

# Thrombus Formation on Atherosclerotic Plaques: Pathogenesis and Clinical Consequences

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**Purpose:** To describe the characteristics of thrombus formation on atherosclerotic plaques, the clinical expression of atherothrombosis in vascular disease, and some of the most recent therapeutic approaches in cardiovascular disease.

**Data Sources:** MEDLINE search for English-language articles on thrombosis and atherosclerosis published up to January 2000. Abstracts of recent international meetings on new aspects of thrombus formation and new therapeutic options were reviewed, and references from identified articles were selected and reviewed.

**Study Selection:** Experimental, basic, clinical, and epidemiologic studies related to the pathophysiology of thrombosis on atherosclerotic lesions. Therapeutic approaches were obtained from experimental studies and large clinical investigations.

**Data Extraction:** Arterial vessel wall substrate, rheologic conditions, and blood thrombogenicity influence the process of thrombus formation in arteries. Thrombus formation on disrupted atherosclerotic plaques or arterial erosions frequently causes acute coronary syndromes. Severe atherosclerosis of the aorta has been

identified as an important morphologic indicator of an increased risk for thromboembolism. Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis.

**Data Synthesis:** Improved understanding of the pathophysiology of thrombus formation on atherosclerotic plaques has led to the development of new therapeutic approaches. Glycoprotein IIb/IIIa, tissue factor, factor Xa, and thrombin inhibitors as well as combined antithrombotic therapy, such as aspirin plus a thienopyridine plus warfarin, are being evaluated as new possible options for the treatment of arterial thrombosis.

**Conclusions:** Long-term treatment with potent antithrombotic drugs, such as tissue factor or factor Xa inhibitors, that effectively block thrombosis without causing bleeding complications could help reduce death from cardiovascular disease.

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I schemic heart disease is the most common cause of death worldwide (1). Thrombi that form on atherosclerotic lesions in coronaries are responsible for myocardial ischemia and progression of atherosclerosis (2–5). Recent pathologic, experimental, and clinical findings have led to a better understanding of the cellular and molecular mechanisms underlying thrombus formation on atherosclerotic plaques. In this review, we describe pathophysiologic mechanisms that lead to arterial thrombosis, the clinical impact of thrombosis on arterial lesions, and new therapeutic developments. With regard to the impact of arterial thrombosis on human mortality, we focus on the thrombotic process in atherosclerotic disease. Recent reviews have summarized the pathophysiologic and clinical aspects of the vulnerable plaque in the development of atherosclerotic lesions (6–9).

## METHODS

We searched MEDLINE for English-language reports on thrombosis and atherosclerosis published from

1966 to the present. Experimental, clinical, and epidemiologic studies related to the pathogenesis and pathophysiology of thrombosis on atherosclerotic lesions were reviewed, and references from identified articles were also selected. Abstracts on new aspects of therapeutic options that were presented at recent international meetings of the International Society of Thrombosis and Haemostasis and the American Heart Association were selected. Therapeutic approaches were derived from experimental studies and large clinical investigations.

## PATHOPHYSIOLOGY AND CLINICAL IMPACT OF THROMBUS FORMATION ON ATHEROSCLEROTIC LESIONS

### The Virchow Triad

As described by Virchow more than 100 years ago, occurrence of arterial thrombosis depends on the arterial vessel wall substrates, the local rheologic characteristics of blood flow, and systemic factors in the circulating blood (Table 1) (2, 3, 8, 10, 11).

### Local Substrates for Thrombosis: Atherosclerotic Plaques

Vulnerable atherosclerotic plaques may cause most acute coronary syndromes (12, 13). Atherosclerotic lesions are found in most major arteries, including the aorta, carotid, iliofemoral, and medium-sized arteries (such as the coronaries) (13). Focal intimal lesions may first develop in the human fetus before birth (14). Autopsy studies in persons without clinical cardiovascular disease showed that intimal alterations occur in the different vascular beds within the first 15 to 20 years of life (15–17). Using histologic characteristics, the American Heart Association has developed a standardized classification of distinct plaque types (Figure 1). Advanced atheromatous lesions are the substrates for arterial thrombosis. In advanced atheromatous lesions, the lipid core of the plaque contains pultaceous debris, apoptotic cells (such as dead macrophages and smooth-muscle cells), mesenchymal cells, and abundant free cholesterol crystals (fatty gruel) (18). The lipid core of these type IV and V lesions is rich in tissue factor, which, upon plaque rupture and exposure to the circulating blood, initiates the coagulation cascade and thrombin generation (Figure 2) (19). Smoking increases tissue factor expression in atherosclerotic plaques. Tissue factor is associated with and probably generated by activated macrophages within the plaque. The degree of plaque disruption (erosion, fissure, or ulceration) and the amount of stenosis caused by the disrupted plaque and the overlying mural thrombus are key factors for determining thrombogenicity at the local arterial site. When deep ulceration occurs, tissue factor from the atherosclerotic lipid core is exposed to flowing blood and released into the lumen (20, 21). Tissue factor interacts with factor VII and subsequently activates factor X, which leads to conversion of prothrombin to thrombin in the prothrombinase complex (Figure 2) (22, 23). The high tissue factor activity contributes to the procoagulant activity of disrupted atherosclerotic lesions and the superimposed mural thrombi (20). Disruption of advanced plaques with exposure of the highly thrombotic lipid core to the flowing blood triggers the formation of thrombi up to 6 times larger than thrombi generated by exposure of other components of the arterial wall (18). Mural thrombus formation may contribute to arterial stenosis, release vasoconstrictors from platelets, and cause ischemic symptoms (6, 8, 24, 25). The vulnerability of a plaque includes the pathoanatomic features that are re-

**Table 1. The Virchow Triad**

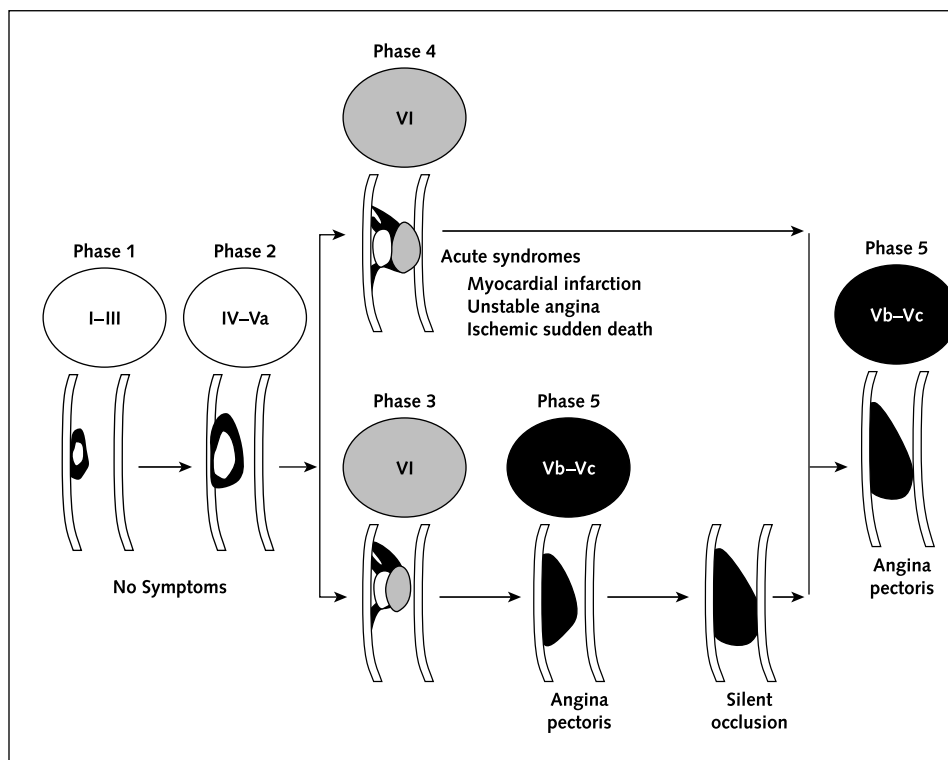
Local vessel wall substrates
Atherosclerosis
Degree of plaque disruption, components of plaque (e.g., lipid core and tissue factor content), generation of microparticles through apoptosis
Vessel wall inflammation
Plaque infiltrates, macrophages (source of tissue factor)
Interventional vessel wall injury
Endothelial denudation; injury of smooth-muscle cells (rich in prothrombin); plaque disruption after percutaneous transluminal coronary angioplasty, atherectomy, or stenting
Rheology
High shear stress
Severely stenotic arteries, dysfunction of endothelium, vasoconstriction
Oscillatory shear stress
Bifurcation of arteries, plaque irregularities
Slow blood flow/local stasis
Dissection of intima, aneurysms
Systemic factors of the circulating blood
Metabolic or hormonal factors
Hyperproteinemia or dyslipoproteinemia [triglycerides, increased low-density lipoprotein or oxidized low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, lipoprotein(a)], diabetes mellitus (glycosylation), catecholamines (e.g., smoking, stress, cocaine use), renin-angiotensin system (e.g., high-renin hypertension)
Plasma variables of hemostasis
Tissue factor, factor VII, factor VIII, fibrinogen, thrombin generation (fragments 1 and 2), thrombin activity (fibrinopeptide A), plasminogen activator inhibitor-1, tissue plasminogen activator
Cellular blood elements
Cell count (leukocytosis, erythrocytosis), blood viscosity, activation of blood particles, cell aggregation (platelet-platelet, platelet-leukocyte), platelet volume

lated to size of the lipid pool, thickness of the fibrous cap, content and metabolic activity of lipids (26, 27), activity and density of macrophages (28, 29), and matrix metalloproteinases (30, 31). The external physical forces that expose the vessel wall to blood flow at different shear rates also influence the occurrence and progression of plaque disruption, thrombosis, and arteriosclerosis (32–35).

### Blood Rheology and Thrombus Formation

Acute changes in rheologic characteristics induced by vasoconstriction, plaque disruption, and thrombus formation induce changes in the shear rate of flowing blood. Thrombus formation increases with increasing shear force (32). Shear force is directly related to flow velocity and inversely related to the third power of the lumen diameter. Thus, acute platelet deposition after plaque disruption depends on arterial size and the geometric changes and degree of narrowing after disruption. Changes in geometry may increase platelet deposition, whereas a sudden protrusion of plaque contents or

**Figure 1. Relation of lesion morphologic characteristics and phases of progression of coronary atherosclerosis to clinical findings.**



An early lesion (phase 1) can become an atheromatous or fibrolipid plaque (phase 2). Phase 2 can progress into an acute phase (phase 3 or 4). Formation of thrombosis or hematoma may cause angina pectoris (phase 3) or an acute coronary syndrome due to occlusive thrombosis (phase 4). Phase 3 and 4 lesions can evolve into a fibrotic phase (phase 5) characterized by more stenotic plaques that may progress to occlusive lesions. Stenosis and myocardial ischemia can induce the growth of collateral vessels. Patients may have angina or silent vessel occlusions in phase 5. White indicates lipid accumulation, gray indicates thrombosis and hemorrhage, and black indicates fibrous tissue. Roman numerals indicate the lesion types. I-III = early lesions with isolated macrophage-foam cells (I), multiple foam-cell layers (II), or isolated extracellular lipids (III); IV-Va = advanced lesions (atheromatous or fibrolipid plaques with confluent extracellular lipid pools [atheroma] [IV] or fibromuscular tissue layers and atheroma [Va]); VI = advanced lesions (complicated plaques with surface defects, hemorrhage, or thrombi deposition); Vb-Vc = advanced lesions with calcifications (Vb) or fibrous tissue (Vc). Reproduced with permission from Fuster and colleagues (8, 11).

growth of thrombus at the injury site may create severe stenosis and thrombotic occlusion. Most platelets are deposited at the apex of a stenosis, which is the site of maximal shear force (32, 36).

Mechanical forces associated with blood flow influence the vascular tone, arterial structure, and location of arterial lesions (32, 36). Thrombin causes vasoconstriction when endothelium is absent or dysfunctional. Arterial vasoconstriction increases the shear force. Systemic risk factors for atherosclerosis, such as smoking, hyperlipidemia, or diabetes mellitus, may cause endothelial dysfunction, promote vasoconstriction, and increase shear force and platelet deposition.

*Contribution of Systemic Risk Factors to Thrombosis*

Systemic factors, including changes in lipid and hormonal metabolism, hyperglycemia, hemostasis, fibrinolysis, and platelet and leukocyte function, are associated with increased blood thrombogenicity or a systemic hypercoagulable state (37). Approximately one third of

patients with acute myocardial infarction and coronary thrombosis have plaque erosions that occurred on non-ruptured, moderately stenotic plaques. The patients who developed coronary thrombosis on erosions had systemic risk factors associated with a hypercoagulable state (38).

Lipoprotein(a), a known risk factor for coronary heart disease, has a structure similar to that of plasminogen and may reduce plasmin formation and impair thrombolysis (39). Elevated low-density lipoprotein cholesterol levels increase blood thrombogenicity (40) and growth of thrombus under defined rheologic conditions (41). Reducing low-density lipoprotein cholesterol levels using statins decreased thrombus growth by approximately 20% (41). The reduction of total vascular events, including death, coronary events, and stroke, by lipid-lowering therapy with statins was documented in several large prospective clinical trials (42-48). Reduced low-density lipoprotein cholesterol levels may also de-

crease vasoconstriction and the size of the lipid core (41).

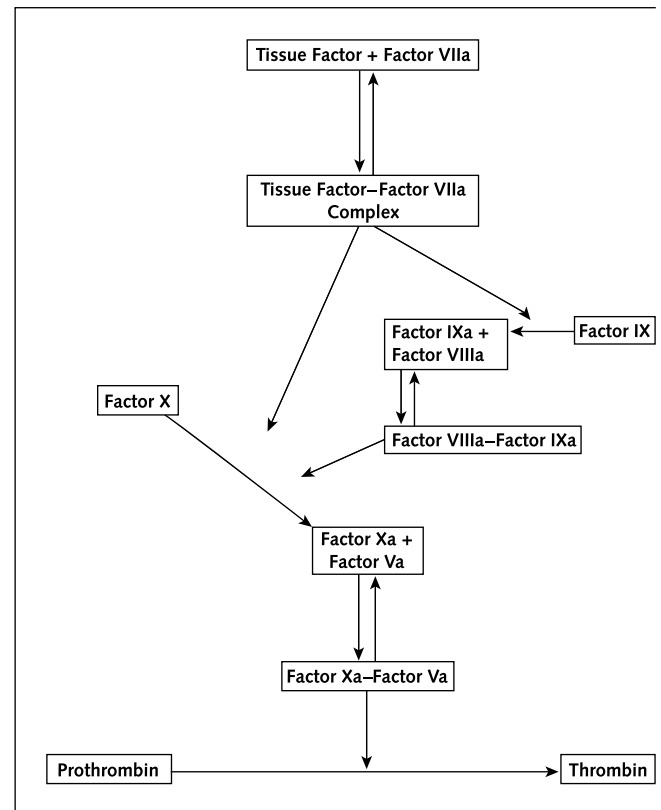
High plasma levels of catecholamines potentiate platelet activation, enhance vasospasm, and increase the incidence of sudden death after emotional and physical stress in patients with acute cardiovascular events. Smoking increases catecholamine release, causes endothelial dysfunction, and is associated with increased levels of fibrinogen (49).

Increased plasma fibrinogen level is an independent risk factor for complications in patients with atherosclerotic disease (50–52). Fibrinogen, factor VIIIc, and von Willebrand factor were shown to be positively related to C-reactive protein (53). C-reactive protein, like fibrinogen, is a protein of the acute-phase response and a sensitive marker of low-grade inflammation. Increased levels of C-reactive protein have been reported to predict acute coronary events (54–56). C-reactive protein seems to be a useful marker for predicting risk for thrombotic events. Whether C-reactive protein reflects only the extent of the acute-phase reaction in response to nonspecific events, such as myocardial ischemia or atherosclerosis, or whether it may directly participate in the process of thrombus formation at the site of the atherosclerotic vessel is not known (56).

Diabetic patients, especially those whose diabetes is poorly controlled, have increased blood thrombogenicity, due in part to glycosylation of collagen and proteins and increased levels of plasma fibrinogen and plasminogen activator inhibitor-1 (57–62). Platelets from patients with diabetes have increased reactivity and hyperaggregability and expose a variety of activation-dependent adhesion proteins (63, 64). Abnormal platelet function is reflected by increased platelet consumption and prolonged accumulation of thrombocytes on the altered vessel wall (64–66). In addition, more leukocyte–platelet aggregates circulate in the blood of patients with diabetes and diabetic vasculopathy (64). The prothrombotic state in diabetes is also associated with increased expression of monocyte procoagulant activity in the presence of diabetic microalbuminuria (67). Increased procoagulant activity in diabetes is attributed to leukocytes (64, 65, 67), which may in part activate the tissue factor pathway (68) and contribute to the high blood thrombogenicity in diabetic patients.

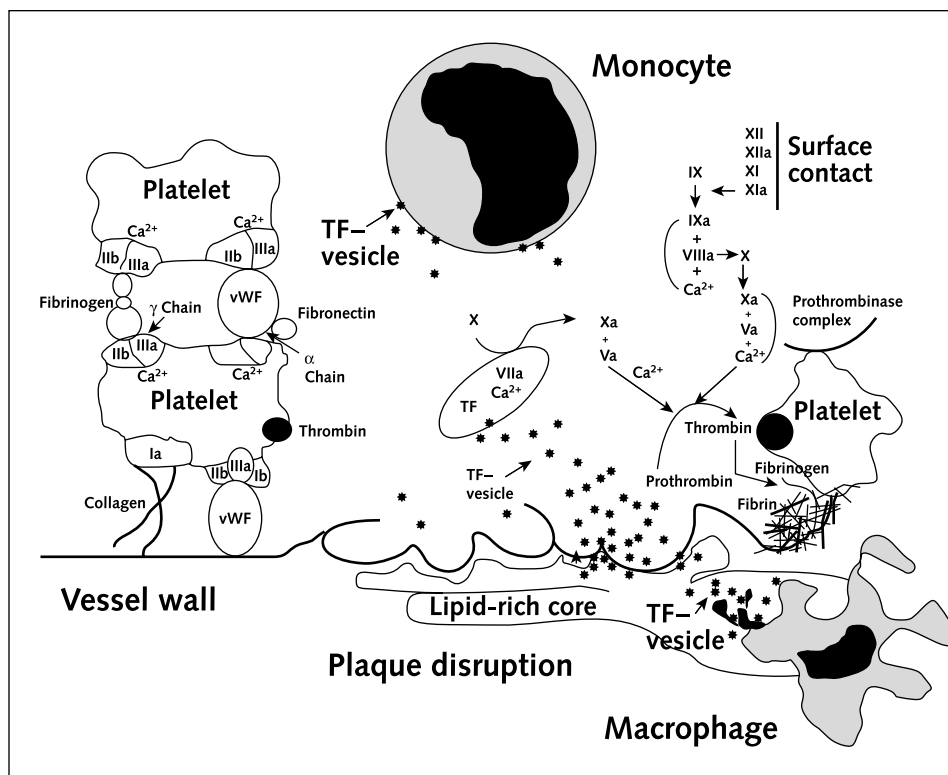
Recent studies showed increased levels of circulating tissue factor antigen in patients with cardiovascular dis-

**Figure 2. The tissue factor pathway activation of coagulation.**



ease (69) and coagulation disorders, such as disseminated intravascular coagulation (70–72). Circulating tissue factor antigen has been associated with increased blood thrombogenicity in patients with acute coronary syndromes (69, 73) and chronic coronary artery disease (74). Increased tissue factor–positive procoagulant microparticles are present in the circulating blood of humans under pathophysiologic conditions (75). Thus far, the cellular origin of tissue factor–positive microparticles in the circulating blood of patients with acute coronary syndromes has not been established. As described, atherosclerotic plaques have been shown to contain tissue factor that is associated with macrophages within the lesion (19). High levels of shed apoptotic microparticles were found in extracts from atherosclerotic plaques (20). The microparticles had tissue factor activity and seemed to be of monocytic origin, suggesting a causal relationship between shed membrane microparticles and procoagulant activity of plaque extracts. In addition, tissue

**Figure 3. Activation and amplification of coagulation by activator complexes (generating thrombin for platelet activation [78] and fibrin formation) and thrombus formation on disrupted atherosclerotic plaques.**



Exposure of subendothelium and plaque contents to circulating blood activates the hemostatic system and generates thrombin. Platelets recognize von Willebrand factor (*vWF*) by glycoprotein Ib (*Ib*) and collagen by platelet glycoprotein Ia (*Ia*) (79). The binding of platelets to these arterial structures leads to intracellular signaling, ion currents, protein kinase activation, polymerization of the platelet cytoskeleton, and arachidonic acid metabolism. Constitutively expressed  $\alpha_{2b}$  integrin (glycoprotein IIb/IIIa [*IIB/IIIa*] complex) changes its steric conformation and exposes the high-affinity binding site for fibrinogen. The cross-bridging of circulating activated platelets to fibrinogen results in platelet aggregation. Thrombin generated at the blood–plaque interface in association with cellular membranes on cells and platelets converts fibrinogen to fibrin, activates platelets and coagulation factors V and VIII, and stabilizes the growing thrombus by cross-linking fibrin. Thrombin activity and continued generation are necessary for maintaining platelet cohesion within mural thrombi and thrombus growth (4). TF = tissue factor.

factor has also been identified within thrombi formed in coronaries. Immunoelectron microscopy demonstrated tissue factor in thrombi within 5 minutes of formation, mainly localized on membrane vesicles attached to platelets and fibrin strands (76, 77). Neutrophils and monocytes have been isolated from the circulating blood by using anti-tissue factor antibodies (76). Monocytes and injured atherosclerotic plaques seem to be a source of tissue factor microparticles that circulate in the systemic blood and may represent an additional risk factor for thrombotic events (Figure 3).

### The Clinical Impact of Arterial Thrombosis

Myocardial ischemia or infarction causes up to 70% of deaths—both long- and short-term—in most patients with generalized atherosclerotic disease (80–82). Cerebrovascular disease causes approximately 10% to 17% of deaths in these patients, and another 10% are caused by ruptured aneurysms or visceral infarctions (81, 83). The risk factor most strongly associated with

postoperative mortality in patients undergoing peripheral artery bypass surgery is a history of myocardial infarction or stroke (80, 84). The rupture of vulnerable plaques and subsequent thrombus formation on disrupted arteries other than the coronaries contribute to acute thromboembolic events and occlusions in peripheral and cerebral arterial beds.

### Association with Thromboembolic Events

Aortic plaques from persons who died of ischemic heart disease often have ulcerations and mural thrombosis. These ulcerated aortic plaques also contain a high proportion of extracellular lipids (>40% of the cross-sectional plaque area) and are characterized by a shift toward greater monocyte–macrophage content relative to smooth-muscle cells in the cap (85). Ulcerated and thrombotic lesions seem to persist or recur and are chronically present in the atherosclerotic aorta (85). Severe atherosclerosis of the ascending aorta has been identified as the most important morphologic indicator of an

increased risk for thromboembolism (86–90). Atheroemboli originating from the atherosclerotic aorta are widely recognized complications of operations involving manipulations of the aorta. Atheroembolic lesions can be found in the brain, spleen, kidney, and pancreas after cardiac surgery. Because the age of patients undergoing these operations has increased, thromboembolism is an increasingly frequent cause of perioperative death (88). In addition, severe atherosclerosis of the aorta is present in one third of patients with cryptogenic stroke (89). The French Study of Aortic Plaque in Stroke Group has recently identified morphologic characteristics of aortic atherosclerosis associated with strokes and other vascular events. Aortic plaques greater than 4 mm in thickness were a significant independent predictor of recurrent brain infarction (90). The thickness of aortic plaque seems to be a marker of severe generalized atherosclerosis; it also reflects vulnerable lesions and predicts a high risk for thrombotic events, including thromboembolism in the lower extremities.

#### *Diagnostic Tools for the Identification of Atherothrombosis*

The development of tools that allow the detection and assessment of vulnerable atherosclerotic plaques in different vascular beds is an important goal in current cardiovascular research. Angiography is an invasive imaging technique that allows assessment of the vascular lumen but not of components of the atherosclerotic plaque. The methods for evaluating atherosclerosis should be safe, noninvasive, sensitive and specific, reproducible, and inexpensive. Vascular ultrasonography, electron-beam computed tomography, and magnetic resonance imaging are noninvasive methods that may prove to be suited for assessment of atherosclerosis (91).

Ultrasonography has been used to detect arterial wall diameter and intima–media ratio (92). Results were correlated with extent of atherosclerosis and cardiovascular risk factors (93). Increased intima–media ratio has been associated with an increased risk for subsequent thrombotic events (94). Noninvasive ultrasonography seems to be a safe and reliable method for detecting early atherosclerotic changes and plaque density.

Coronary atherosclerosis can be visualized by electron-beam computed tomography, a noninvasive technique that analyzes coronary calcifications (95). Calcium

uptake into the plaque is an active process that is significantly correlated with the extent of atherosclerosis (95, 96). Contrast enhancement allows the assessment of coronary luminal size and accurately identifies high-grade coronary stenoses or occlusions (97). However, smaller atheromatous plaques, which are prone to plaque disruption, have been reported to lack calcium (98). Therefore, assessment of vulnerable plaques may not be possible by electron-beam computed tomography.

Specific tissue characterization of the arterial wall seems to be best accomplished by magnetic resonance imaging. This technique allows determination of the different plaque components, such as lipid core, fibrosis, calcifications, and thrombus deposits. In humans, magnetic resonance imaging has been used for the study of lesions in carotid arteries (99), has more recently been used for the assessment of human aortic atherosclerosis, and is now being evaluated for assessment of human coronary artery disease (100). Identification of vulnerable atherosclerotic plaques and measurement of the extent of human atherosclerosis are the subject of ongoing studies to assess the clinical usefulness of magnetic resonance imaging as a diagnostic tool.

#### **IMPLICATIONS FOR THERAPY**

Recent studies showed that at least 30 days after an acute myocardial infarction was successfully treated with thrombolysis, mural thrombi with a layered appearance were still present in the infarct-related artery. Therapeutic approaches aimed at reducing the risk for recurrent thrombosis by reducing blood thrombogenicity after the initial phase of an acute thrombotic event have been developed. Antiplatelet drugs reduce platelet reactivity and aggregation. Anticoagulants aim to inhibit thrombin and fibrin formation. Limited effectiveness or adverse side effects of established drugs have led to development of alternative therapeutic approaches (101).

#### **The Search for Effective Long-Term Treatment: Combined Therapy**

Aspirin has been the major agent of antiplatelet therapy over the years (102–104). Aspirin blocks the synthesis of thromboxane A<sub>2</sub> but fails to block platelet activation by thrombin, adenosine diphosphate, or collagen. Several trials showed that more than aspirin alone is needed in patients with acute coronary syndromes

during and after the acute hospitalization and for secondary prevention of thrombotic events. In the Antithrombotic Therapy in Acute Coronary Syndromes trial, unfractionated heparin plus aspirin followed by warfarin plus aspirin was more effective than aspirin alone for preventing acute thrombotic events during hospitalization and the subsequent 2 months (105). In the Fragmin during Instability in Coronary Artery Disease (FRISC-I) study of patients with unstable angina or non-Q-wave myocardial infarction, low-molecular-weight heparin plus aspirin, started during hospitalization and continued for 6 weeks, was more effective than aspirin alone both short-term and at 6 weeks of follow-up (106). A decreased benefit in the incidence of death or myocardial infarction occurred when the dose of low-molecular-weight heparin (107) was reduced and given only once (instead of twice) daily after hospital discharge (106). In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study, recombinant hirudin—a direct thrombin inhibitor (101, 108, 109)—was superior to heparin plus aspirin in reducing death, myocardial infarction, and refractory angina at 7 days after the start of treatment, compared with heparin plus aspirin followed by aspirin alone (110). An even greater reduction in event rates occurred when these patients were also treated with warfarin (mean international normalized ratio [INR], 2.2) plus aspirin compared with aspirin alone for 3 months after hospital discharge (111).

Another study compared the use of heparin plus aspirin followed by either warfarin (INR, 2.0 to 2.5) plus aspirin or aspirin alone after 10 weeks in a small group of patients with unstable angina and acute myocardial infarction. The end point was either clinical myocardial infarction or angiographic occlusion of the culprit coronary artery (112). All patients had angiography with documentation of the patency and minimal lumen diameter of the culprit lesion. This study showed that treatment with warfarin plus aspirin (150 mg/d) for 10 weeks resulted in a lower incidence of myocardial infarction or new angiographic occlusion at the end of 10 weeks (7%) compared with treatment with aspirin alone (39%). The incidence of myocardial infarction plus angiographic occlusion was 39% in the group treated with aspirin alone compared with 7% in the group treated with warfarin plus aspirin after discharge from the hospital. In addition, quantitative angiography

documented progression of the culprit lesion in the group treated with aspirin alone. Warfarin plus aspirin stabilized the culprit lesion and prevented reduction of the minimal lumen diameter (112). The FRISC and OASIS pilot studies suggested that at least 3 months of combined therapy might be needed for more effective prevention of acute thrombotic events. The incidence of death, myocardial infarction, or urgent revascularization in patients receiving aspirin alone in the FRISC-I study was 5% to 10% at 1 week, 20% at 40 days, and 40% at 150 days (107). The FRISC-II trial suggested that high-risk patients with acute coronary syndromes could be stabilized with low-molecular-weight heparin plus aspirin for up to 60 days until coronary intervention (113). However, the Coumadin Aspirin Reinfarction Study (CARS) (114) combining low-dose warfarin (INR < 1.5) and aspirin and the recently presented trial on Combination, Hemotherapy, and Mortality Prevention (CHAMP) (115) with warfarin (median INR, 1.8) plus aspirin showed that warfarin with an INR less than 2.0 plus aspirin does not provide clinical benefits greater than those achievable with aspirin alone. Ongoing experimental and clinical trials are assessing the clinical effectiveness, safety, and side effects of more prolonged outpatient therapy with combined treatment strategies, such as warfarin plus aspirin (Warfarin Re-Infarction Study II [WARIS II], which uses warfarin with an INR of 2.0 to 3.0) and combined aspirin and adenosine diphosphate platelet inhibition.

Ticlopidine and clopidogrel are established as orally bioavailable platelet antagonists that effectively reduce the occurrence of thromboembolic events in patients with arteriosclerotic disease. Ticlopidine and clopidogrel are thienopyridines and irreversibly inhibit the adenosine diphosphate-induced and shear force-induced platelet activation and aggregation for the life of the platelet (116, 117). Neither continuous blood levels nor monitoring of therapy are necessary for clopidogrel or aspirin. Monitoring of platelet and differential leukocyte counts twice monthly for 3 months is necessary for ticlopidine treatment because of the risk for neutropenia or thrombocytopenia. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, the efficacy of clopidogrel in reducing the risk for a combined outcome cluster of myocardial infarction, ischemic stroke, or vascular death was tested in patients with different forms of atherosclerosis. Patients were di-

vided into three subgroups according to the primary clinical manifestation: myocardial infarction, ischemic stroke, or peripheral artery disease. Those treated with clopidogrel had a lower average combined event rate per year than those treated with aspirin (116). These rates show that patients receiving clopidogrel had a small but statistically significant reduction in relative risk (9%). For all patients enrolled in the CAPRIE study, clopidogrel significantly reduced the relative risk for myocardial infarction by 19.1% and had a significant beneficial effect on patients with peripheral artery disease. The combination of ticlopidine and aspirin was shown to be superior to aspirin alone or warfarin plus aspirin for the reduction of thrombotic events in patients receiving coronary artery stents (117). Several clinical studies on the effectiveness of combining clopidogrel with aspirin have shown a benefit equal to that of ticlopidine plus aspirin in coronary stenting (118–121). The prospective Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) showed equal effectiveness of clopidogrel plus aspirin and ticlopidine plus aspirin in coronary stenting; however, the incidence of side effects was 50% lower with clopidogrel plus aspirin (122). Although clopidogrel or ticlopidine may be slightly more effective than aspirin in reducing thrombotic events in patients with coronary artery disease, a larger randomized clinical trial of acute coronary syndromes is under way to determine whether the addition of a thienopyridine to aspirin increases the benefits in the longer term compared to aspirin alone.

#### A New Approach: Oral Glycoprotein IIb/IIIa Inhibitors

The activation of platelets leads to conformational changes in glycoprotein IIb/IIIa ( $\alpha_{IIb}\beta_3$  integrin), the major fibrinogen receptor on platelets. Several glycoprotein IIb/IIIa receptor antagonists have been developed (123) and clinically tested in large phase III trials. Clinical trials have recently been reviewed in detail (124, 125). The inhibitors compete with fibrinogen for the occupancy of the glycoprotein IIb/IIIa receptor and prevent cross-linkage of platelet-bound fibrinogen, which inhibits platelet aggregation and thrombus formation. The first glycoprotein IIb/IIIa antagonist tested in large clinical trials was a recombinant chimeric antibody fragment that consisted of the murine variable part of the *Fab* fragment combined with the human constant re-

gion (abciximab) (123). Intravenous administration of abciximab has been demonstrated to reduce the occurrence of death and myocardial infarction and the need for acute revascularization when given before and during percutaneous coronary interventions in patients with an acute coronary syndrome (126, 127). Synthetic inhibitors of glycoprotein IIb/IIIa, such as eptifibatid (128, 129), tirofiban (130–132), and lamifiban (133), have also been assessed in large clinical trials of patients with unstable angina and non-Q-wave myocardial infarction. Overall, intravenous application of eptifibatid (128, 129) or tirofiban (131, 132) in addition to intravenous heparin plus oral aspirin demonstrated benefits in the reduction of death or nonfatal myocardial infarction compared with placebo plus aspirin. In the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network trial (PARAGON), patients were randomly assigned to receive lamifiban with or without heparin or heparin alone. Treatment groups did not differ significantly in occurrence of death or nonfatal myocardial infarction at 30 days (133). The three large studies of oral glycoprotein IIb/IIIa did not show a clinical benefit (134, 135). Pharmacokinetic characteristics, such as the uptake or elimination of oral glycoprotein IIb/IIIa inhibitors, may differ from patient to patient and lead to possibly insufficient or even high plasma concentrations. Bedside tests that assess platelet function seem to be necessary in order to ensure the safety and efficacy of oral glycoprotein IIb/IIIa therapy (136). Upregulation of glycoprotein IIb/IIIa receptors may occur in the longer term.

#### Possible Future Options: Tissue Factor and Factor Xa Inhibitors

The clinical use of anticoagulants, such as unfractionated heparin and coumarin, is limited because of the narrow therapeutic window and the variable dose response (137, 138). Because of the risk for bleeding and maintaining a therapeutic dose, patients need to be closely monitored by laboratory tests. Since tissue factor in disrupted atherosclerotic plaques initiates thrombosis, alternative therapeutic approaches directed toward inhibiting the tissue factor pathway have been investigated in animal models (Table 2). Tissue pathway inhibitor forms a complex with factor Xa that binds to tissue factor–factor VIIa and inhibits thrombin generation

**Table 2. Summary of Recent Preclinical and Clinical Trials on Tissue Factor Pathway and Factor Xa Inhibitors**

Therapy	Mechanism of Action	Model	Observation	References
Tissue factor inhibitors				
Tissue factor pathway inhibitor	Direct binding to factor Xa Inhibition of the tissue factor–factor VIIa complex	Animal studies	Coronary thrombosis Stenosis after percutaneous transluminal coronary angioplasty Thrombosis or mortality in disseminated intravascular coagulation/sepsis	139, 140 140, 141 143–145
Gene transfer of tissue factor pathway inhibitor	Local expression of tissue factor pathway inhibitor	In vitro studies Animal studies	Thrombosis on human atherosclerotic lesions Cyclic flow variations in injured carotid arteries	142 146, 147
Monoclonal antibodies	Inhibition of tissue factor activity	Animal studies	Arterial thrombosis Hyperplasia in vein grafts Coagulation Mortality in disseminated intravascular coagulation/sepsis	148 149 150 151
Dithiocarbamates	Inhibition of tissue factor gene transcription	In vitro studies Animal studies	Human thrombi on artificial surfaces Morbidity in disseminated intravascular coagulation/sepsis	76, 152 153, 154
Active site–inactivated factor VIIa	Competitive inhibition of tissue factor–dependent activation of factor X	Animal studies In vitro studies	Arterial thrombosis Restenosis Thrombi on artificial surface	155–157 158 76, 159
Factor Xa inhibitors				
Tick anticoagulant peptide	Direct inhibition of factor Xa	Animal studies In vitro studies	Arterial thrombosis, restenosis Human thrombi on artificial surfaces	162, 164 162, 163
Antistasin	Direct inhibition of factor Xa	Animal studies	Arterial thrombosis, restenosis	164
DX9065	Reversible inhibition of factor Xa	Animal studies	Thrombosis and coagulation in arteriovenous shunts	165 166
Pentasaccharide	Selective catalyst of the inhibitory effect of human antithrombin on factor Xa	Human studies (phase I) Animal studies	Coagulation time and safety profile Venous thrombosis	167

(168). Tissue factor pathway inhibitor is available as a recombinant drug and has been evaluated for its antithrombotic and antihemostatic effect in animal models of arterial injury (139–141), in vitro studies of thrombus formation (142), and models of disseminated intravascular coagulation (143–145). Since large doses of tissue factor pathway inhibitor are required to interfere with arterial thrombosis, its clinical application has been delayed (139–141). After downward adjustment or elimination of heparin dosage, bleeding complications associated with systemic administration of tissue factor pathway inhibitor may no longer be an issue. However, since systemic doses of recombinant tissue factor pathway inhibitor are substantial, transfer of the human tissue factor pathway inhibitor gene has recently been accomplished by using adenoviral vectors (146, 147). Local transfer of the tissue factor pathway inhibitor gene into animal carotid arteries prevented thrombosis and flow reduction at sites of arterial injury (146, 147).

High levels of circulating tissue factor are associated with a hypercoagulable state in patients. Studies in animals (148–151) and more recently in humans (76, 152)

have demonstrated the efficacy of tissue factor antibodies in reducing thrombosis (76, 148, 152) and intimal hyperplasia after vessel injury (149). The efficacy of tissue factor pathway inhibitors has been reported in preclinical studies in animal models of disseminated intravascular coagulation and sepsis (150, 152). Another novel therapeutic approach tested in a rat model of disseminated intravascular coagulation is the inhibition of tissue factor gene transcription (153). The nuclear factor- $\kappa$  B pathway is a key transcriptional mechanism in induction of tissue factor activity. Persistent binding of nuclear factor- $\kappa$  B in mobility shift assays was found in patients who died of disseminated intravascular coagulation due to acute sepsis (169). Survivors exhibited decreased nuclear factor- $\kappa$  B binding (169). Dithiocarbamates, specific inhibitors of this pathway (154), reduced tissue factor induction and have been shown to ameliorate disseminated intravascular coagulation in animal models (153).

The blockade of tissue factor–induced thrombin generation was studied by using inactivated factor VIIa, a competitive inhibitor of tissue factor–dependent fac-

tor X activation. In animal studies (155–158) and in vitro studies in humans (76, 170), thrombus formation on injured vasculature or artificial surfaces was prevented by infusing inactivated factor VIIa. Most remarkable, the antithrombotic effect was achieved without prolonging the bleeding time (155, 171). This suggests that inhibitors of tissue factor activity have antithrombotic effects without compromising hemostatic function. The presence of tissue factor in the circulating blood in combination with its potential thrombogenicity may explain why experimental therapies, such as anti-tissue factor antibodies and inactivated factor VIIa, are extremely antithrombotic but cause no bleeding in animal studies. These therapies seem to inhibit circulating bloodborne tissue factor at levels far below those required for inhibiting the hemostatic tissue factor in the vessel wall.

Direct inhibitors of factor Xa, such as tick anticoagulant peptide (172, 173), antistasin (160), and DX-9065 (161), have been evaluated in preclinical and human phase I studies. Tick anticoagulant peptide and antistasin are recombinant-available and have been shown to reduce arterial thrombosis (162, 163) and restenosis (164). DX-9064, a nonpeptic, low-molecular-weight, reversible inhibitor of factor Xa, has been shown to exhibit oral bioavailability in animal studies and human phase I trials (161, 164–166). Thus far, direct factor Xa inhibitors show a profound antithrombotic efficacy and a promising hemostatic safety profile. Synthetic analogues of the heparin pentasaccharide sequence have a high affinity for antithrombin and indirectly inhibit factor Xa through an antithrombin-dependent pathway (167). Antithrombotic efficacy has been demonstrated in animal models of venous thrombosis (167). In summary, tissue factor and factor Xa inhibitors may prove to be safe and effective therapeutic options for patients with acute thrombotic events. Clinical trials involving tissue factor pathway and factor Xa inhibitors are under way or in preparation.

## CONCLUSIONS

As discussed, plaque disruption, subsequent thrombosis, and thromboembolism can affect different arterial beds and, depending on arterial size and severity of the distal occlusion, may lead to acute clinical symptoms. The available therapeutic approaches are often unable to

prevent short- and longer-term progression of disease and ischemia because they are not potent enough to block thrombus formation, may be administered for too short a time, or both. This shows the urgent need for more potent but safe antithrombotic therapy that effectively blocks thrombosis without causing bleeding and may be administered for an extended period. Although suitable diagnostic tools for the assessment of atherothrombosis are evolving, the therapeutic options for treatment of the disease are still limited. The search for a more effective long-term therapy for this chronic disease is a major issue currently being addressed.

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