes next and how can physicians integrate into their practice the new sciences of genetics, genomics, and proteomics? Francesco Bernardi looks at current knowledge on genetics and thrombosis, with the question "What is the impact of genetics on the thrombotic process?" Finally, Carlo Patrono addresses the long-standing and somewhat elusive concept of aspirin nonresponsiveness, and asks "What are the current issues regarding aspirin and other cyclooxygenase inhibitors?" These issues are a real challenge for our practice, as increasing numbers of new and effective antithrombotic drugs are being incorporated into the therapeutic armamentarium.

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Thrombosis in coronary artery disease: what are clinical trial and registry data telling us?

Keith A. A. Fox, FRCP, FESC
Cardiovascular Research Unit - Department of Medical and Radiological Sciences - Royal Infirmary of Edinburgh - Edinburgh - UK

The clinical consequence of thrombosis, superimposed upon ruptured or eroded plaque in coronary arteries, is an acute coronary syndrome. The clinical manifestations are dependent upon the extent of obstruction to perfusion, microembolization, and the volume of muscle affected. Even in the absence of complete occlusion, about 8% to 13% of patients die within 6 months. Antiplatelet and antithrombin therapies have been tested in large-scale clinical trials with consistent and robust findings. In addition to the benefits of aspirin, thienopyridines and intravenous glycoprotein IIb/IIIa inhibitors improve outcome. Combined antithrombin and antiplatelet treatment is more effective than either alone. Unfractionated and low-molecular-weight heparins reduce cardiac events, but direct antithrombins (hirudin) have not shown convincing clinical benefit. Novel preparations are in development, and show promising results.

Keywords: acute coronary syndrome; platelet; thrombosis; antiplatelet; antithrombin; anticoagulant
Address for correspondence: Keith A. A. Fox, FRCP, FESC, Cardiovascular Research Unit, Dept of Medical and Radiological Sciences, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK (e-mail: k.a.a.fox@ed.ac.uk)

Trials and Registries in Acute Coronary Syndromes: Differences and Similarities

If appropriately designed, clinical trials and registries provide different, but complementary, perspectives on acute coronary syndromes (ACS). To assess the impact of specific treatments, clinical trials are restrictive in their inclusion and exclusion criteria and in the definition of the population to be studied. Thus, the number of patients required to demonstrate a treatment effect is minimized and the dilutional impact of comorbidity (producing “noise” in the data) is limited. This strategy has been very successful in defining the impact of specific treatments in defined risk populations. However, caution must be exercised when the results of such trials are extrapolated to broader unselected populations or when the outcomes of the trials are interpreted as reflecting the outcome of the disease in the wider population. For example, in a study examining the characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants, those randomized in trials were significantly more likely to be less than 70 years old (odds ratio [OR] 3:1) and more likely to be male (OR 2:1), and to have lower comorbidity scores (OR 2:1). In addition, in the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO-I) trial, those randomized, compared with those not randomized, had a more than twofold increased likelihood of undergoing coronary revascularization. As a consequence, in-hospital mortality rates were substantially lower (6.9% in the GUSTO-I trial and 6.6% in the Late Assessment of Thrombolytic Efficacy (LATE) trial, compared with 16.8% and 19.7%, respectively, \( P<0.001 \)). The survival remained more than twofold higher among trial participants even after adjustment for age, gender, revascularization and comorbidity. Thus, there is substantial evidence of selection bias in those included into trials.

Registries can, if appropriately designed, define management and outcome in a geographically representative and unselected population. However, extrapolations from registries about the impact of therapeutic interventions must be viewed with caution because such comparisons are nonrandomized and can be subject to systematic bias. Thus, trials and registries provide complementary, but different, perspectives on the same clinical problem.

In acute coronary artery disease, large-scale registries (Prospective Registry of Acute Ischaemic Syndromes in the UK Organization to Assess Strategies for Ischemic Syndromes [OASIS]) have shown promising results.
istry of Acute Ischaemic Syndromes in the UK [PRAIS-UK], Global Registry of Acute Coronary Events [GRACE],4 and EURO-HEART SURVEY (A. Battler, European Society of Cardiology (ESC) 2001, oral presentation), have defined the scale of the problem, and recent large randomized trials have assessed the impact of antiplatelet and antithrombotic therapy. Registries that are conducted alongside clinical trials may, potentially, suffer from bias if they are restricted to trial centers or to recruitment sites with skewed referral practice. In a recent editorial, Alpert defined a series of characteristics as quality standards for registries. These included: standardized definitions, robust sampling techniques, randomized or community-wide data collection, measures to ensure training of personnel, and avoidance of selection bias and compliance with appropriate ethical and institutional Review Board requirements. The largest contemporary registry of acute coronary syndromes, the GRACE registry, fulfills each of these reference standard criteria and includes more than 10 000 patients per annum from clusters of hospitals in four continents. These findings are more comprehensive and representative, but, not surprisingly, exhibit higher rates of morbidity and mortality during follow-up than seen in recent clinical trials.4

The Outcome: Where Does the Truth Lie?

Prior to the recent large-scale systematic registry studies, with consistent disease definitions, estimates of outcome were confounded by different definitions of the clinical syndrome and dilution of the population with nonischemic chest pain. The recent large-scale registries (refs 2-4 and A. Battler, ESC 2001, oral presentation) have employed consistent disease definitions (the clinical syndrome of ischemic pain plus ECG evidence of ischemia and/or biochemical markers) and have produced similar estimates of outcome (Figure 1) and novel insights into the disease process.

In unselected patients, the risks of death (from admission to 6 months) for hospitalized patients with an ACS are 5% to 8% for unstable angina (the clinical syndrome and ECG changes only), 13% for non–ST-segment-elevation myocardial infarction (MI) (the clinical syndrome, ECG changes, and CK-MB or troponin markers of injury) and 12% for ST-segment elevation MI.6 However, in those with ST-segment elevation MI, there are additional risks of death prior to hospitalization (mainly arrhythmic deaths). This risk varies with age; only 40% of those above 85 years survive to reach hospital alive, compared with 80% of men and women younger than 55 years.7

Remarkably, the risks of death are similar among those surviving to reach hospital alive, irrespective of whether they sustain an ST-segment elevation MI or a non–ST-segment elevation MI.4 It is possible that the more extensive myocardial damage sustained by the ST-segment elevation population is offset by the continuing hazard of further thrombotic and occlusion events among
the remainder. Furthermore, in contrast to the situation with ST-segment elevation MI, where most of the hazard is early, the remainder of ACS patients have a relatively low in-hospital risk of death (6% for non–ST-segment elevation MI and 3% for unstable angina), but a continuing risk of death, MI, stroke, and rehospitalization for unstable angina over the succeeding months.

ANTIPATELET THERAPY

Antiplatelet therapy aims to reduce the acute and longer-term consequences of platelet aggregation and the impact on intracoronary thrombus generation. In addition, the consequences of platelet-monocyte interaction and indirect consequences of platelet aggregation (via released products) contribute to changes in the inflammatory response in the vessel wall and potentially to hazards of further plaque rupture.

Aspirin

The Anti-Platelet Trialists’ Collaboration has recently undertaken a further meta-analysis, and the results demonstrate convincing evidence of benefit. By far the most commonly used oral agent is aspirin, and based upon seven trials in patients with unstable angina, there is a 46% risk reduction compared with about a 35% risk reduction seen in all of the other populations studied, including stable angina, post–percutaneous transluminal coronary angioplasty (PTCA), and post–coronary artery bypass grafting (CABG). The risks of acute MI are reduced from 14.2% to 10.4%. These findings reinforce the earlier meta-analysis. The risk of bleeding is increased with aspirin, but this risk is dose-related, modest, and more than offset by the substantial reduction in hazards of thrombotic events.

ADP-receptor antagonists

The thienopyridines ticlopidine and clopidogrel inhibit the P2T receptor of the platelet, and these agents have been widely used to prevent coronary graft occlusion and subacute stent thrombosis. Ticlopidine has been superseded by clopidogrel, which lacks the problems of neutropenia and thrombocytopenia seen with ticlopidine. Clopidogrel was tested against aspirin in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial of 19 185 patients with vascular disease, and this resulted in a modest, but significant, risk reduction of 8.7%. Clopidogrel exhibited a similar side effect profile to aspirin, but with less gastrointestinal bleeding.

The combination of cyclooxygenase and adenosine diphosphate (ADP) antagonism produces even more effective inhibition of platelet aggregation in vitro and in vivo. The large-scale Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial compared clopidogrel (300 mg, then 75 mg daily) with placebo in 12 562 aspirin-treated patients. The drugs were initiated within 24 hours of onset of ACS and administered for up to 1 year. The primary end point was cardiovascular death, MI, and stroke and this was reduced from 11.47% to 9.28% (relative risk [RR] 0.80, CI 0.72-0.90, P=0.00005). Importantly, the beneficial effects were not confined to specific risk groups (similar risk reduction in males/females, diabetics, hyperten-
sives, and all age-groups). Most of the benefit occurred during the first 30 days, but the curves continued to diverge up to the end of follow-up of 1 year. The risk of major bleeding was increased from 2.7% to 3.6% (P=0.03) and the need for transfusion was increased by 6%. There was no excess in life-threatening bleeding and no thrombocytopenia or neutropenia.

The Percutaneous Coronary Intervention–Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial analyzed those patients proceeding to percutaneous intervention and demonstrated a 30% risk reduction. Again, the curves continued to diverge out to 1 year. Overall, there was 12.6% cardiovascular death or MI in the placebo group and 8.8% in the clopidogrel-treated group, (RR 0.69; CI 0.54-0.87; P=0.002). The implications of these large-scale trials with relatively broad inclusion criteria are that combination therapy with aspirin and clopidogrel will form the basis of antiplatelet therapy in patients with clear evidence of ACS.

**GP IIb/IIIa receptor antagonists**

Activated platelets express a series of receptors, including the glycoprotein (GP) IIb/IIIa receptor, and these receptors contribute to aggregation by bridging platelets via fibrinogen or von Willebrand factor.

Extensive large-scale trials have investigated the role of oral and intravenous GP IIb/IIIa inhibitors in patients with ACS and in patients undergoing percutaneous coronary intervention (PCI). The overall findings based upon a meta-analysis of all trials demonstrate a convincing treatment effect equivalent to 20 fewer deaths or MI (predominantly MI) per 1000 patients treated and 30 fewer deaths or MI or revascularizations per 1000 patients treated. However, these overall results do not necessarily reflect the treatment groups with most benefit. For example, an analysis of trials of higher-risk patients (as reflected by troponin positivity) has demonstrated much more marked treatment effects than for patients with no elevation in troponin (Figures 2 and 3).

Similarly, the majority of treatment effect is in patients at higher risk who proceeded to coronary intervention. In contrast, large-scale trials of GP IIb/IIIa inhibitors in predominantly medically treated patients (Global Use of Streptokinase and Tissue plasminogen activator for Occluded arteries [GUSTO-IV] ACS), there was no evidence of any improvement in death or MI from

![Figure 2. The impact of glycoprotein (GP) IIb/IIIa inhibitors in troponin-positive patients. In both the CAPTURE and PRISM trials, the impact of GP IIb/IIIa inhibitors (for the outcome of death or MI) show marked benefit (principally in MI) in those patients at high risk, including those that are troponin-positive.](image)

Study acronyms: CAPTURE and PRISM, see reference citations below.

either 24 hours or 48 hours of abciximab treatment versus placebo. Furthermore, there was an increase in bleeding risk. The very large-scale Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial (PURSUIT) included a broad spectrum of ACS patients, 37% of whom proceeded to PCI or CABG. With eptifibatide treatment, the risk of death or MI at 30 days was reduced by 1.5% (P=0.042), but this absolute reduction was rather modest. In contrast to the findings with intravenous GP IIb/IIIa inhibitors, a meta-analysis of oral agents demonstrated an increase in mortality (OR 1.37; CI 1.13-1.66; P=0.001) with trends for increased risks of MI. The oral agents have low bioavailability and transient receptor occupancy, potentially resulting in upregulation of platelets and paradoxical increases in risk. Thus, despite convincing in vitro and preliminary data, the large-scale clinical trials have convincingly shown: (i) no evidence of benefit; and (ii) evidence of increased hazard.

**Antithrombin Therapy**

Arterial thrombosis is triggered following exposure of procoagulant components of atheromatous plaque and constituents of the vessel wall (Figures 4 and 5, see next page). Platelet adhesion and aggregation markedly amplify this prothrombotic response.

**Unfractionated and low-molecular-weight heparins**

Unfractionated heparin forms a complex with antithrombin III, inhibiting the development of thrombin. Maintaining accurate anticoagulation with unfractionated heparin is difficult because acute-phase proteins interfere with anticoagulation, and studies have demonstrated that despite attempts at meticulous control, only a minority of patients are in the therapeutic range for anticoagulation (approximately one third at 24 hours). More sustained and predictable anticoagulation is therefore required.

In a meta-analysis of twelve trials, 17 157 patients received aspirin in addition to unfractionated heparin or low-molecular-weight heparin (LMWH). The results were convincing, the use of a form of heparin compared with placebo almost halves the rates of death or MI (OR 0.53; CI 0.38-0.73, P=0.0001). In pooling all of the LMWH results, a trend for an advantage was demonstrated over unfractionated heparin (OR 0.88; CI 0.69-1.12), but this analysis (only up to 72 hours) is inappropriate for longer treatment duration trials. Also, the meta-analysis assumes no heterogeneity among LMWH preparations, and this is incorrect in view of differences in anti-Xa/anti-IIa ratios and in the half-life of the preparations. In contrast, a meta-analysis of the trials involving one LMWH (enoxaparin) showed the OR for death or MI was 0.77 (CI 0.62-0.95) at 8 days and remain significant at 43 days and 1 year. These findings suggest that some LMWHs are superior to unfractionated heparins in the treatment of patients with unstable angina or non-ST-segment elevation MI. Other trials, including FRagmin In unstable Coronary artery disease (FRIC) and FRAXiparin in Ischemic Syn-
dromes (FRAXIS), have not shown a significant advantage over unfractionated heparin. Overall, the most cautious interpretation from these studies is that the LMWH preparations, in general, are at least equivalent to unfractionated heparin and that they have the clinical advantage of subcutaneous administration and no requirement for monitoring.

Direct antithrombins

Despite demonstrated advantages in vitro, the large-scale clinical trials of the direct thrombin inhibitors have been disappointing. Hirudin was investigated as an adjunct to thrombolysis with tissue plasminogen activator (t-PA) and showed no benefit (TIMI-9b).20 In the Global Use of Strategies To open Occluded arteries in acute coronary syndromes [GUSTO-IIb] trial, 12 142 patients with or without ST-segment-elevation were randomized to hirudin or heparin.21 There was no significant benefit in death or MI, and some increase in bleeding risk. In the OASIS-II trial (10 141 patients with ACS), patients were randomized to hirudin or unfractionated heparin, and the primary end point of cardiovascular death or MI occurred in 3.6% (hirudin) versus 4.2% (unfractionated heparin) of patients (RR 0.84; CI 0.69-1.01; P=0.064).22 The meta-analysis of hirudin trials indicates a 10% risk reduction in death or MI at 35 days, but this benefit is at the cost of an increase in bleeding. Thus, despite their promise, direct antithrombins have not shown a clinically meaningful advantage over unfractionated heparin. Compared with LMWHs, their therapeutic window is more narrow, and antithrombins require very careful monitoring to minimize bleeding risk. Currently, the direct antithrombins are only used in patients with heparin-induced thrombocytopenia.

IMPLICATIONS OF REGISTRY DATA FOR CLINICAL PRACTICE

Registries can provide a reference standard against which hospitals or regional/national health care systems may compare their own practice. In contrast, trials provide evidence of what is possible, in similarly se-
lected patient groups. Registries provide evidence of the extent to which trial data and guidelines are adopted in practice. For example, in the ESC survey and GRACE registries, the use of aspirin is adopted widely (greater than 90% of ACS patients) (reference 4 and A. Battler, ESC 2001, oral presentation). In contrast, β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently used on discharge in only half of ACS patients, and β-blockers in 70%, but there are marked regional variations (reference 4 and A. Battler, ESC 2001, oral presentation). In addition, 46% of unstable angina and 51% of non-ST-segment-elevation MI patients and 41% of ST-segment elevation MI patients received LMWH (the latter prior to published evidence). GP Iib/IIa usage is relatively low in clinical practice (20% in non-ST elevation MI and 23% in ST-segment elevation MI). PCI is undertaken in 18% of unstable angina, 28% of non-ST-segment elevation MI, and 40% of ST-segment elevation MI (less than half of this is primary PCI). Thus, there are considerable disparities between clinical practice and published guidelines with underuse of some therapies and overuse of others (eg, PCI beyond the time interval for myocardial salvage after MI). Such registry data demonstrate considerable disparities in health care systems in the extent to which newer evidence-based therapies are adopted. It is likely that the availability of such international comparators will help guide practice in hospitals and health care systems.

**PROSPECTS FOR THE FUTURE**

Registry studies in ACS have demonstrated that even in the absence of ST-segment elevation MI this syndrome is not benign; 8% to 13% of patients die within 6 months, and approximately 30% suffer death/MI or rehospitalization for ACS within 6 months. These event rates occur despite current treatment with aspirin and antianginal therapy. The large-scale clinical trials have revealed the importance of thrombosis not only in the adverse events that immediately follow presentation with ACS, but in the subsequent weeks and months. Such patients are susceptible to further thrombotic events and disruption of other atheromatous plaques. The development of thrombosis is a fundamentally important biologically process and pharmacological inhibitors of a single pathway have only had limited success. A combination of antplatelet and antithrombin therapy is required. Cyclooxygenase inhibition with aspirin provides the cornerstone of antplatelet treatment, and clear evidence now supports the addition of ADP inhibitors (clopidogrel) in the acute phase and longer term. In the context of PCI, and especially in high-risk patients, GP Iib/IIa inhibitors provide clear advantages, but longer-term oral GP Iib/IIa inhibitors have failed. LMWH therapy is progressively replacing unfractionated heparin, both as background antithrombotic treatment and in the context of thrombolytic treatment and PCI. More potent and specific antithrombins have not yet demonstrated significant clinical advantage, but they do increase risks of bleeding. Novel oral thrombin inhibitors are in development, and synthetic pentasaccharides demonstrate high affinity for, and selective inhibition of, factor Xa. Trials of venous thromboprophylaxis have shown benefit, and studies in ACS are under way. In addition, S18886, a thromboxane A2/prostaglandin H2 (TXA2/PGH2) receptor antagonist, now under development, could be of benefit in patients with coronary artery disease. 

In conclusion, antiplatelet and antithrombin therapy now form an integral part of the management of patients with ACS, and robust evidence demonstrates improved short- and longer-term outcome. Novel therapies, now in early clinical development, may offer improved antithrombotic efficacy, but the potential hazards of increased risk bleeding will need careful assessment.

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Antiplatelet strategies.
What is the impact of genetics on the thrombotic process?

Francesco Bernardi, MS
Department of Biochemistry and Molecular Biology - University of Ferrara - Ferrara - ITALY

Although family and twin pair studies provide evidence of the contribution of genetic components to arterial thrombotic disease, these are difficult to detect because of their high number, small individual effect on thrombosis, and complex interaction with environmental factors. Despite extensive investigation of several candidate mutations, particularly in genes involved in the hemostatic process, there is still only weak reproducible evidence for their role in arterial thrombosis. In contrast, a number of defects and functional polymorphisms lead to increased risk for venous thromboembolism. Taken together, epidemiological and molecular studies suggest that we need to study multiple DNA-sequence variations defining functional haplotypes and their relationships with environmental factors in large cohorts of patients with better-defined end point phenotypes.

There is currently much interest in the understanding of the genetic components of thrombotic disease. Knowledge of genes and gene variations making humans prone to thrombosis could help define the mechanisms of the disease, thus improving the design of innovative therapy or prophylaxis. After a recent detailed review of the abundant literature on this topic and with the help of an updated list of candidate genes and polymorphisms, I would like to answer two basic questions, particularly for those who are not involved in molecular genetic research, but are eager to know the current importance of gene variations for thrombotic disease: (i) are genes involved in thrombotic disease? and (ii) are there any gene variations that are reproducibly and consistently associated with thrombotic disease?

ARE GENES INVOLVED IN THROMBOTIC DISEASE?

While the involvement of genes in a disease inherited in a Mendelian fashion would appear to be self-evident, it is necessary to prove that genes are actually involved in common diseases like arterial thrombotic disease that have a complex multifactorial etiology, and aggregate—but do not segregate—in families in accordance with Mendelian expectations. The familial resemblance in clinical manifestations suggests familial influence in the mechanisms determining the clinical expression of arterial thrombotic disease. Many retrospective and prospective studies, as well as angiographic studies, have clearly demonstrated a familial aggregation for coronary heart disease. However, humans give their children their environment in addition to their genes, and this environment includes multiple factors, such as risk factors for atherosclerosis and thrombosis. The challenge faced by research into the genetic basis of a complex disease like thrombosis is to identify genes responsible for small and additive relative effects—defined as quantitative trait loci (QTL)—against a background of substantial environmental variation.

Before one starts the hunt for loci and loci variations, it is necessary to show that the disease, or its risk factors, are genetically influenced. This is made possible thanks to twin and family studies, which have been largely instrumental in showing the effects of genetic variance on a complex multifactorial trait.

The twin pair model is based on the fact that monozygotic twins share all their genes, whereas dizygotic twins are related in the same way as normal siblings and share 'on average' half their genes. Environmental confounders are minimized because twins are usually exposed to similar environments during childhood. Thus, it was twin
studies that first showed that blood pressure was heritable and that lipoprotein parameters exhibited an impressive heritability.

Surprisingly little information is available on the relative importance of genetic factors in thrombosis risk from family-based studies. It was recently estimated that more than 60% of the predisposition to thrombosis was attributable to genetic components. Interestingly, the magnitude of the genetic heritability was found to be greater than or equal to that seen in other common complex diseases such as type 2 diabetes and obesity.

Although there is strong evidence in favor of the contribution of genetic components to arterial thrombotic disease, these are difficult to detect due to their high number and small individual effect on thrombosis. Arterial thrombosis may result from the interaction of a large number of altered biological processes, each involving dozens of genes bearing several functional polymorphisms. Frequent single genetic changes are not expected to have a “dominant” role, and only combinations of several mutations are likely to produce significant prothrombotic alterations of biological functions.

The predominant role of environmental factors and of their unexpected interactions must also be taken into account. The recent history of the epidemiology of thrombotic disease, when set against the very ancient existence of gene variations in human populations, suggests that only polymorphisms able to produce deleterious gene-environment interactions (Figure 1) are likely to contribute significantly to the disease. Combinatorial and gene-environment issues further complicate the detection of genetic components and require an ad-hoc design of epidemiological and molecular genetic studies.

ARE THERE ANY GENE VARIATIONS THAT ARE REPRODUCIBLY AND CONSISTENTLY ASSOCIATED WITH THROMBOTIC DISEASE?

Once genetic heritability is established, at the heart of the problem of the genetics of common diseases is the need to dissect the underlying DNA-sequence variations to understand the number, nature, and arrangement of mutations in the genome. In particular, we need to determine the haplotypes, which specify the phase relationship of all heterozygous polymorphic sites in a gene in a given individual and, interacting with other genetic and environmental factors, produce a given amount of a functional polypeptide, encoded by a single chromosome (Figure 2). Haplotype determination has important implications for the understanding of the impact of genetic differences on function variation. Although the fact that multiple mutations and polymorphisms occur in a given gene is common knowledge, the allelic complexity of haplotypes often appears to be underappreciated, or even ignored, in several studies.

The common approach has been essentially based on the search for mutations in candidate genes involved in biological functions likely to participate in the thrombotic process, and on genotyping in case-control studies for one or several polymorphisms. Often, the absence of a clear relationship between most genetic markers and variations of biological phenotypes, which necessarily mediate the participation of genetic components in the thrombotic process, hinders the interpretation of results obtained in association studies. The number of genes involved in multiple functional pathways potentially participating in
What is the impact of genetics on the thrombotic process? - Bernardi

The thrombotic process is increasing exponentially. The endothelium, which acts as an integrator and transducer of humoral and biomechanical stimuli, represents a main target for present and future studies. A striking example is provided by endothelial cells, in which the expression of 52 different genes is upregulated or downregulated when they are subjected to shear stress.12 We do not know at present if variations in these genes make humans prone to thrombosis. Their interaction with genes involved in lipid and glucose metabolism, as well as in blood pressure control, inflammation, and hemostasis represents an additional stimulating target.

Among the numerous candidate pathways, I shall briefly summarize findings on genes with a role in hemostasis, which have emerged from a body of work and discussion carried out over the past 10 years. This work looked at the role of variations in hemostatic genes in producing modified coagulation phenotypes liable to alter the hemostatic balance and favor the development of thrombosis.

**Genetic determinants of venous thromboembolism in arterial thrombotic disease**

A number of well-characterized defects in candidate genes have been shown to lead to increased risk for venous thromboembolism. These abnormalities are generally associated with hyperactivity of the coagulation system, resulting in hyper-coagulable states. These relatively infrequent mutations, which are strong predictors of venous thromboembolism, do not constitute the primary genetic influences with respect to risk of common late-onset artery thrombosis. They have been found to confer a modest increase in risk of arterial thrombotic disease and may be involved in a minor fraction of cases:

- Deficiencies of natural anticoagulants (protein C, antithrombin, protein S) are likely to be associated with arterial thrombotic disease, particularly in very young individuals with acute cerebral ischemia.
- FV Leiden and prothrombin 20210A mutations, which are very frequent in patients with venous thromboembolism and cause activated protein C resistance and slightly increased prothrombin levels in plasma, respectively, are not major arterial thrombosis risk factors. The presence of these mutations could influence the arterial thrombosis risk in particular groups of patients, such as children with arterial stroke, and young women with other risk factors having suffered a myocardial infarction (MI).
- Although there is evidence that activated protein C resistance may...
influence the risk of arterial thrombotic disease, the prominent role of the FV Leiden mutation in determining this plasmatic phenotype is less evident than in the case of venous thromboembolism.

These findings are not surprising in view of the fundamental differences between arterial and venous disease, and especially the major role of diseased vessels in arterial thrombosis. However, heritability analyses of venous and arterial thrombosis in large Spanish families indicate that there must be substantial overlap in the genetic determinants of the venous and arterial forms of thrombosis. These findings suggest that major genetic components of both venous and arterial thrombosis are still unknown.

**Polymorphisms in paradigmatic coagulation genes and arterial thrombosis**

Several lines of evidence suggest that increased levels of circulating coagulation factors are risk factors for venous and arterial thrombosis, and that strong genetic correlations exist between coagulation factor levels and thrombosis. Very likely, there are sets of genes that jointly influence quantitative physiological variation and disease risk. The detection of genetic effects that act on both quantitative risk factors and disease liability is critically important for subsequent genetic analyses. The identification of polymorphisms within genes of coagulation and fibrinolysis pathways has stimulated their evaluation as markers of circulating levels of protein in plasma and as genetic susceptibility markers in an impressive number of epidemiological studies of arterial thrombotic disease. For several important genes, such as factor VIII and von Willebrand factor, we have no candidate polymorphisms for the control of levels of the corresponding proteins in plasma. In contrast, it has been possible to evidence polymorphisms associated with fibrinogen and factor VII (FVII) levels in plasma.

**Fibrinogen**

Even though plasma fibrinogen levels have been associated, in several prospective studies, with an increased risk of MI and stroke, and polymorphisms of the beta fibrinogen gene have been associated with efficiency of promoter transcription, the relationship between polymorphisms in the fibrinogen gene cluster—particularly in the beta gene—and the risk of arterial thrombotic disease, is controversial. Some large studies found no such association, casting doubt on the existence of a cause-effect relationship between genetic control of fibrinogen levels and artery thrombosis. The change in plasma levels of fibrinogen determined by a single gene variation (5%-10%) could be too low to be associated with a detectable effect upon disease.

**Factor VII**

The association between increased FVII activity levels and fatal ischemic heart disease, the high degree of genetic control of FVII level variations in plasma (>30%) due to FVII gene polymorphisms (Figure 3), and the association between FVII levels and triglyceride levels, make the FVII gene a paradigm for the study of genetic components in artery thrombosis. However, the association between ischemic heart disease and FVII levels has not been confirmed in subsequent prospective studies, and several case-control studies found no association between FVII gene polymorphisms and the risk of MI or stroke. Two Italian studies found a significant association with MI in young adults with familial MI, as well as in adult patients with severe multivessel coronary atherosclerosis. These two studies suggest that FVII genotypes that include the 10 bp insertion at −323 and the 353Gln (Fig-
Atherosclerotic plaques in men with coronary thrombosis and complicated increased frequency of acute coronary artery disease has been associated with an increased risk of coronary heart disease or stroke. This genetic variation has been investigated in genetic studies, with the size needed to dissect gene-gene and gene-environment interactions, are now in the pipeline together with the microchips that will enable us to boost genotyping.

Taken together, these controversial results do not support a major role for FVII gene variation as a risk factor for arterial thrombotic disease and point instead to population differences, which, however, require further exhaustive genetic studies. The search for mutations reducing the efficiency of fibrinolysis has also revealed a candidate that needs further evaluation: a polymorphism in the promoter of plasminogen-activator inhibitor–1 (PAI-1), which has been found to confer increased risk of MI, particularly in populations with high risk factors.

**Polymorphisms in glycoprotein platelet receptors and arterial thrombosis**

The pivotal role of platelets in thrombus formation has stimulated the study of polymorphisms in platelet receptors for fibrinogen (IIb/IIIa), collagen (Ia/IIb), and von Willebrand factor (Ib/IX).

- The association between a common genetic isoform (PLA2) of glycoprotein IIa, a subunit of the IIb/IIa receptor, and increased thrombotic tendency has been investigated in more than 20 studies. This genetic variant has been associated with an increased frequency of acute coronary thrombosis and complicated atherosclerotic plaques in men with fatal MI.
- An allele (807T) of the glycoprotein Ia (Ia/IIb receptor) has been shown to be associated with increased receptor density in platelets, and its prothrombotic role is supported by large case-control studies. This variant could be a genetic risk factor for early-onset arterial thrombotic disease.
- Several case-control studies have reported that a variant (145 Met or VNTR-B) of the glycoprotein Ib (Ib/IX receptor) was associated with increased risk of coronary heart disease or stroke.

Lack of consistency of outcome between studies makes it necessary to carry out further molecular analysis and classification of patients, in order to be able to assess the role of these glycoprotein gene mutations. It emerges from these epidemiological and molecular studies that we need to assess DNA-sequence variations with functional roles in large numbers of patients with very well-defined end point phenotypes.

**Perspectives**

Gene-mapping approaches have identified a number of chromosomal regions where candidate susceptibility genes may be found soon. Characterization of the candidate genes will be facilitated by the knowledge of the complete sequence of the human genome. Moreover, millions of sequence variations spread in the genome have been collected and candidate genes will be rapidly resequenced in patients and controls from different populations, thereby providing a complete spectrum of mutations. Biochemical and molecular biological approaches will make it possible to dissect the functional role of polymorphisms and of their combinations. Well-designed epidemiological studies, with the size needed to dissect gene-gene and gene-environment interactions, are now in the pipeline together with the microchips that will enable us to boost genotyping.

An important question in the study of the genetics of the thrombotic process is whether knowledge about genetic variation will improve our ability to predict arterial thrombotic disease better than through established risk factors. This question is especially relevant with respect to the identification of young, asymptomatic adults, who would benefit most from interventions to reduce risk. Since perceptions of familial tendencies toward the various manifestations of thrombosis are common, and important for health-related behaviors, we should prevent increased “geneticization” of this common disease from leading to a misappreciation of the importance of environmental factors. Increased fatalism, resulting from misunderstanding of the role of genetics in thrombotic disease, could undermine successful initiatives aimed at reducing noxious behaviors. Selective and individualized pharmacological aids, possibly stemming from pharmacogenomic approaches, together with lifestyle advice, could counterbalance the psychological burden conferred by becoming aware of genetic risk factors.

Among such future aids, a prominent role could be exerted by local gene transfer aimed at preventing thrombosis and hyperplasia after vascular injury. Expression studies of the endothelium, intima, and vascular smooth muscle cells provide plenty of models for single or combined approaches. Although molecular genetic studies might not reveal markers useful for diagnosis on an individual basis, they are likely to disclose genes useful for treatment and direct intervention.
What is the impact of genetics on the thrombotic process? - Bernardi

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What are the current issues regarding aspirin and other cyclooxygenase inhibitors?

Carlo Patrono, MD
Department of Pharmacology - La Sapienza University of Rome - Rome - ITALY

Low-dose aspirin (75-100 mg/day) is indicated in patients at moderate to high cardiovascular risk (stable angina, prior myocardial infarction or stroke/transient ischemic attack) in whom its potential benefit clearly outweighs the risk of serious hemorrhage. If a concomitant nonsteroidal anti-inflammatory drug (NSAID) is required, gastrointestinal safety and the absence of pharmacodynamic interaction with low-dose aspirin make a specific cyclooxygenase (COX)-2 inhibitor preferable to a conventional NSAID. In low cardiovascular risk, however, low-dose aspirin is not routinely indicated due to the uncertain benefit/risk profile in this setting.

The role of aspirin and other platelet-active drugs in the treatment and prevention of atherothrombosis has been reviewed by the Sixth American College of Chest Physicians’ (ACCP) Consensus Conference on Anti-thrombotic Therapy. Moreover, additional information on the efficacy and safety of antiplatelet therapy is provided by the recent collaborative meta-analysis of 266 secondary prevention trials, prepared by the AntiThrombotic Trialists’ (ATT) Collaboration. The place of aspirin in the current therapeutic armamentarium of ischemic heart disease is discussed by Keith Fox and Pierre Theroux elsewhere in this volume. What follows is aimed at addressing some open questions on the efficacy and safety of aspirin and how these are influenced by underlying cardiovascular risk and concomitant medication of the exposed patients.

**BALANCE OF BENEFITS AND RISKS**

The absolute benefits of aspirin therapy substantially outweigh the absolute risks of major bleeding (particularly, gastrointestinal) complications in a variety of clinical settings characterized by moderate to high risk of occlusive vascular events (Table I, next page). However, in low-risk individuals the benefit/risk profile of such a preventive strategy is uncertain. Thus, a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue bleeding complications. The risk of upper gastrointestinal tract bleeding associated with medium-to-high doses of aspirin can be reduced to a relative risk of 2.0 vs nonusers by using the lowest effective dose of the drug (ie, 75 to 160 mg daily). However, this risk can not be further reduced by other strategies since it is most likely related to the antiplatelet effect of aspirin, which is

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**Keywords:** ischemic heart disease; cardiovascular risk; stroke; antiplatelet therapy; aspirin; nonsteroidal anti-inflammatory drug; coxib; gastrointestinal hemorrhage; prevention trial; meta-analysis

**Address for correspondence:**
Prof Carlo Patrono, Department of Pharmacology, La Sapienza University of Rome, Rome, ITALY (e-mail: cpatrono@unich.it)

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**SELECTED ABBREVIATIONS AND ACRONYMS**

| ATT | AntiThrombotic Trialists’ (Collaboration) |
| CLASS | Celecoxib Long-term Arthritis Safety Study |
| COX | cyclooxygenase |
| HOT | Hypertension Optimal Treatment |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| PGI2 | prostacyclin |
| PHS | Physicians’ Health Study |
| PPP | Primary Prevention Project |
| SAPAT | Swedish Angina Pectoris Aspirin Trial |
| TPT | Thrombosis Prevention Trial |
| TXA2 | thromboxane A2 |
| VIGOR | Vioxx Gastrointestinal Outcomes Research |
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largely dose-independent for daily doses in excess of 30 mg. Thus, recent studies have attempted to determine which groups of patients may derive particular benefit or experience harm from the use of low-dose aspirin for the primary prevention of ischemic heart disease. Subgroup analysis of the Thrombosis Prevention Trial (TPT) suggests that the benefit of low-dose aspirin may occur mainly in men with lower systolic blood pressures, although it is not clear even in these men that the benefit outweighs the potential hazards. A recently discontinued trial of low-dose aspirin in general practice failed to demonstrate a clearly favorable benefit/risk profile in men and women aged 50 years or older with one or more major cardiovascular risk factors.

A meta-analysis of four primary prevention trials suggests that aspirin treatment is safe and worthwhile at coronary event risk equal to or greater than 1.5% per year. However, as depicted in Figure 1, we substantially lack clinical trial data in this critically important area of cardiovascular risk that is intermediate between the observed risk in the placebo arm of the TPT and that of the Swedish Angina Pectoris Aspirin Trial (SAPAT) in patients with chronic stable angina. The apparently nonlinear relationship between the underlying cardiovascular risk (ie, the observed rate of major vascular events in the placebo arm) and the absolute benefit of aspirin prophylaxis in the six “primary” prevention studies represented in Figure 1 may reflect the composite nature of the main outcome used for these analyses, ie, nonfatal myocardial infarction, non-

**Clinical setting** | **Benefit**<sup>*</sup> | **Risk**<sup>**</sup>
---|---|---
Men at low to high cardiovascular risk | 1-2 | 1-2
Essential hypertension | 1-2 | 1-2
Chronic stable angina | 10 | 1-2
Prior myocardial infarction | 20 | 1-2
Unstable angina | 50 | 1-2

*Benefits are calculated from randomized trial data reviewed in references 1 and 2.
**Risks of upper gastrointestinal bleeding are estimated from a background rate of 1 event per 1000 per year in the general population of nonusers, and a relative risk of 2.0 to 3.0 associated with aspirin prophylaxis. Such an estimate assumes comparability of other risk factors for upper gastrointestinal tract bleeding, such as age and concomitant use of nonsteroidal anti-inflammatory agents (NSAIDs), and may actually underestimate the absolute risk in an elderly population exposed to “primary” prevention. The absolute excess of major bleeding complications in the “primary” prevention trials reviewed in reference 1 ranged between 0.3 and 1.7 per 1000 patient-years.

*Figures are plotted from placebo-controlled aspirin trials in different settings characterized by variable cardiovascular risk, as noted on the abscissa. The benefit (○) is reported on the left ordinate axis as the number of subjects in whom an important vascular event (ie, nonfatal myocardial infarction, nonfatal stroke, or vascular death) is prevented by treating 1000 subjects with low-dose aspirin for 1 year. The bleeding risk (□) is reported on the right ordinate axis as the number of subjects in whom a major bleeding complication is caused by treating 1000 subjects with low-dose aspirin for 1 year. For each of the six trials, a couple of symbols denote benefit (○) and bleeding risk (□) associated with long-term aspirin prophylaxis.

**Abbreviations:** HOT, Hypertension Optimal Treatment; PHS, Physicians’ Health Study PPP, Primary Prevention Project; SAPAT, Swedish Angina Pectoris Aspirin Trial; TPT, Thrombosis Prevention Trial; UK Doc, British Doctors Trial.
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Fatal stroke, or vascular death. It should be emphasized that while aspirin has a substantial effect on each of these components of the composite outcome in “high-risk” clinical settings (including chronic stable angina), the measurable impact of long-term antiplatelet prophylaxis in “low-risk” individuals is largely restricted to nonfatal myocardial infarction.

Another important lesson that can be derived from the analysis of “primary” prevention trials is that the actual rate of major vascular events recorded in trials that recruited individuals considered to be at “high” cardiovascular risk was lower than expected and quite comparable with that recorded in earlier trials of American and British doctors (eg, compare the event rate of the Primary Prevention Project [PPP]) with that of the Physicians’ Health Study [PHS] and that of the TPT with that of UK-Doctors in Figure 1. Aggressive treatment of modifiable risk factors within the context of the most recent randomized trials (eg, PPP) is likely to substantially reduce the rate of thromboxane A2 (TXA2) biosynthesis related to complex metabolic disorders and cigarette smoking, and therefore the rate of aspirin-sensitive thrombotic complications and the need for long-term aspirin prophylaxis. The ATT Collaboration is currently conducting an overview of all randomized trials of aspirin vs placebo in low-risk subjects, based on individual patient data, in an attempt to identify particular subgroups of individuals for whom the benefits of aspirin may clearly outweigh the bleeding risks.

Thus, aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting.

**ASPIRIN RESISTANCE**

The issue of aspirin “resistance” continues to be debated. This term has been used to describe a number of different phenomena, including the inability of aspirin to do the following: (i) protect individuals from thrombotic complications; (ii) cause a prolongation of the bleeding time; or (iii) produce an anticipated effect on one or more in vitro tests of platelet function. Based on measurements of optical platelet aggregation in response to arachidonate and adenosine diphosphate (ADP), 5% and 24% of patients with stable cardiovascular disease who were receiving aspirin (325 mg/day for ≥7 days) were defined as “resistant” and “semiresponders,” respectively. However, the lack of appropriate controls in this study (eg, patients treated with another antiplatelet agent) precludes unequivocal interpretation of these findings. Resistance to thienopyridines has been reported recently.

At least three potential mechanisms may underlie the occurrence of aspirin-resistant TXA2 biosynthesis. The transient expression of cyclooxygenase-2 (COX-2) in newly formed platelets in clinical settings of enhanced platelet turnover deserves further investigation. Extra-platelet sources of TXA2 (eg, monocyte/macrophage COX-2) may contribute to aspirin-insensitive TXA2 biosynthesis in acute coronary syndromes. Catella-Lawson et al have recently reported that concomitant administration of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ibuprofen) may interfere with the irreversible inactivation of platelet COX-1 by aspirin. This is due to competition for a common docking site within the cyclooxygenase channel (Arg120), which aspirin binds with weak affinity prior to irreversible acetylation of Ser529.

This pharmacodynamic interaction does not occur with rofecoxib or diclofenac, drugs endowed with variable COX-2 selectivity. Thus, concomitant treatment with readily available over-the-counter NSAIDs may limit the cardioprotective effects of aspirin and contribute to aspirin “resistance.” Investigative tools are readily available to evaluate potential sources of aspirin “resistance” (Table II).

Several relatively small studies in stroke patients have suggested that aspirin “resistance” may contribute to treatment “failure,” ie, recurrent ischemic events while on antiplatelet therapy, and that doses higher than 500 mg may be more effective than lower doses in limiting this phenomenon. The uncontrolled nature and small sample size of these
What are the current issues regarding aspirin and other cyclooxygenase inhibitors?

Studies make it difficult to interpret the results. As reviewed elsewhere, a much larger database failed to substantiate a dose-dependent effect of aspirin in stroke prevention, an effect that one would theoretically expect if aspirin “resistance” could be overcome, at least in part, by increasing the daily dose of the drug. The apparent discrepancy between the theoretical predictions originating from studies of aspirin “resistance” and the actual findings of approximately 100 randomized clinical trials of aspirin prophylaxis in high-risk patients can be reconciled by acknowledging the limitations of platelet function studies. Thus, platelet aggregation as measured by conventional methods ex vivo has less than ideal intrasubject and intersubject variability and displays limited sensitivity to the effect of aspirin, often considered a “weak” antiplatelet agent based on such measurements. Moreover, the relevance of changes in this index of capacity to the actual occurrence of platelet activation and inhibition in vivo is largely unknown.

Thus, in summary, both the mechanism(s) and clinical relevance of aspirin “resistance” remain to be established. Until its true nature and prevalence are better defined, no
test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.1

**ASPIRIN VIS-À-VIS REVERSIBLE CYCLOOXYGENASE INHIBITORS**

A variety of NSAIDs can inhibit TXA2-dependent platelet function through competitive, reversible inhibition of platelet COX-1. In general, these drugs, when used at conventional analgesic dosage, inhibit platelet COX activity reversibly by 70% to 90%.1 This level of inhibition may be insufficient to adequately block platelet aggregation in vivo, because of the very substantial biosynthetic capacity of human platelets to produce TXA2 (Figure 2).19 In fact, in a prospective population-based observational study of approximately 165 000 postmenopausal women, chronic use of nonaspirin NSAIDs was not associated with a protective effect against the risk of a first myocardial infarction (relative risk [RR] 1.32; 95% confidence interval [CI] 0.97-1.81).20 Because nonaspirin NSAIDs have been inadequately investigated in terms of their potential cardiovascular effects, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue low-dose aspirin, even though concomitant administration of the two may amplify the risk of upper gastrointestinal tract bleeding.1

The cardiovascular safety of selective COX-2 inhibitors (coxibs) (Figure 3) in arthritic patients at low cardiovascular risk is currently being debated.18,21 based on the recently reported results of two relatively large gastrointestinal safety studies, the Vioxx Gastrointestinal Outcomes Research (VIGOR)22 study and the Celecoxib Long-term Arthritis Safety Study (CLASS).23 with short follow-up and inadequate statistical power to detect a realistic difference—one way or the other—in vascular end points between coxibs and conventional NSAIDs. At least three distinct explanations can be entertained in accounting for the statistically significant difference in myocardial infarction between rofecoxib and naproxen (0.4% vs 0.1%), as reported by the VIGOR trial: a cardioprotec-

(Figure 2). A thrombogenic effect of coxibs has been attributed to reduced prostacyclin (PGI2) biosynthesis in the face of unopposed TXA2 production. However, the size of the effect is not biologically plausible if due to incomplete inhibition of a single mediator of “thromboresistance,” ie, PGI2.24,25 Moreover, such an explanation is not substantiated by the CLASS results,23 though a smaller coxib effect cannot be excluded. Topol and his associates21 have reported an indirect comparison of the annualized myocardial infarction rate in the arthritic patients treated with rofecoxib (0.74%) and celecoxib (0.80%) in the VIGOR and CLASS trials, respectively, with the weighted mean myocardial infarction rate (0.52%) in the placebo arms of four of the six “primary” prevention trials described above (ie, PHS, Hypertension Optimal Treatment [HOT], UK-Doctors, and TPT). Although such a compar-

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**Figure 2.** Coxsibs, selective inhibitors of COX-2. The figure depicts a constitutive pathway of AA metabolism on the left-hand side and a largely inducible pathway on the right-hand side generating the same lipid mediator, ie, PGE2, through a cascade of coordinate enzymatic reactions involving constitutive vs inducible enzymes, respectively.

**Abbreviations:** AA, arachidonic acid; COX-1, -2, cyclooxygenase-1, -2; EP1, 2, 3, 4, specific PGE2 receptors; LPS, lipopolysaccharide; NSAIDs, nonsteroid anti-inflammatory drugs; PGE2, prostaglandin E2; PGH2, prostaglandin H2; PL, phospholipids; PL-A2, phospholipase A2; PGES, PGE-synthase (c and m denote the constitutive and inducible isoforms of the enzyme, respectively).
ison of patients with quite different profiles of cardiovascular risk factors suggested a statistically significant difference between each coxib and the “placebo” group,21 a more detailed analysis of these data as that shown in Figure 4 clearly outlines the misleading nature of this exercise. Thus, the variability in myocardial infarction rates among the four individual “primary” prevention trials is much larger than any alleged difference between their weighted mean rate and that recorded in the coxib trials. Visual inspection of these data also reveals that the myocardial infarction rate of patients with rheumatoid arthritis treated with rofecoxib is well within the range of relatively low-risk individuals randomized to the placebo arm of these aspirin trials, despite a large body of epidemiological evidence suggesting that rheumatoid arthritis is an independent cardiovascular risk factor.26 Finally, the apparent difference in VIGOR might represent uneven distribution of a small number of events occurring over a short time frame in a low-risk population, as suggested by a recent meta-analysis of all rofecoxib trials.27 An independent overview of all randomized comparisons between any coxib (celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib) and any nonselective NSAID appears to offer a feasible strategy to answer this question, one that would not require a very large head-to-head randomized trial with vascular end points.28

**CONCLUSION**

Patients at moderate to high cardiovascular risk (eg, those with chronic stable angina, prior myocardial infarction, or stroke/transient ischemic attack) should be prescribed low-dose aspirin (75-100 mg daily) because its potential benefit clearly outweighs the risk of serious bleeding complications.1,2 Should these patients require NSAID therapy, safety considerations as well as the lack of pharmacodynamic interactions with low-dose aspirin would favor a specific COX-2 inhibitor over conventional NSAIDs.18 Patients at low cardiovascular risk (ie, those without a prior vascular event) are not likely to be prescribed low-dose aspirin because of the uncertain benefit/risk profile of such a strategy in this setting.1-2 In these patients, the absolute benefit to be derived from COX-1 sparing by specific COX-2 inhibition, in terms of reduced burden of serious gastrointestinal complications vis-à-vis conventional NSAIDs, is likely to outweigh any potential harm to be derived from inhibition of COX-2-dependent PGI2 biosynthesis.18

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Surfing the Heart

**Martindale’s—The Reference Desk – National Library of Medicine Gateway**

**metaRegister of Controlled Trials – National Guideline Clearinghouse**

Claudio Ceconi, MD
e-mail: cceconi@libero.it - Cardiovascular Research Center - S. Maugeri Foundation - Gussago - ITALY

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**Martindale’s—The Reference Desk**
http://www-sci.lib.uci.edu/HSG/Ref.html

This extraordinary reference resource site has been maintained by James Martindale, a consultant to the University of California at Irvine College of Medicine since 1994. It covers a wide range of topics, including international business, astronomy, entertainment, and the arts. The topics are divided into different “Information Centers.” The “Cardiology and Pulmonary Center” (http://www-sci.lib.uci.edu/HSG/MedicalCardio.html) is a comprehensive, but not always easy to use, resource about the most disparate areas of cardiopulmonary medicine: if you are searching for something unusual that is not indexed in the usual search engines, then this can be a good starting point. Are you looking for videos on physical examination or for an atlas of perfusion SPECT? Try here. Yahoo! rated this among its “50 most incredibly useful sites.”

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**metaRegister of Controlled Trials**
http://www.controlled-trials.com/mrct/

Several sites provide databases of clinical trials, but the “metaRegister of Controlled Trials” (mRCT) is likely to be the richest one, with 10 875 records listed in February 2002! This is a free resource, but registration is required.

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**National Guideline Clearinghouse**
http://www.guideline.gov/index.asp

The National Guideline Clearinghouse (NGC) is a comprehensive database of evidence-based clinical practice guidelines produced by the Agency for Healthcare Research and Quality (AHRQ) in partnership with the American Medical Association and the American Association of Health Plans. The aim of NGC site is to provide physicians, nurses, and other health professionals with accessible and objective information on clinical practice guidelines. Key components of the NGC site include summaries, a comparison tool, links to full-text guidelines, annotated bibliographies, and even an electronic discussion list. In February 2002, the guidelines relevant to cardiovascular diseases numbered 106.
Plants and the heart

Aspirin and salicylates

Anirban Banerjee, PhD

Department of Surgery (C-320) - University of Colorado Health Sciences Center - Denver - Colorado - USA

Despite its very simple structure (a hydroxyl group placed next to a carboxylic group on a 6-carbon benzene ring), salicylic acid and its derivatives are arguably one of the most popular drugs worldwide. The synthesis of its acetyl derivative (Aspirin) at Bayer, is credited with virtually launching the pharmaceutical industry and, more importantly, introducing humans to counter-top inflammation science via antipyretics, analgesia, and antiprostanoids. Salicylic acid is very corrosive, but its acetyl (and other ester derivatives) are agreeably nontoxic. Both salicylate and its various esters are found throughout in higher plants, in particularly high concentrations in willows (Salix), spireas (where the “spirin” comes from), and poplars, to name a few.

While the first decoctions from willow bark may have been inspired by the Doctrine of Signatures (wherein the Good Lord provides plants growing in bogs and swamps with therapies against associated aigues and fevers),1 legendary medical greats such as Hippocrates, Galen, but also tribes worldwide, may have been inspired by careful ethnobotanical observations.

Cardiovascular pharmacologists initially related salicylates to a propensity for bleeding. This led to a spectacular theory of anticoagulation, discovery of platelet actions in thrombosis, and, thereafter, the individual cyclooxygenase (COX) isoforms that produce eicosanoids responsible for many inflammatory and pyretic actions were identified.1,6

COX-1 is the constitutively expressed enzyme and produces eicosanoids— including thromboxane A\(_2\) (TXA\(_2\)), which is essential for platelet-induced coagulation. This isoform is irreversibly acetylated (aspirin donates its acetyl group very readily) when we take a few pills (325 to 650 mg, low dose) to produce a physiological concentration of around 100 µM.6 COX-2, on the other hand, is induced by transcriptional promoters such as nuclear factor kappa B (NF-κB) and produces a variety of proinflammatory prostanooids, prolifi- cally.7,8 COX-2 is weakly inhibited by aspirin at physiological concentrations around 1 mM (intake several grams of aspirin).1,9 Though newer and better COX-2–directed inhibitors are in vogue, aspirin remains the only inhibitor that modifies both COX enzymes covalently (by acetylation).8 In contrast, the un-acetylated salicylate can appear inactive against both isoforms when tested in broken cells or in purified forms.1,10

However, the synthesis of more selective drugs showed that simple acety-
lution of COX-1 and other enzymes did not quite explain all the observations. Indeed, salicylate itself has antipyretic and analgesic effects. Many salicylate-derived drugs that are in clinical use as nonsteroidal anti-inflammatory drugs (NSAIDs) lack any acetyl group to transfer! (eg, diflunisal, salazine). We may conclude that salicylate itself must be a credible anti-inflammatory agent in vivo, which, in whole cells, inhibits COX-1 and 2 at about 2 µM and <0.5 mM, respectively.9

Vane’s coworkers and others continue to find interesting mechanisms that go beyond the well-known acetylation mechanism.2 Mitchell showed that the presence of arachidonic acid causes salicylate to inhibit very weakly. This interpretation fits well with the crystal structure of COX-2, which shows that arachidonic acid can bind in a channel at the base of the COX-2 active site. Mechanistically, the full implications of COX-2 inhibition must be incomplete, since COX-2 inhibition involves subtle time-dependent kinetics.8 Most astoundingly, Serhan and Oliw show that aspirin-modified COX-2 produces anti-inflammatory eicosanoids that suppress polymorphonuclear functions!7 Indeed, specific receptors for these aspirin-triggered lipids (lipoxin A₄ receptor [ALXR]) have thus gained for aspirin a rank among the select plants that can legitimately claim a human protein christened after themselves.

A radical line of inquiry arose with the seminal observation that both Na-salicylate and aspirin inhibit NF-κB activation in vitro.11 The mechanism that prevents the phosphorylation and degradation of inhibitor protein IκB was attacked by several groups, yielding a selective blockade of an upstream I-KK kinase (IKΚβ, at its ATP-binding site),12 that was reported amidst great ferment. And justifiably so, since influencing NF-κB transcription would have a big impact on not only an extremely wide variety of inflammatory mechanisms in vivo, but, pertinently, on COX-2 expression as well.13 However, evidence on whether salicylates affect COX-2 expression remains conflicting, particularly in vivo. While carefully controlled over-expression of tagged COX-2 mRNA in transformed cultured cell lines suggests a direct inhibition of transcription (at the surprisingly low doses of 0.1 to 100 M),14 others do not find changes in COX-2 expression in animal models.9 Thus, the expression of COX-2 enzyme may be difficult to anticipate from a single transcription factor such as NF-κB, and, in fact, Xu et al14 did decipher an upstream site (192-2) that is different from the two NF-κB consensus sites upstream of COX-2. Indeed, some workers have shown that salicylates may inhibit activation of activator protein-1 (AP-1), and affect several other COX-independent signaling pathways as well.13

Nevertheless, the activation of NF-κB is turning into major mechanistic snafu, and not only because of interactions among promoter sites. Novel sites in NF-κB are phosphorylated, leading to subtle changes in its stability and transcriptional efficacy.15 The same goes for upstream elements of its transduction cascade.12,15 Alpert and Vilcek16 reproduced the inhibition of IKΚβ kinase activity by salicylate in vitro, but found, at least in transformed COS1 cells, that salicylates only inhibit tumor necrosis factor alpha (TNFα), but not interleukin–1 (Il-1)-stimulated signal transduction to IKΚβ. Curiously, these and other authors16,17 find that IKΚβ activation is inhibited by p38 mitogen-activated protein kinase (p38MAPK), but others suggest that p38MAPK is necessary for NF-κB driven transcription.15 Or is the whole approach moot, since p105 knockouts (precursor for a NF-κB subunit) are still repressed by salicylates?18

Shaking the bushes harder, other mechanistically inclined investigators recognized the potent antioxidant and metal chelation properties of the adja-

*Spiraea ulmaria (meadowsweet): its medicinal properties were already known during the Renaissance, but were forgotten until a French country priest rediscovered them in the early 19th century. Spirea gave its name to aspirin.

cent phenol and benzoic acid groups and have sporadically championed therapeutic mechanisms based on these. And why not? At concentrations close to millimolar in the plasma (and probably intracellularly), and given that a significant fraction of the cell volume is occupied by large proteins and organelles, local concentrations of salicylate might be orders of magnitude higher. The consequence of this powerful binding group sandwiching itself between with dozens of residues interacting at protein-protein binding surfaces or at catalytic sites could be mechanistically diverse.

In short, significant concentrations of salicylate probably affect large numbers of pathways, albeit to a small degree. It is the cumulative impact on several vulnerable pathways that, say: (i) somewhat inhibits transcription for an enzyme, (ii) that enzyme is weakly inhibited; but (iii) then proceeds to manufacture anti-inflammatory agents! Interestingly, these large studies continue to confound individual (mechanistic) outcome measures, but instead prove overall survival.

After midwifing the pharmacological industry, the arenas of prostaglandins, coagulation, COX IKK, and more recently Q-waves, angiotensin II (AT-II) signaling, and breast and colon cancer, salicylates have more to teach us. I should think. Perhaps we need to look again to the plant. Plants lack a beating heart and circulatory system. Each cell must fend for itself as best as it can against infection. The best they can do for the organism is to convey “under attack signals” throughout the plant. This is why plants produce diffusible salicylates: to boost resistance gene expression in concert with reactive oxygen species (ROS) and nitric oxide (NO)-related amplificatory loops. Indeed, plants utilize versions of the NF-κB and COX-2 genes to mount their systemic defense mechanisms.

Perhaps Old Man Willow will next make us wonder if the Doctrine of Mechanism is getting up there with the Doctrine of Signatures or the Quantification of Angles Dancing on a Pinhead?

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PHOX, a new pathogen-induced oxygenase with homology to animal cyclooxygenase.
When published in 1980, this study represented the largest experience gained with coronary angiography performed during the very acute phase of an evolving ST-segment elevation myocardial infarction. It included 322 patients representative of 1210 patients admitted for an acute myocardial infarction during the period of recruitment from March 1971 until December 1978. A signed informed consent was obtained from patients, which explained the nature of the research and potential benefits in selecting the best treatment, which could include coronary artery bypass surgery.

The study population was relatively young, only 6.2% of patients being older than 65 years, 80% were male and 20% female. Subgroups were formed according to time from onset of symptoms to performance of angiography from 0 to 4 hours, 4 to 6 hours, 6 to 12 hours, and 12 to 24 hours, each group comprising 126, 82, 57, and 57 patients, respectively. The angiographic findings were classified as total coronary occlusion in the absence of forward flow of contrast material in the involved coronary artery, and as subtotal occlusion when more than 95% narrowing was found by visual inspection.

The proportion of patients with total occlusion was highest in the group catheterized early, 87.3%, and decreased subsequently to 85.3% between 4 and 6 hours, 68.4% between 6 and 12 hours, and 64.9% between 12 to 24 hours. Following angiography, 79 patients underwent emergency surgical revascularization. A thrombus was retrieved by Fogarty catheter in 72% of these patients, 88% of those with an angiographic image suggestive of a thrombus, and 25% of those without such an image. The recovered thrombus contained variable quantities of acute inflammatory cells and a thickened layer of fibrin and platelets interspersed with red cells in its middle portion, creating a layering effect. The authors concluded that total coronary occlusion is frequent during the early hours of ST-segment elevation myocardial infarction and that the frequency decreased in the following 24 hours, suggesting that coronary spasm or thrombus formation with subsequent recanalization or both could be important in the evolution of infarction. They did not take into account the frequency of subtotal occlusion, which would likely correspond to TIMI grade 1 and 2 flow according to the more dynamic TIMI grade flow classification now used. The proportions of patients with subtotal occlusion in the study increased during the initial 24 hours. Combining the patients with total and subtotal occlusion yielded a frequency of total or near-total occlusion of 97.6% in the first 4 hours, 96.2% between 4 and 6 hours, 85.9% between 6 and 12 hours, and 70.7% between 12 and 24 hours. These figures are in line with our actual understanding that a thrombus is present in practically all patients, with subsequent spontaneous reperfusion in a certain number. A complication rate of 10.8% was reported with the procedure: nonfatal ventricular fibrillation in 30 cases, intramyocardial injection of dye in 1 patient, disruption of a nonculprit plaque in 2 patients, and 2 fatalities. Transient hypotension was observed in 29 patients.

This study was performed before the era of balloon angioplasty. Controversies then existed on the exact etiology of myocardial infarction; coronary spasm was seen by many as the major contributor to plaque disruption, followed by thrombus formation by blood flow stasis. It was also a time of changes in concepts and attitudes. Reports were already coming out in the literature on intracoronary instillation of nitroglycerin and of streptokinase. This study by DeWood et al contributed to the revolution that occurred in the following years in the management of ST-segment myocardial infarction.
Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group

Lancet. 1988;2:349-360

The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI) and Second International Study of Infarct Survival (ISIS-2) trials were two landmark trials that were decisive for the worldwide introduction of thrombolysis as standard therapy for acute myocardial infarction. ISIS 2, in addition, convincingly showed the benefit of aspirin used alone or in combination with streptokinase in reducing cardiac death.

The GISSI trial (Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico [GISSI]. Lancet. 1986;1:397-402) was an open-label study that enrolled 11,806 patients from 171 coronary care units. Patients admitted within 12 hours after the onset of symptoms and with no contraindications to streptokinase were randomized to receive streptokinase in addition to usual treatment. Overall mortality at 21 days was reduced from 13.0% in controls to 10.7% with streptokinase (relative risk [RR] 0.81, \( P=0.0002 \)).

ISIS-2 enrolled 17,187 patients from 417 hospitals up to 24 hours after the onset of suspected acute myocardial infarction. Patients were randomized double-blind to: (i) a 1-hour IV infusion of 1.5 MU of streptokinase; (ii) 1 month of 160 mg/day enteric-coated aspirin; (iii) both active treatments; or (iv) neither. Streptokinase reduced the 5-week vascular mortality from 12.0% to 9.2% (odds reduction: 25%, \( P<0.00001 \)), and aspirin from 11.8% to 9.4% (odds reduction: 23%, \( P<0.00001 \)). The individual effects of each drug appeared to be additive, with 8.0% vascular death with the combination and 13.2% with neither drug. Aspirin significantly reduced nonfatal reinfarction (1.0% vs 2.0%) and nonfatal stroke (0.3% vs 0.6%). An excess of nonfatal reinfarction was reported when streptokinase was used alone, but this appeared to be entirely avoided by the addition of aspirin.

The trial validated the use of an antiplatelet therapy as primary care in acute myocardial infarction and as adjunctive antithrombotic therapy to thrombolysis. Given the safety, ease of administration, and low cost of aspirin, the results were rapidly extrapolated to all acute ischemic syndromes, including non-ST-segment elevation myocardial infarction and unstable angina. Aspirin, since this trial, is first-line therapy in these syndromes. Prompt administration is recommended when an acute coronary syndrome is suspected, although a relationship between time of administration and benefit had not been documented in ISIS-2, as was the case for streptokinase. Prehospital administration is also widely practiced. The benefits of aspirin with streptokinase were also extrapolated to thrombolytic agents other than streptokinase and have stimulated research for more effective adjunctive therapy.

Since, all clinically effective anticoagulants and antiplatelet drugs have been tested as adjunctive therapy to thrombolysis. Hirudin failed to show a favorable risk-benefit ratio. Heparin is routinely used with tissue plasminogen activator, and optionally with streptokinase. Many recent studies, although of small sample sizes, showed a clear gain with enoxaparin over unfractionated heparin when combined with either tissue plasminogen activator (tPA), streptokinase, reteplase or tenecteplase (TNKase). GP IIb/IIIa (GP, glycoprotein) antagonists combined with half-dose reteplase and TNKase were also shown to be very effective, but associated with a significant increase in the risk of bleeding that precludes their routine use. Clopidogrel in combination with aspirin is currently under investigation.

1988

UN Peacekeeping Forces receive Nobel Peace Prize; 200th anniversary of the birth of Arthur Schopenhauer, the profoundly pessimistic German philosopher; and US Navy cruiser “Vincennes” mistakenly shoots down Iran Air A300 Airbus, killing 290 persons
Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients

Antithrombotic Trialists' Collaboration

BMJ. 1994:308;71-77, 81-106

The extensive collaborative overview carried out by R. Collins, R. Peto, and C. Baigent from Oxford, and by P. Sandercock, D. Dunbalin, and C. Warlow from Edinburgh had a major impact on the use of antiplatelet therapy worldwide, mainly of aspirin. It will last as a classic piece of work. The analysis included more than 100 000 individuals from 145 randomized trials performed before March 1990 of prolonged antiplatelet therapy versus controls, and 29 randomized comparisons between antiplatelet regimens. All risk categories combined, antiplatelet therapy reduced events by about 25%. In the heterogeneous groups of trials and patients, the benefits were apparent irrespective of age, gender, blood pressure, and the presence or absence of diabetes. Treatment of high-risk patients reduced by one third the risk of nonfatal myocardial infarction, by one third the risk stroke, and by one sixth the risk of vascular death. Treatment of 1000 patients with acute myocardial infarction prevented 40 vascular events over 1 month, and that of patients with unstable angina prevented 50 events over 6 months. The benefit in low-risk individuals without a previous vascular event was less apparent, possibly because of a low overall incidence. Nevertheless, treatment in about 28 000 individuals resulted in a statistically significant reduction of 5 per 1000 in nonfatal myocardial infarction and of 2 per 1000 in nonfatal stroke, with no effect on survival.

The main conclusions drawn by the authors of the meta-analyses were that: (i) antiplatelet therapy protected a wider range of patients at risk than previously treated, (ii) it should be considered for almost all with suspected acute myocardial infarction, unstable angina, or a history of myocardial infarction, angina, stroke, transient ischemic attack, arterial bypass surgery, or angioplasty; and (iii) medium-dose aspirin (75-325 mg/day) was the treatment most widely used, while no other regimen appeared significantly more effective in preventing myocardial infarction, stroke, or death. The authors recommended lifelong therapy in the absence of contraindications, although the duration of observation in trials averaged 2 years. The gain with treatment across a wide range of patients and the power of the analysis were strong incentives to wide application and to further research on antiplatelet treatment.

The meta-analysis was recently updated to include 212 000 individuals from trials performed up to September 1997. Among these, 135 000 subjects had been enrolled in trials comparing antiplatelet therapy with controls, and 77 000 were from trials comparing different antiplatelet regimens. The trials added reinforce the data in acute stroke and in certain chronic conditions such as atrial fibrillation and peripheral vascular disease, and provide new data on different doses of aspirin and different antiplatelet agents.

The 1994 meta-analysis had a ratio of comparison trials to control trials of 0.2 (29/145). The ratio rose in 1997 to 0.5 (93 comparisons trials and 194 control trials), reflecting a major shift in clinical practice and clinical research over a short period of time. Not only have new agents been introduced into clinical practice but combination therapy is also increasingly used. Thus, a combination of aspirin, clopidogrel, and a glycoprotein (GP) IIB/IIIa receptor antagonist is routinely prescribed in stent implantation procedures, and the combination clopidogrel aspirin is gaining wide acceptance in high-risk patients.

Cesar Romero, US actor best known for playing “The Joker” in the cult television “Batman” series, dies, aged 86; ice skater Nancy Kerrigan is attacked with a crowbar by Tonya Harding’s bodyguard during practice for the US Championship; and 34 die, and $7 billion damage is caused, when a major earthquake rocks Los Angeles
A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease (ESSENCE)


The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events) Study Group directly compared enoxaparin with unfractionated heparin in 3171 patients with a non–ST-segment elevation acute coronary syndrome. Previous studies had independently shown the efficacy of unfractionated heparin in these syndromes as well as the efficacy of low-molecular-weight heparin (LMWH) against placebo.

The entry criteria in the ESSENCE trial were: (i) angina at rest of recent onset lasting at least 10 minutes and occurring within hours before randomization, with evidence of underlying coronary disease manifested by either ST-segment shift or T-wave changes in two contiguous leads; (ii) previous myocardial infarction (MI) or revascularization procedure; or (iii) ischemic heart disease suggested by the results of noninvasive or invasive testing. These criteria did not specifically identify a particularly high-risk category of patients. Enoxaparin, 1 mg/kg SC q 12 hours, or IV unfractionated heparin, 5000 U bolus, followed by an infusion titrated to an activated partial thromboplastin time (aPTT) of 55 to 85 seconds, were administered double-blind. All patients received aspirin. The study drugs were administered for a minimum of 48 hours and up to a maximum of 8 days. The median duration of treatment was 2.6 days in both groups. Enoxaparin was discontinued before percutaneous procedure or coronary artery bypass surgery, to be replaced with unfractionated heparin. The primary outcome of death, MI, or recurrent angina at 14 days occurred in 16.6% of enoxaparin patients and 19.8% of unfractionated heparin patients (odds ratio [OR] 0.8, \( P=0.02 \)) and the composite end point of death or MI in 14.3% and 17.4% of patients (NS), respectively. At 30 days, the triple end point occurred in 19.8% and 23.3% of patients, respectively (OR 0.81, \( P=0.02 \)) and the end point of death or MI in 16.8% and 19.6% of patients, respectively (NS). The need for revascularization at 30 days was significantly less frequent among patients assigned to enoxaparin than among those assigned to unfractionated heparin (27% vs 32.2%, \( P=0.001 \)). A subsequently published 1-year follow-up of patients showed maintained benefit. No significant differences existed in the risk of major bleeding between both groups, with rates of 6.5% with enoxaparin and 7.8% with unfractionated heparin. Minor bleeding, however, occurred more frequently with enoxaparin (11.9% vs 7.2%). Cost-effectiveness analyses were favorable to enoxaparin.

The ESSENCE trial was therefore successful in showing that the advantages of LMWH over unfractionated heparin could translate into clinical benefit in patients with an acute coronary syndrome. These advantages are a more predictable anticoagulation response allowing subcutaneous administration with no need for monitoring, a higher ratio of inhibition (factor Xa/thrombin), less platelet effect, and less heparin-induced thrombocytopenia. Subsequently, three other trials compared an LMWH and unfractionated heparin in similar populations. One of the trials tested enoxaparin and showed benefits in the same range as those observed in the ESSENCE trial. The two others trials tested different formulations of LMWH and could not show a gain over unfractionated heparin. The long-term use of enoxaparin after hospital discharge resulted in no benefit, but in excess bleeding. Favorable results have been obtained with LMWHs as adjunctive therapy to thrombolysis in patients with ST-segment elevation MI.

1997

Cathy Freeman of Australia wins the world 400-meter title, becoming the first athlete of Aboriginal descent to win a gold medal in the Championships; India celebrates 50 years of independence from British rule; and Diana, Princess of Wales, and her companion, Dodi Fayad, are tragically killed in a car crash in Paris.
Aspirin, heparin, or both to treat acute unstable angina


Patients with unstable angina were included in this randomized, double-blind, 2×2 factorial trial to study the usefulness of aspirin, heparin, and their combination. A total of 479 patients were randomized as soon as possible after hospital admission and within 24 hours after the last episode of pain. Doses of aspirin of 650 mg daily were used and heparin was administered as a bolus of 5000 units followed by an infusion titrated to an activated partial thromboplastin time (aPTT) of 1.5 to 2 times control values. Coronary angiography was performed in the majority of patients a mean of 4 days after randomization. End points were assessed when the final decision for patient orientation to medical management, percutaneous intervention, or coronary artery bypass surgery had been made.

The study drugs were administered for a mean of 6 days. Refractory angina, myocardial infarction, or death occurred in 22.9%, 11.9, and 1.7% of patients, respectively, in the placebo group. The rates were significantly reduced in the three treatment arms, to 3.3% with aspirin (*P*<0.01), 0.8% with heparin (*P*<0.0001), and 1.6% with the combination treatment (*P*<0.01), respectively. The two deaths that occurred in the study were in the placebo group. The number of patients who experienced a fatal or nonfatal myocardial infarction was reduced from 14 in the placebo group to 4, 1, and 2 patients, respectively, in the active treatment groups. Myocardial infarction was less often associated with a Q-wave in patients treated with active drug compared with patients receiving placebo (86% vs 29%, *P*<0.01) and accompanied by lesser peak creatine kinase (CK) elevation. Only heparin significantly reduced the occurrence of refractory angina, from 31% of patients receiving placebo to 9.7% of patients receiving heparin alone or in combination with aspirin. Aspirin resulted in a trend to a reduction, with an incidence of refractory angina of 17%. Bleeding complications in the trial were mainly related to cardiac catheterization, and in excess only with the administration of heparin with or without aspirin.

The study, despite the limitations of a small sample size and a composite end point, assessed short-term, promoted the use of antithrombotic in clinical practice for the management of acute coronary syndromes. It came at a time when a need for more intensive management of patients with unstable angina was becoming apparent. The results of the Second International Study of Infarct Survival (ISIS-2) trial were published the same year, and thrombolysis for the management of ST-segment elevation myocardial infarction was being generalized. Two trials had previously documented the usefulness of aspirin initiated during the subacute phase of unstable angina and one randomized trial had suggested that heparin could be efficacious.

Since, the acute coronary syndromes have become a platform for the evaluation of new antithrombotic drugs. Thrombolysis failed to show a benefit despite some angiographic improvement. Low-molecular-weight heparins have been successfully introduced in clinical practice, and hirudin has shown greater efficacy than heparin during the acute phase. Glycoprotein (GP) IIb/IIIa receptor antagonists have also been introduced for the management of high-risk patients and patients undergoing a percutaneous procedure. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial recently documented an additive gain when clopidogrel was added to aspirin compared with aspirin alone; patients were administrated heparin in the trial.
The prognostic value of serum troponin T in unstable angina

C. W. Hamm, J. Ravkilde, W. Gerhardt, P. Jorgensen, E. Peheim, L. Ljungdahl, B. Goldmann, H. A. Katus


This seminal paper was the first to describe the diagnostic value of troponin T in patients with unstable angina. It further explored whether its detection in the circulation might be a useful predictor of prognosis. The study included 109 consecutive patients hospitalized in four European centers. At admission, diagnosis of acute myocardial infarction was an exclusion criterion, including creatine kinase (CK) activity 200 U/L or more, as well as a myocardial infarction within the previous 2 weeks. Blood samplings were obtained within 6 hours of admission and every 8 hours thereafter for 48 hours.

Patients were categorized using the Braunwald classification into class 1 (severe or accelerated angina of new onset), class 2 (angina at rest not active within the previous 48 hours), and class 3 (angina at rest within the previous 48 hours). All therapeutic decisions were made without knowledge of troponin T levels.

All 25 patients with class 1 and class 2 angina had normal total CK, CK-MB (membrane-bound) activity, and troponin T values at admission and during the 48-hour sampling period. They also showed no ECG changes and had no cardiac events. In contrast, an elevation in troponin T was seen in 33 of the 84 patients with class 3 angina (39%). Noteworthy was that the elevation was seen early and was of modest amplitude, with median values of 0.50 µg/L, (range 0.20-3.63 µg/L). It was present at admission or in the second sampling in 84% of patients, in the other patients it occurred after repeated episodes of chest pain in-hospital. CK-MB activity was elevated in 4% of patients. ECG changes were present in 78% of the patients with negative troponin T values and in 85% of those with positive values. Coronary angioplasty and bypass surgery were performed as frequently in patients with elevated and normal troponin T levels.

Thirty percent of patients with elevated levels experienced myocardial infarction with ST-segment elevation within 2 to 10 days after admission and 13% died. One patient with no elevation had a myocardial infarction (MI) and died. Thus, elevated troponin T levels preceded 10 out of the 11 myocardial infarctions (3 occurred perioperatively) and 5 of the 6 fatalities (3 after coronary artery bypass grafting), yielding a positive predictive value of 30% and a negative predictive value of 98%.

The study, so small it was, was a landmark observation that changed our management approach to acute coronary syndromes. Numerous observations from various investigators have since confirmed the high frequency of troponin T or troponin I elevation in patients with an acute coronary syndrome as well as the impaired prognosis associated with an elevation. On the other hand, the favorable prognosis observed in patients with no elevation permits more appropriate management. The assessment of troponin levels is now the most important tool for decision-making besides clinical evaluation. Its value adds to other markers of risk including the ECG, CK-MB levels, Holter monitoring, and the exercise test. Importantly, the test has become a marker of the underlying pathophysiology and, accordingly, a help for treatment selection. Elevated troponin levels reflect cell necrosis associated with an ongoing intracoronary thrombotic process. In large MI with concomitant CK-MB elevation, the thrombus is most likely occlusive, in smaller MI with normal or only mildly elevated MI, cell necrosis is likely caused by distal embolization of thrombogenic material. These patients profit most from an intensive antithrombotic therapy, as was documented with low-molecular-weight heparins and GP IIb/IIIa receptor antagonists. They also profit from an aggressive management strategy that includes revascularization procedures.
Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty

The EPIC Investigators


Epic (Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications) was the first large-scale placebo-controlled trial ever performed with a glycoprotein (GP) IIb/IIIa receptor antagonist (the monoclonal antibody abciximab). The drug was initiated in the catheterization laboratory before coronary angioplasty. A total of 2099 patients at high-risk of complications due to severe unstable angina, evolving myocardial infarction (MI), or complex plaque characteristics were enrolled. (These situations are particularly appropriate to test a potent antagonist to platelet aggregation.) The patients were randomized to placebo, abciximab as a bolus, or abciximab as a bolus followed by a 12-hour infusion. The primary end point at 30 days was a composite of death, nonfatal MI, and the need for unplanned interventions, including surgery, repeated percutaneous revascularization, stent implantation, and intra-aortic balloon counterpulsation. As compared with placebo, the bolus and infusion dose of abciximab reduced the risk of an adverse outcome event by 35% (8.3% vs 12.3%; P=0.008). The risk reductions were in the same range for the end points of unplanned procedures and MI, and were consistent across the various subgroups analyzed. Most events in the placebo group occurred within 6 hours after the procedure. With the bolus, events were delayed for several hours, corresponding to the time of maximal occupancy of the receptor, and were not statistically different from those occurring in the placebo group after 30 days.

Abciximab was associated with a doubling of hemorrhagic events and bleeding events that required administration of blood products. Major bleeding occurred in 7% of placebo patients, 11% of abciximab bolus, and 14% of abciximab bolus followed by infusion. In the latter group, 15% of patients received red cell transfusions and 6% platelet transfusions. Bleeding occurred mainly at arterial punctures sites and was a frequent complication in coronary artery bypass surgery.

Despite the excess bleeding, the drug was approved for clinical use based on the efficacy results. The bleeding risk was largely controlled in subsequent studies by the administration of lower doses of heparin and its early discontinuation after procedures, and by withdrawing vascular sheaths after a few hours when the activated partial thromboplastin time (aPTT) values were back to near control values (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIa receptor blockade [EPILOG] trial). The usefulness of abciximab was also subsequently documented in patients with refractory unstable angina submitted to angioplasty within the following 24 hours (Chimeric 7E3 AntiPlatelet in Unstable angina REfractory to standard treatment [CAPTURE] trial), patients undergoing an elective percutaneous procedure (EPILOG trial), or stent implantation (Evaluation of Platelet IIb/IIa Inhibitor for STENTing trial [EPISTENT] trial). The Global Use of Streptokinase and Tissue plasminogen activator for Occluded arteries (GUSTO-IV) trial failed, however, to show a benefit of the drug in patients with a non–ST-segment elevation acute coronary syndrome managed medically; in the Global Use of Strategies To open Occluded arteries in acute myocardial infarction (GUSTO-V) trial that included patients with ST-segment elevation MI, no reduction in mortality was shown with the combination of full-dose abciximab and half-dose reteplase. Abciximab remains indicated in patients with ST-elevation MI when a primary intervention is indicated. In the ADMIRAL study (Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up), the prompt administration of abciximab before referral to the catheterization laboratory for primary stenting resulted in better TIMI 3 grade flow before the intervention, after the intervention, and after 6 months, as well as in a marked reduction in event rates.

1994

Ex-US president Richard Nixon dies after a stroke, aged 81; US scientists discover the top quark, the missing atomic component; and hundreds of thousands die in two weeks of tribal slaughter in Rwanda
Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators


The study tested the hypothesis that abciximab will be particularly effective in patients with elevated troponin T levels, a surrogate marker of thrombus formation, because of the properties of the glycoprotein (GP) IIb/IIa receptor antagonist to block platelet aggregate formation. For this purpose, the authors assessed the value of troponin T levels that were collected at baseline in the Chimeric 7E3 Anti-Platelet in Unstable angina REfractory to standard treatment (CAPTURE) trial to predict the benefit of abciximab. The double-blind randomized trial compared abciximab with placebo in 1265 patients with refractory unstable angina. The patients were randomized in the trial after the angiographic identification of a culprit lesion suitable for percutaneous revascularization. The interventions were performed 18 to 24 hours after randomization. Cardiac events were monitored during a 6-month follow-up period. Patients with a recent myocardial infarction were excluded from the present study since troponin levels can remain elevated in blood for many days after a myocardial infarction.

Baseline troponin T values below the cutoff value of 0.1 ng/mL or less were found in 69.1% of patients. Among these patients, the rates of death or myocardial infarction were similar with abciximab treatment and with placebo. They occurred during the phase of medical management before angioplasty in 10% of patients, at 1-month in 5.2% and 4.9%, and at 6 months in 9.4% and 7.5% of patients, respectively. Among the 31.9% of patients with values ≥0.1 ng/mL, abciximab significantly reduced the rates of death or myocardial infarction. The rates were 0.7% and 6.6% (P=0.02) before angioplasty, 5.8% and 19.6% (P=0.002) at 30 days, and 9.5% and 23.9% (P=0.002) at 6 months, respectively. Abciximab, therefore, reduced the risk of an event in patients with increased troponin T levels to that of patients with troponin T levels below the diagnostic cutoff values. The reduction was present before as well as after the revascularization procedure and maintained over a period of 6 months.

Creatine kinase, myocardial band (CK-MB) values were elevated at baseline in 13% of patients. An elevation was a significant predictor of increased risk at all time points. However, regression analysis, which included interaction with treatment, indicated no relation between the benefit of abciximab and the CK-MB level. The same absence of interaction was seen with ST-segment depression and T-wave inversion.

The study nicely correlated the mechanisms of action of the drug with the pathophysiology of the disease and with the clinical benefit. The benefit extended to medical management as well as to reperfusion procedures. The elevation of troponin T is believed to represent distal embolization of thrombotic material that can occur spontaneously and that can be provoked by catheter manipulation, balloon inflation, and stent deployment. The study further defined modalities for optimal benefit of treatment in patients with an acute coronary syndrome. Indeed, the main study revealed that the early gain and the gain at 30 days with abciximab were not maintained after 6 months. The present study showed that treatment of 100 patients with elevated troponin T prevents 15 cases of death or myocardial infarction at 6 months. Similar results have been published with dalteparin, showing that the benefit of treatment was mainly confined to patients with elevated troponin T levels.

British actor Oliver Read dies of a heart attack while drinking in a bar; a US expedition to Everest finds the body of British climber George Mallory, missing for 70 years—the find fails to resolve the question of whether he was the first to conquer the mountain; and Yugoslavian president Slobodan Milosevic becomes the first serving head of state to be indicted as a war criminal.
Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators

S. Yusuf, F. Zhao, S. R. Mehta, S. Chrolavicius, G. Tognoni, K. K. Fox


CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) is a randomized double-blind trial comparing the combination of clopidogrel and aspirin with aspirin alone among 12,562 patients with a non-ST-segment elevation acute coronary syndrome (ACS). The inclusion criteria, which were refined to higher-risk patients during the recruitment period, included compatible symptoms plus the presence of ischemic ST-T changes or an elevation of the cardiac markers to two times or more the upper limit of normal. Patients were randomized within 24 hours of the last episode of chest pain and administered the study drugs for 3 to 12 months. A bolus dose of 300 mg clopidogrel was administered first, followed by 75 mg/day. The doses of aspirin were between 75 and 325 mg/day.

The study had two primary end points, the first was composed of cardiovascular death, myocardial infarction, or stroke and the second of the same components plus refractory ischemia. The first primary end point occurred at 30 days in 11.47% of the patients in the placebo group and 9.3% of patients in the clopidogrel group (relative risk [RR] 0.80, *P* = 0.00005), and the second, in 19% and 16.7% of patients, respectively (RR 0.86, *P* = 0.0004). The benefit of clopidogrel emerged early after randomization, with risk reductions of 20% and 26% observed 24 hours after randomization for the two primary end points. The benefit continued long-term with an additional risk reduction from day 30 to 12 months. All subgroup analyses showed a 15% to 25% risk reduction favoring clopidogrel. There was significant excess in rates of major bleeding with the combination therapy (3.6% vs 2.7%, *P* = 0.003), including life-threatening bleeding (2.1% vs 1.8%, *P* = 0.27), minor bleeding (15.3% vs 8.6%, *P* < 0.0001), and number of patients administered two or more blood units (2.8% vs 2.2%, *P* < 0.03). Thrombocytopenia and neutropenia were infrequent and not in excess with clopidogrel.

The excess bleeding is of concern, but consistent with the greater antiplatelet effects and clinical benefit of the combination. Indeed, the efficacy of clopidogrel and ticlopidine had been previously well documented in numerous placebo-controlled trials. Ticlopidine was further shown to be slightly superior to aspirin for the secondary prevention of stroke, while clopidogrel was superior to aspirin in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial for the prevention of vascular events in patients with recent stroke, recent myocardial infarction, and patients with symptomatic peripheral vascular disease. On the other hand, there was clinical evidence of added benefit with combined antiplatelet therapy. Thus, the combination of aspirin and a glycoprotein (GP) IIb/IIIa receptor antagonist is used in ACS, the combination of aspirin, clopidogrel, and a GP IIb/IIIa receptor antagonist is used in coronary stenting, and the combination aspirin and dipyridamole is used in stroke. Clopidogrel should clearly be preferred over ticlopidine, because it does not possess the serious adverse events of the latter. It is also well tolerated in a bolus dose, which is required for rapid antiplatelet effect.

The impressive results of the CURE trial mandate an evaluation of the combination therapy against other drug therapies that have been shown useful in ACS, such as the GP IIb/IIIa receptor antagonists, enoxaparin, and hirudin. They are also incentives to evaluate other combination therapies. Beyond the results and beyond the constraints of the protocol, the CURE trial showed the appropriateness of the concept that blocking platelets through different pathways of activation has the potential to magnify the clinical gain. The aspirin-clopidogrel combination may now be a new standard for the management of acute thrombogenic situations as well as for secondary prevention in selected high-risk patients. The hypotheses need clinical testing.

2001

A Palestinian suicide bomber kills 8 people and injures about 100 in a Jerusalem restaurant; violence erupts following the seizure of white-owned farms in Zimbabwe; and Larry Adler, the world’s best-known exponent of the mouth organ, dies aged 87
Multiple complex coronary plaques in patients with acute myocardial infarction

J. A. Goldstein, D. Demetriou, C. L. Grines, M. Pica, M. Shoukfeh, W. W. O’Neill


This study shares analogies with the one by DeWood et al previously discussed. Both studies were descriptive of angiographic findings obtained in small series of patients with ST-segment elevation myocardial infarction. The two were published in the same journal, but 20 years apart. The first established the importance in clinical practice of thrombus formation in causing the infarction and contributed to a profound change in the therapeutic approach. The study by Goldstein et al provided a different perspective on the mechanisms of acute coronary syndromes by showing clinicians angiographic images of a diffuse disease, beyond the concept of a single culprit lesion that has influenced our practice for years. We are now learning that the disease is inflammation, which can have multiple etiologies, including risk factors and infectious or autoimmune processes, and which degrades plaques and leads to thrombus formation and myocardial infarction.

The authors examined the coronary angiograms of 253 patients with acute myocardial infarction for the presence of complex plaques at sites other than the infarcted-related lesion. The exact timing of the angiogram with regard to onset of chest pain is not stated. Plaques with 50% or more lumen diameter reduction at quantitative analysis were scrutinized for the presence of an intraluminal filling defect, ulcerations, irregularities, or impaired distal flow. The presence of two or more of these features defined a complex plaque. The plaques were considered anatomically remote from the main culprit lesion when located in a different artery, or a different branch, or located at least 5 cm away from the main lesion with an intervening disease-free segment. Patients with single and multiple complex plaques had the same demographic characteristics, risk factors, and previous cardiac history. A single complex plaque was identified in 60.5% of patients, and multiple complex plaques in 39.5%. Among the patients with multiple plaques, 83% had 2 and 17% had 3 or more complex plaques. The severity of stenosis of these secondary complex plaques tended to be less than in the infarct-related plaque, yet distal flow was impaired in 27% of cases. Patients with complex plaques more often required urgent bypass surgery in-hospital (27% vs 5.2%); they also experienced more frequently in the following year a recurrent acute coronary syndrome episode (19.0% vs 2.6%) and underwent more often repeated angioplasty (32% vs 12.4%), particularly of non-infarct-related lesions (17% vs 4.6%), and coronary-artery bypass graft surgery (35% vs 11.1%). Multivariate analysis showed that the presence of multiple complex lesions was the strongest predictor of a complicated course.

These observations are in line with the autopsy findings of numerous ruptured plaques and of thrombus located at various sites in patients dying suddenly from a cardiac cause. The observations also help to explain the rapid angiographic progression in the severity of the disease frequently seen in patients with unstable angina.

A new era in investigation and management is already present: reliable markers of thrombosis and inflammation are available, such as troponin T and I levels and C-reactive protein, while work is being done on identifying new markers and new visualization methods of the complex plaque at risk of an event. Noninvasive methods are particularly appealing as they permit large-scale applicability. Potent antithrombotic drugs and potent drugs like statins, which stabilize the active atherosclerotic plaque, are available, and new therapies are emerging at an accelerating pace.

Denmark votes to not adopt the single European currency; Pierre Trudeau, former Canadian prime minister, dies of prostate cancer, aged 80; and British rower Steve Redgrave becomes the first man to win five gold medals in consecutive Olympics in an endurance event.
Thrombosis & Platelets

Bibliography of One Hundred Key Papers

selected by Pierre Theroux, MD

Department of Medicine - Montreal Heart Institute - University of Montreal
5000 Belanger East - Montreal - Quebec - CANADA (e-mail: theroux@ICM.Umontreal.ca)

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