MEDICAL GRAND ROUNDS

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ANTITHROMBOTIC AND THROMBOLYTIC THERAPY FOR CORONARY HEART DISEASE: CONSENSUS AND CONTROVERSY

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Introduction

The use of antithrombotic and thrombolytic agents in patients with coronary heart disease has a remarkably on-again, off-again history. Much of the controversial history owes to the uncertainties of the role of thrombus in the development of acute myocardial ischemia. Independently, in 1910 in Germany and in 1912 in the United States, acute occlusive coronary thrombosis was proposed to cause a syndrome of acute myocardial infarction. By contemporary accounts, these descriptions were met with little interest or attention. Within a few decades, however, this proposal came to be accepted. Furthermore, it became clear that three serious complications of myocardial infarction were related to thrombosis. Thromboembolism to the cerebral arteries, causing stroke, and to other peripheral arteries soon after myocardial infarction is usually due to dislodgement of left ventricular thrombus at the site of the infarction. Deep venous thrombosis and pulmonary embolism occur in close relationship to the severity of depressed cardiac output and prolonged bed rest and inactivity following infarction. With the introduction of effective anticoagulant agents, anticoagulation after myocardial infarction became a routine part of patient management. Thrombolytic therapy for myocardial infarction, with streptokinase, was applied as early as 1959. By the late 1960's and early 1970's, however, the role of coronary thrombosis in the pathophysiology of acute coronary ischemia was highly questioned and use of antithrombotic therapy waned and the pace of clinical research with thrombolytic therapy slowed. In the last decade, however, a large body of clinical research made the role of thrombosis in the pathogenesis of acute myocardial ischemia much clearer. Completion of many clinical trials has allowed the development of consensuses on the use of antithrombotic and thrombolytic therapy in several clinical settings. The pace of basic and clinical research has accelerated dramatically in the last few years and new controversies have arisen as the practicing community digests the fruits of the research efforts.

There are two major purposes of this review. The first is to provide some essential background information on thrombosis, thrombolysis, antithrombotic and thrombolytic therapies, and the relationship of thrombosis to coronary heart disease. The second is to identify the major areas of consensus and controversy regarding the use of antithrombotic and thrombolytic therapy that now exist. The scope of this review is too broad to provide an analytical review of each of these areas. Major clinical trials and analytical reviews are referenced for the reader who wishes to explore individual areas in greater depth. Identification of areas of consensus and controversy is somewhat arbitrary on my part. Whenever possible, I have relied upon the proceedings of recent meetings, symposia, and conferences devoted to these issues. Especially helpful in this regard is the National Consensus Conference on Antithrombotic Therapy sponsored jointly by the American College of Chest Physicians (ACCP) and the National Heart Lung and Blood Institute (NHLBI) (1-3).

Conversion From Chronic To Acute Myocardial Ischemia

The sudden thrombotic occlusion of a coronary artery is one of the major disasters confronted in clinical medicine, often resulting in sudden cardiac death or myocardial infarction. Coronary atherosclerosis is the underlying cause in the overwhelming majority of cases. But coronary atherosclerosis develops over several decades and is often associated with only mild to moderate symptoms or none at all until a sudden conversion to a state of acute myocardial ischemia occurs. The cause of this conversion has been the subject of intense interest and clinical research in the last 15 years. The evidence is now strong that this conversion is due to "dynamic" coronary stenoses (transient, usually reversible limitations in coronary blood flow)

superimposed onto fixed atherosclerotic stenoses. (4-7) These dynamic stenoses appear to be the result of a complex and interrelated mixture of abnormal vasoconstriction, platelet plugging, and non-persistent thrombus formation at the site of an atherosclerotic plaque. (8) Investigations using coronary arteriography and coronary angioscopy support the thesis that deterioration of a "simple" atheroma to a "complex one" with acute plaque disruption (ulceration, fissuring, partial plaque rupture, etc.) is often the event that underlies the development of dynamic stenoses. (9,10) The syndrome of unstable angina appears to be a paradigm of this process. (7) The process of the dynamic coronary stenoses in acute myocardial ischemia thus appears to be pre-thrombotic or thrombotic. The pathophysiology of most cases of all forms of acute myocardial ischemia (unstable angina, non-Q-wave myocardial infarction, Q-wave myocardial infarction, and sudden cardiac death due to severe ischemia) can probably be thought as being on a continuum: unstable angina being a syndrome of repetitive dynamic stenoses without persistent total occlusion; non-Q-wave infarction being a syndrome of persistent but non-total coronary occlusion or total coronary occlusion followed within a short time with some degree of reperfusion; and Q-wave infarction being a syndrome of persistent thrombotic coronary occlusion. At least half of the cases of myocardial infarction occur in the wake of a syndrome of unstable angina. Further support for the above postulate comes from the protective effects which patients with unstable angina receive with antiplatelet (11,12) or anticoagulant (13) therapy. Aspirin reduces death and progression to definite myocardial infarction by about 50%; heparin probably reduces progression to myocardial infarction. In spite of anti-platelet therapy with aspirin, many thrombotic events still occur, with resulting infarctions and deaths. Obviously a better anti-thrombotic regimen than aspirin alone would be desirable. Several alternatives are being considered and studied and include low dose aspirin plus warfarin, anti-platelet aggregatory prostanoids, thromboxane synthetase inhibitors, thromboxane receptor antagonists, serotonin antagonists, thrombolytic agents such as tissue-type plasminogen activator, and doubtless others.

One of the more fascinating aspects of unstable angina as a paradigm for the conversion from chronic to acute myocardial ischemia is the observation that the process often appears to be self-limited, even in the absence of antithrombotic therapy. Studies with unstable angina in the last 15 years show that about 80-90% of patients with this syndrome will restabilize with only quiet bed rest and treatment with conventional anti-anginal agents. It is tempting to speculate that the dynamic stenoses subside as the disrupted atherosclerotic plaque stabilizes. (7)

In the last few years, it has been shown that some regimens of thrombolytic therapy can effectively open acutely thrombosed coronary arteries and improve the outcome of the majority of patients in the first few hours of an evolving acute transmural myocardial infarction. The disrupted plaque persists, however, and early rethrombosis occurs in 15 to 35% of cases in spite of therapy with anticoagulants or anti-platelet therapy. (14,15)

It is possible that the speed and adequacy of regeneration of endothelium on the disrupted plaque is the crucial factor in determining the arrest of progression of occlusive thrombosis or rethrombosis in these cases. But it is interesting to speculate that there may be something different about the control and localization of thrombosis in the patients with acute myocardial ischemia who do not progress to persistent occlusive thrombosis or who do not rethrombose after successful thrombolysis from the patients who do. If definable differences in the tendency for blood to clot in the patients who are treatment successes from those who are

treatment failures can be identified, these differences may well point the way to improved antithrombotic and thrombolytic therapy.

Much of the recent work on preventing coronary thrombosis in syndromes or models of acute myocardial ischemia have dealt with blocking platelet adhesion and aggregation and the mechanical effects of platelet plugging or blocking the vasoconstricting influences (especially thromboxane A_2 and serotonin) of aggregating platelets. But activation of platelets and generation of thrombin are not totally independent nor sequential processes. Activation and aggregation of platelets and thrombin generation occur simultaneously and each process augments and accelerates the other. Recent work on the naturally occurring processes that control and localize the clotting cascade may have important implications for future work in preventing or mitigating coronary thrombosis.

Limiting Thrombosis - Natural Anticoagulant Systems

The basic concepts of the activation and propagation of the molecular coagulation process are reasonably well established. (16) Although not functionally correct, the coagulation scheme has been classically divided into two pathways according to activation mechanism. The pathways consist of a series of plasma serine protease precursors, two binding protein cofactors, the final substrate (fibrinogen), and a transpeptidase (factor XIII) stabilizing factor. The two activation pathways merge at factor X to a common pathway that eventually leads to the generation of thrombin (IIa). The scheme is illustrated in figure 1. In the 23 years since the classic proposal of Davie and Ratnoff (17) of this "waterfall sequence", all of the clotting factors have been purified to homogeneity, amino acid sequences determined, glycosylation sites identified, and, for several, the genes have been cloned and localized on specific chromosomes.

Six of these clotting factors, factors XII, XI, IX, VII, X, and II are serine proteases of restricted specificities. The serine residue of the active site is generally found in the carboxy-terminus of the protein. The amino termini of these factors have sequence differences which confer the individual specificities. The proteases are secreted into the circulation as inactive precursors or zymogens; their proteolytic activities are not expressed because their active sites or substrate binding sites are blocked. Activation is associated with proteolytic clips which expose the serine protease part of the molecule. Two of the clotting factors, VIII and V, are not proteases, but function as binding protein cofactors. They coordinate complex formation on membrane surfaces of platelets and endothelium and serve as receptors for factors IXa and Xa respectively, thus increasing the activity of these proteases for their substrates [factors X and II (prothrombin) respectively] by several orders of magnitude.

From a regulatory standpoint, the eventual rate of fibrin formation depends on thrombin activity and the availability of its substrate, fibrinogen. The intrinsic clotting cascade is initiated when blood contacts negatively charged subendothelial structures such as collagen. At least four plasma proteins, factors XII, XI, prekallikrein, and high molecular weight kininogen interact in a complex series of reactions defined as the contact system. Factor XII binds strongly to these negatively charged surfaces and becomes more susceptible to activation. A reciprocal activation of prekallikrein and factor XII leads to factor XI activation. Unknown at present is the initial trigger of the reciprocal activation process. Eventually, however, prothrombin (II) is activated to thrombin (IIa) and it proteolytically modifies fibrinogen by the sequential removal of small N-terminal peptides (fibrinopeptides A and B) from the A alpha and B beta chains to form fibrin monomers. These fibrin

monomers undergo a spontaneous self-assembly to form insoluble polymers. Thrombin-activated factor XIII stabilizes the fibrin gel through formation of intermolecular epsilon-(gamma-glutamyl) lysine covalent cross-links. This resulting fibrin web stabilizes platelet plugs via specific membrane receptors and forms a thrombus.

The extrinsic system requires an exogenous activating factor in addition to circulating factor VII to initiate the cascade. This tissue factor, also called thromboplastin, is a lipoprotein that is present in nearly every tissue. Many cells appear to synthesize tissue factor constitutively. On the other hand, endothelial cells and monocytes show low basal rates of tissue factor synthesis, but can be stimulated to increase tissue factor expression under various stimlui, such as immune complexes, interleukin I, endotoxin, tumor necrosis factor and lymphokines. Tissue factor from a variety of sources such as human brain and placenta has been purified and the structure shown to be a lipoprotein with no apparent enzymatic activity. Activation of the extrinsic system in certain disease states (e.g. disseminated intravascular coagulation) results from tissue break down or stimulation of vascular cellular components such as endothelial cells and monocytes. This may result in microthrombotic complications or possibly large vessel thrombosis. Inactivation of the tissue factor - factor VIIa complex is regulated by a serum factor that has been partially characterized and termed TFI (tissue factor inhibitor) or ESI (extrinsic system inactivator). (18)

There must be factors that can stop the clotting cascade and localize thrombosis to the site of vascular injury or disruption. Otherwise total body blood clotting would result. A large body of work in recent years has elucidated four natural anticoagulant systems that modulate the clotting cascade. They are illustrated in figure l along with the clotting cascade. They are: the protein C/ protein S/ thrombomodulin system, the antithrombin III/ heparin/ heparin cofactor II system, the fibrinolytic system, and local vascular production of prostacyclin, a prostanoid with potent efficacies for inhibiting platelet aggregation and promoting vascular relaxation.

The most recently elucidated of these control mechanisms is called, for the purpose of this discussion, the protein C/ protein S/ thrombomodulin system. (19-23) Protein C, like factors II, VII, IX, and X of the clotting cascade, is a vitamin-K-dependent glycoprotein zymogen with a potential active-site serine. However, it has anticoagulant, not procoagulant, properties. It is converted to an active protease by thrombin proteolysis. Conversion to the active form by thrombin is enhanced 1000-fold by binding of thrombin to the recently discovered protein, thrombomodulin, which is expressed on the surface of endothelial cells. (Furthermore, the thrombin-thrombomodulin complex reduces thrombin-related procoagulant activity by the removal of circulating thrombin.) Activated protein C exerts its anticoagulant activity by the proteolytic destruction of activated factors V and VIII, the two factors that bind to platelet and endothelial membranes and serve as receptors for other clotting factors. This proteolytic action on factors Va and VIIIa is markedly enhanced by protein S, which serves as a cofactor for activated protein C. Like protein C, protein S is a vitamin-K-dependent protein. Protein S is synthesized by endothelial cells and megakaryocytes as well as the liver. (24,25) It circulates as a free, active form and an inactive form bound to the C4b binding protein. Activated protein C exerts a profibrinolytic (26,27) effect by binding to and inactivating the circulating inhibitor of tissue plasminogen activator, PAI-1. (28) (The binding of PAI-1 to activated protein C, however, also inactivates protein C and may be one mechanism for control of activated protein C). This effect on inactivation of PAI-1

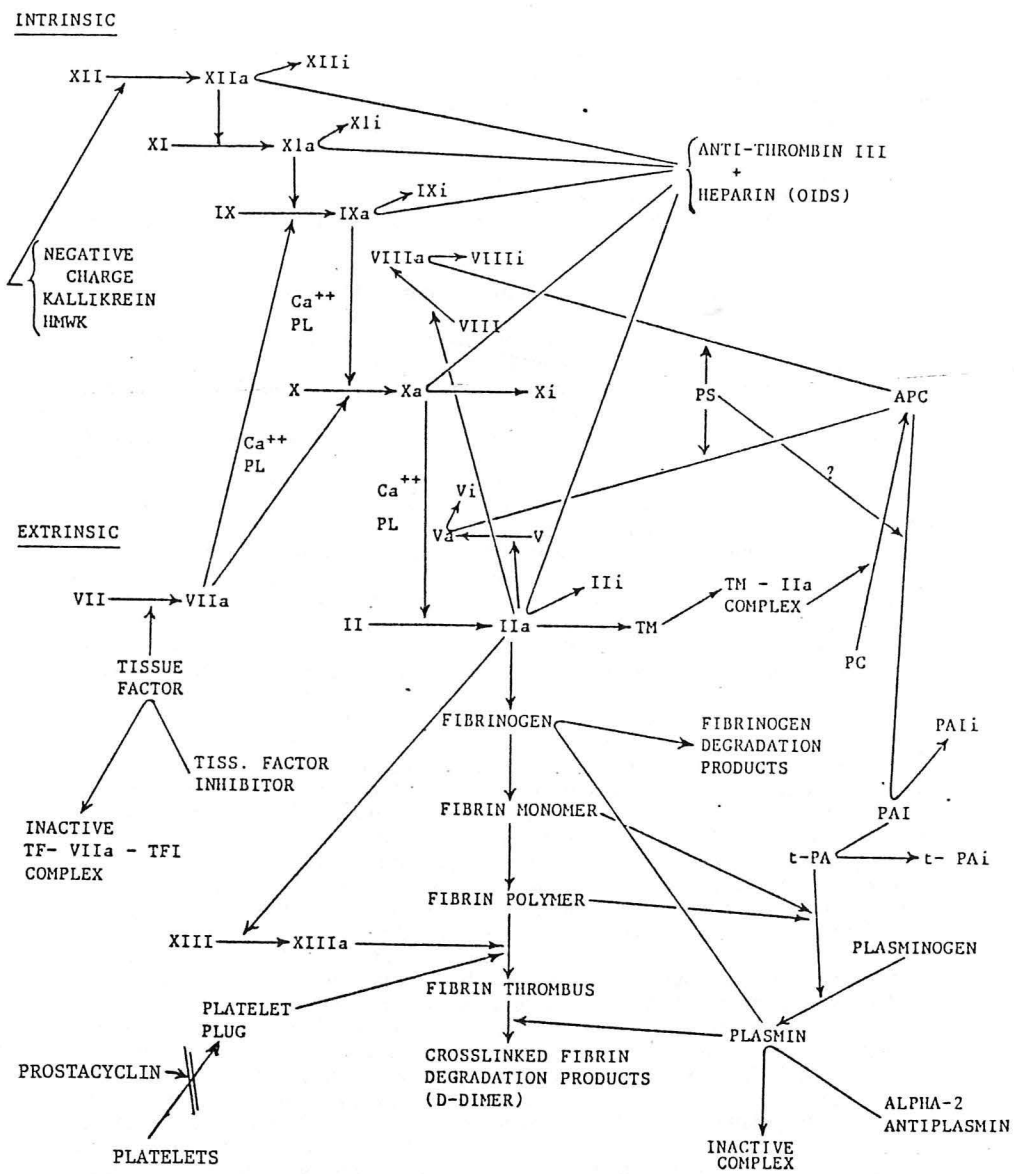
has been shown to be enhanced by protein S. Whether complex formation with the inhibitor or proteolytic inactivation is the mechanism of this action of activated protein C in vivo is uncertain.

Antithrombin III, an alpha-2-globulin, is an inhibitor of coagulation and a member of the serpin family of protease enzyme inhibitors. The tertiary structure of the functional inhibitor contains a reactive center, which serves as a substrate for thrombin, and also for factors XII, XI, IX, X, and (perhaps to a lesser degree) VII. Unlike other substrates, however, antithrombin-III binds avidly to the serine proteases after proteolysis of the Arg-Ser bond and remain as tight complexes that are removed from the circulation. Heparin-like substances, which are naturally present on blood vessel lumina, are cofactors for this inactivation reaction. The mechanism by which heparin participates in this process is still incompletely understood. Some evidence suggests a change in conformation at the reactive center upon binding of heparin. Heparin cofactor II, another plasma protein of the serpin family, also inactivates thrombin. Circulating levels of heparin cofactor II are approximately half those of antithrombin III on a molar basis. (29)

The third natural anticoagulant system is fibrinolysis. (30) Plasminogen, the circulating plasma protein precursor of the active serine protease, plasmin, is converted into its active form by the action of plasminogen activators. Plasmin degrades fibrin, fibrinogen, and other circulating proenzymes and cofactors. After activation, plasmin activity is neutralized by a circulating binding protein, alpha-2-antiplasmin (alpha-2-plasmin inhibitor). Quantitatively, there is more plasminogen than antiplasmin activity so that significant conversion of plasminogen to plasmin can result in total consumption of antiplasmin and unchecked plasmin activity. When this occurs, clotting factors are consumed and a potential bleeding state ensues. Various tissues express different plasminogen activators. The principal one in blood is endothelial cell-derived tissue-type plasminogen activator (t-PA). It has a high affinity for fibrin and requires fibrin to optimally activate plasminogen; therefore, its action is largely limited to the region of fibrin formation and accounts for the direction of fibrinolysis towards specific degradation of fibrin clots *in vivo*. Further regulation of plasmin activity also occurs at this level. During factor XIIIa-dependent covalent crosslinking of polymerized fibrin, small amounts of alpha-2-antiplasmin are attached to the fibrin clot by covalent bonds. This localizes it to the site of t-PA-mediated plasminogen activation, and thus plasmin can be inhibited at this level of fibrin polymers. In addition to the release of t-PA, the endothelial cells also produce and release plasminogen activator inhibitor (PAI)-1, which prevents plasminogen activation by t-PA. (31) An identical PAI is also found in platelets, probably stored in the alpha granules. Fibrin degradation results in various soluble degradation products including the terminal product, the D-dimer. The two D structures are linked together by means of covalent bonds, due to the action of thrombin-activated factor XIII in the presence of calcium. The D-dimer product of fibrin does not occur with fibrinogen degradation and it has antigenic sites that do not appear to be shared with the degradation products of fibrinogen. Quantification of D-dimer in the plasma provides an indication of the degree of fibrinolytic activity *in vivo*. (32)

Local production of prostacylin provides a fourth control mechanism for thrombosis by its action on platelets and local vascular tone. It increases platelet content of cyclic AMP which greatly decreases platelet aggregability and has a marked relaxing effect on vascular smooth muscle, thus opposing the vasoconstricting effects of the products of the platelet release phenomenon.

FIGURE 1
THE CLOTTING CASCADE AND ITS REGULATORY CONTROLS



Abbreviations: APC, activated protein C; PC, protein C, PS, protein S; HMWK, high molecular weight kininogen; PAI, plasminogen activator inhibitor; PL, phospholipids; TM, thrombomodulin; t-PA, tissue type plasminogen activator; TF, tissue factor; TFI; tissue factor inhibitor. The suffix "a" denotes the activated form of a substance; the suffix "i" denotes the inactivated or the inhibited form of the previously activated substance.

The role of the normal endothelium in controlling and localizing blood clotting bears emphasis. Normally, the endothelium is an effective surface for the resistance of blood clotting. Functions that have an an anticoagulant effect that have been identified include production of plasminogen activators, prostacylin, and protein S, the expression of thrombomodulin, and the presence of heparin-like substances. Endothelial cells also have procoagulant functions, including the synthesis of plasminogen activator inhibitor, von Willebrand factor, and support of the assembly of clotting factors on their surfaces. Normally, the thromboresistant effects predominate.

Congenital And Acquired Abnormalities In The Control Mechanisms Of Thrombosis.

Recurrent thrombosis, principally venous, has been reported with congenital deficiencies of antithrombin III, protein C, protein S, plasminogen, tissue-type plasminogen activator, and a high content of plasminogen activator inhibitor (19,31,33,34). The protein S deficiency syndromes may be due to either an absolute deficiency of the protein or a deficiency of the functional protein. In the latter case, which is the more common, there is a maldistribution of protein S in the circulation, the inactive, protein-bound form predominating over the free, active form. (35) Arterial thrombosis with these congenital abnormalities appears to be rare. Congenital homozygous deficiency of one of these proteins, however, is unlikely to be of great importance for coronary thrombosis from a statistical point of view.

With growing experimentation, however, increasing numbers of acquired abnormalities of these proteins are being reported in disease states associated with increased propensity to thromboembolism; and it is likely that information gathered so far represents only the "tip of the iceberg" of thrombotic disorders that are induced or promoted by acquired abnormalities in the clotting cascade and its controlling proteins. (19,31,33,34) Nephrotic syndrome is associated with a deficit of antithrombin III [but not protein C (36)] due to urinary losses of the protein. Depressed anti-thrombin levels in the plasma have also been reported in women who use oral contraceptives and in patients with advanced liver disease. Protein C depletion has been reported in patients with malignant neoplasms, following surgery, and with disseminated intravascular coagulation. (19,33-35) An aging-associated increase in thrombin generation from prothrombin, increase in fibrinogen conversion to fibrin, and decreased activation of protein C *in vivo* (with normal circulating levels of protein C antigen) has recently been reported. (37) The coagulopathy that is associated with endotoxin administration in baboons was blocked with administration of activated protein C and administration of an antibody that blocked protein C activation worsened the coagulopathy. (38)

Transient dysfunction of the endothelium, with changes resulting in a less than a normally thromboresistant surface, occur in some circumstances associated with thrombotic tendencies. Exposure of cultured endothelial cells to endotoxin suppresses thrombomodulin expression resulting in impaired activation of protein C. (39) Exposure to tumor necrosis factor or interleukin-1 causes enhanced synthesis of tissue factor, decreased expression of endothelial receptors for protein S, and increased expression of receptors for factor IX/IXa. (40,41) A number of circumstances that are associated with an increased thrombotic potential are associated with increased endothelial release of PAI, including administration of endotoxin or interleukin-1, pregnancy, surgery, and trauma. (The clinical importance of these observations with PAI is unclear at this time, however. It has been suggested that PAI may behave in plasma as an acute phase reactant protein inasmuch as

elevated plasma values have also been observed in hospitalized subjects with a wide variety of critical illnesses.) (31) It is tempting to speculate that similar transient abnormalities in endothelial function might occur near an acutely changing and disturbed atheroma, with or without loss of endothelial continuity, resulting in a loss of normal resistance to thrombus formation. In such a case, this "sick" endothelium would tend to favor blood clotting at this site, perhaps even in the absence of exposed subendothelial tissue. There is precedent for this possibility in arterial disease. In a dog model of myocardial ischemia and endothelial injury, vascular production of prostacyclin declined and thromboxane rose. (42)

Hypercoagulability And Coronary Heart Disease.

There is evidence from epidemiologic studies that ambulatory subjects who have elevated levels of fibrinogen, factor VII, and factor VIII have an increased risk of subsequent coronary events (43-45). Plasma levels of antithrombin III were not predictive of coronary events. There has been considerable experimentation with platelet reactivity and vessel wall prostanoid production in coronary heart disease, as mentioned above. (46) To date, however, the presence of acquired abnormalities in the coagulation control and localization systems that are described above have been little explored in patients with syndromes of acute myocardial ischemia. There are a few reports on t-PA and its inhibitor in patients with acute myocardial infarction showing increased plasma inhibitory activity along with a decreased level of t-PA activity or antigen. (46-52) The possibility that there is an increase in the circulating plasma t-PA inhibitor levels as a non-specific acute phase reactant mentioned above complicates the current interpretation of these data. An additional confounding feature of measurement of plasma levels of PAI is that two pools of the protein exist in the circulation, one in the platelet poor plasma and one in the platelet rich plasma. Of PAI in the plasma, about 80% is in the platelets. During coagulation, the PAI of platelets may play an important role in preventing premature clot lysis and local concentrations in the clot may be orders of magnitude higher than that in the plasma. There are also reports that elevated PAI plasma levels and depressed t-PA levels are present in some survivors of myocardial infarction and that the changes represent risk factors for subsequent coronary events. (53-57)

There are only scant data in the published literature regarding protein C and antithrombin III in acute myocardial ischemia. Somewhat higher than normal levels of protein C antigen have been reported in patients with coronary heart disease (57,58), while high, low, and normal levels have been reported in patients with acute myocardial ischemia. (57,59,60) These results did not include functional protein C assays, so it cannot be determined from these data whether the protein C was functional or inactivated. In several small studies, both slightly depressed and normal levels of antithrombin III in acute myocardial infarction have been reported. (59,60) These surveys generally represented a single determination per subject.

Control of Thrombosis with Drug Administration.

Currently available means of altering coagulation do so by one of three mechanisms: decreasing thrombin generation and thereby limiting fibrinogen conversion to fibrin, altering platelet function, or by activation of plasminogen, thereby increasing the rate of fibrinolysis.

Heparin

Heparin is widely distributed in the body and is commercially derived from porcine intestinal mucosa and beef lung. It is a mucopolysaccharide with sulfate

groups bound to amino groups to form sulfaminic linkages. The sulfate groups make heparin a strong organic acid. The anticoagulant activity of the heparins is similar to the activity of the heparin-like compounds found in vessel walls that is discussed above. They activate anti-thrombin III and heparin co-factor II, serpin proteases that inactivate thrombin as well as factors XII, XI, X, IX, and, perhaps to a lesser degree, VII. The resulting decrease in thrombin formation and availability limits fibrin formation from fibrinogen.

Coumarin and Indandione Derivatives

The fundamental actions of all of these drugs on the coagulation cascade are the same. They prevent gamma carboxylation of coagulation factors II, VII, IX, and X during their synthesis, thus rendering them inactive. The resulting decrease in thrombin formation and availability limits fibrin formation from fibrinogen.

Anti-platelet Drugs

The physiology of platelet adhesion and aggregation have been understood in the past only rather superficially. The list of drugs that were known to influence platelet function was a long one. In the last few years, this list has grown longer as there has been an explosion in knowledge regarding receptors on the surface of the platelet and the mechanisms of signal transduction and amplification following stimulation of the platelet. Stimulation of platelets with ADP, epinephrine, collagen, thrombin, serotonin, and aggregatory prostanoids cause aggregation *in vitro*. Collagen, ADP, and thrombin are probably the most important natural stimulators of aggregation *in vivo*. These discoveries are leading to new ways to influence platelet function. Nevertheless, for this review of antiplatelet therapy in coronary heart disease, the discussion has to be limited to aspirin, dipyridamole, and sulfinpyrazone, as there are extensive data only for these three agents. (61)

Aspirin

Aspirin does not appear to affect platelet adhesion to subendothelial substances. However, it markedly inhibits collagen-induced platelet aggregation and the second wave of epinephrine- and ADP-induced platelet aggregation. It has very little effect on thrombin-induced aggregation. The anti-aggregatory effect is mediated through inhibition of thromboxane synthesis. Aspirin permanently acetylates platelet cyclooxygenase. As new protein synthesis is virtually absent in the anuclear circulating platelets, a platelet thus affected is permanently altered. This inhibitory action occurs at lower concentrations than are necessary to block prostacyclin production by vascular endothelium and smooth muscle. However, aspirin administration does not lengthen platelet survival in patients with shortened platelet survival, but does prolong the bleeding time.

The ideal dose of aspirin in coronary disease remains somewhat uncertain. Nevertheless, based on clinical trials and pharmacologic studies, a consensus has developed that low-dose aspirin (about 325 mg daily) is as effective as high-dose aspirin (about a gram daily) and is not associated with frequent gastrointestinal problems as is the high-dose regimen. (1,61) When used with dipyridamole, high-dose therapy may be necessary to achieve the desired additive effect. (61)

Dipyridamole

Dipyridamole has an inhibitory action on platelet aggregation that has been more easily demonstrated with studies of circulating platelet aggregates than with *in vitro* platelet aggregation studies. Dipyridamole inhibits platelet interaction with damaged vascular endothelium and artificial surfaces. This action appears to be mediated through inhibition of platelet phosphodiesterase with a consequent

increase in platelet cyclic AMP content. This action allows it to act as a potentiator of the effects of prostacyclin.

Sulfinpyrazone

The uricosuric agent, sulfinpyrazone, has antiplatelet activities that are not clearly understood. It is chemically related to the non-steroidal antiinflammatory drug (NSAID), pheylbutazone, but its antiplatelet activity cannot be accounted for exclusively by the reversible inhibitory effects on cyclooxygenase typical of drugs in this family. Sulfinpyrazone inhibits platelet aggregation and the release reaction, but only in very high concentrations that are not achieved with standard dosing regimens. Some of its antiplatelet effect persists after the drug has left the circulation. Metabolites may account for this. It normalizes shortened platelet survival in patients with artificial heart valves and decreases the frequency of thrombosis in patients with arteriovenous shunts.

Plasminogen Activators

This is an extremely active area of basic and clinical research. All the fibrinolytic agents currently in use or under development act as plasminogen activators, either directly or indirectly. (62,63) Three plasminogen activators, streptokinase, urokinase, and recombinant t-PA (rt-PA) are commercially available in the United States and approved by the Food and Drug Administration for the treatment of acute myocardial infarction. Streptokinase is approved for intracoronary and intravenous use. Recombinant t-PA is approved for intravenous use. Urokinase is approved for intracoronary use. Urokinase has been used intravenously in clinical trials and occasionally in clinical practice. Active investigation with intravenous urokinase is underway and it is likely that it will be approved for intravenous use in this country in the not-too-distant future. Clinical research with an acylated plasminogen-streptokinase activator complex (APSAC) is in an advanced state and this agent is also likely to be available in the United States in the near future. Clinical research with a recombinant form of single-chain urokinase type plasminogen activator(scu-PA, pro-urokinase) is well underway. Basic research with "third generation" plasminogen activators such as anti-fibrin antibody/plasminogen activator complexes and mutant forms of rt-PA and scu-PA with favorable characteristics for fibrinolytic therapy is being conducted in many laboratories worldwide and commencement of clinical trials in men with such agents can be expected in the next few years. Thrombolytic agents will be tested in combination with other agents such as beta-blockers, calcium blockers, free radical scavengers, and natural anticoagulants such as activated protein C. An appreciation of the differences among the actions of streptokinase, APSAC, urokinase, scu-PA, and rt-PA is necessary to understand some of the areas of consensus and controversy in current fibrinolytic therapy for myocardial infarction.

Streptokinase is a product of streptococci. It activates plasminogen molecules by binding on a one-to-one ratio with a plasminogen molecule. The streptokinase/plasminogen complex leads to a change in the associated plasminogen molecule so that an enzyme center is exposed that is able to convert other plasminogen molecules to plasmin. It reacts with plasmin in the circulating blood as well as plasmin bound to fibrin.

APSAC is a plasminogen/streptokinase complex that has been made inactive by acylation of the enzymatic center of the plasminogen part of the complex. While the acylated complex is enzymatically inert and does not react with plasmin inhibitors or with plasmin, it can still bind to fibrin. Gradual deacylation occurs spontaneously, especially after binding to fibrin, and produces active streptokinase/plasminogen complexes.

Urokinase is a double-chained molecule that is a product of urinary tract cells. Formerly prepared by concentration from urine, it is now made in tissue culture. Urokinase activates plasminogen directly. It is active on circulating plasminogen molecules as well as fibrin-bound plasminogen.

Single-chain urokinase-type PA, formerly obtained in tissue culture from a hypernephroma cell line, is now made by recombinant DNA techniques. On the fibrin molecule, urokinase is assembled from two scu-PA molecules. Single-chain urokinase-PA appears to have considerable specificity for fibrin-bound plasmin. This may be due to a much higher propensity for scu-PA to activate lys-plasminogen (the molecular form that is attached to fibrin) than for activation of glu-plasminogen (the type that is in the circulating blood).

Both single-chain and double-chain t-PA have been used clinically. They are made by recombinant DNA techniques in tissue-culture. The single-chain form is produced by a suspension-culture technique; the double-chain form is made by a roller-bottle technique. The single-chain form is more fibrin-specific than the double-chain form and it is thought to be rapidly assembled into the double-chain form *in vivo*.

ANTICOAGULANT THERAPY FOR MYOCARDIAL INFARCTION - SECONDARY PREVENTION

Anticoagulant therapy for myocardial infarction has been **controversial** for several decades. It was embraced enthusiastically as an important part of therapy after publication of the first clinical trial in 1948. (64) By the late 1960s and early 1970s, interest began to wane as doubts grew about the importance of thrombosis in acute myocardial infarction and with the publication of several large randomized studies on this subject. (65-77) The ACCP-NHLBI consensus panel stated, however, that "critical review of the evidence for the possible value of anticoagulant therapy in acute myocardial infarction suggests that neither the initial enthusiasm nor the subsequent loss of interest is justified by the published reports." (1) Discussion of anticoagulants for myocardial infarction is conveniently divided into four parts: short-term treatment soon after myocardial infarction to prevent death and reinfarction, short-term treatment soon after myocardial infarction to prevent embolism from the left heart, short-term treatment soon after infarction to prevent deep venous thrombosis and pulmonary embolism, and long-term treatment for survivors of myocardial infarction to prevent death and reinfarction.

Short-term Anticoagulant Therapy Soon After Myocardial Infarction to Prevent Death and Reinfarction

More than 30 trials of anticoagulant therapy after MI have been identified (78) Nevertheless, there are only three randomized studies of sufficient size to have a reasonable change of demonstrating a clinically important reduction in death and reinfarction. (65-67)

The Medical Research Council of the United Kingdom (MRC) Trial (65) was a single-blind controlled study in which 1,427 patients with acute MI were randomly allocated to anticoagulation or control therapy for 28 days. Active therapy was intravenous heparin followed by phenindione. The control group received homeopathic doses of phenindione and no heparin. Death was reduced 11%, from 18% in the control group to 16.2% in the active-treatment group (NS). Reinfarction was reduced from 13% in the control group to 9.7% in the anticoagulated group (NS).

The Bronx Municipal Hospital Center Trial (66) was a randomized, placebo-controlled, single-blind trial in 1,136 patients of anticoagulants or placebo within 24 hours of admission. Active therapy was heparin (the first dose was intravenous, the following doses were subcutaneous) followed by phenindione. Control patients received placebos. The duration of therapy was not specified. Death was reduced by 30% from 21.2% in the control group and 14.9% in the anticoagulated group ($P<0.005$). Reinfarction was reduced from 13% in the control group to 11.8% in the actively-treated group (NS).

In a VA Cooperative Trial (67), 999 male patients were randomly allocated to anticoagulant or placebo therapy within 72 hours of the onset of their symptoms. Active therapy was subcutaneous heparin followed by warfarin. They were treated for 28 days. Death was reduced by 14%, from 11.2% in the control group to 9.6% in the anticoagulated group (NS). Reinfarction was reduced 50%, from 4% in the control group to 2% in the actively-treated group. (NS).

Chalmers and his associates reviewed and reanalyzed the results of all of the adequately-designed, randomized studies of anticoagulant therapy in acute myocardial infarction. (78) They identified more than 30 studies. The results of analysis of the pooled data suggested a reduction in death of 21%. This type of analysis of data pooled from more than one trial has proponents and detractors among biostatisticians and epidemiologists.

After decades of **controversy**, based upon the above data, there is now a **consensus** that short-term anticoagulation soon after myocardial infarction may produce a modest reduction (about 20%) in early mortality in patients with acute myocardial infarction. Nevertheless, the recent data showing that the majority of patients with acute MI already have an occlusive coronary thrombus at the time of hospital admission make it unlikely that anticoagulant therapy alone would have a major influence on infarction size and, therefore, have a major effect on early mortality after MI that is related to the extent of loss of working ventricular myocardium. The effectiveness of anticoagulants soon after acute MI was probably chiefly a function of maintenance of patency of coronary arteries following spontaneous fibrinolysis and thus prevention of death and reinfarction related to reocclusion of the affected arteries. (1) A few deaths were clearly prevented by prevention of stroke and pulmonary embolism, issues that are discussed below. Therefore, the current **consensus** is that the roles of short-term anticoagulant therapy soon after myocardial infarction are largely limited to the following: as an adjunct to coronary fibrinolytic therapy, prevention of thromboembolism from the left ventricle, and prevention of deep venous thrombosis and pulmonary embolism. (1,61,79)

Short-term Therapy After Myocardial Infarction to Prevent Systemic Thromboembolism from the Left Heart

Modern coronary care has greatly reduced death after MI from cardiac rhythm disorders in patients once they are attended by appropriately trained health-care workers. Most in-hospital deaths are now from left ventricular pump failure. Only about 10% of in-hospital deaths after MI are due to systemic embolism and the great majority of those are the result of strokes. (80) In the MRC study (65), the relative risk of stroke was reduced by anticoagulant therapy by 55%, from 2.5% to 1.1%, ($P<0.037$). In the Bronx Municipal Hospital study (66), the relative risk of stroke was reduced 24%, from 2.3% to 1.7% (NS). In the VA study (67), the relative risk of stroke was reduced by 75%, from 3.2% to 0.8% ($p<0.005$).

The risk of systemic embolism is not equally distributed among all patients with acute MI. It is highest in patients with acute anterior wall infarcts associated

with wall motion abnormalities. In these patients, the risk is about 30-40%, approximately twice the risk of all patients with MI. This group also has the highest incidence of mural thrombi detected by echocardiography. Nevertheless, about 20% of ventricular thrombi are not detected by echocardiography, Furthermore, it has not been shown clearly that patients with anterior wall infarctions without echocardiographically detectable thrombus are at substantially less risk for thromboembolism than are similar patients with detectable thrombus. Therefore, a strong **consensus** has developed that patients with anterior wall myocardial infarction should receive heparin therapy followed by oral anticoagulant therapy (prolonging the prothrombin time 1.2 - 1.5 times the control value) for 1-3 months.

Other risk factors for systemic embolism include large infarcts, dilation of the left ventricle, congestive heart failure, atrial fibrillation, and ventricular aneurysms, and history of previous systemic or pulmonary embolism. Therefore, a **consensus** has also developed that patients with acute myocardial infarction who are at increased risk of systemic embolism because of atrial fibrillation, history of previous systemic or pulmonary embolism, or congestive heart failure should receive heparin therapy followed by oral anticoagulants to prolong the prothombin time to 1.2-1.5 times the control value for at least three months. (1). This recommendation might be extended to other patients deemed to be a high risk on an individual basis.

Short-term Anticoagulant Therapy to Prevent Deep Venous Thrombosis and Pulmonary Embolism.

The risk of pulmonary embolism that was diagnosed clinically was reduced in all three of the large anticoagulant trials mentioned above. The relative risk was reduced from 5.6 to 2.2% ($P<0.01$) in the MRC study (65), from 6.1 to 3.8% (NS) in the Bronx Municipal Hospital study (66), and from 2.6% to 0.2% ($P<0.005$) in the VA Cooperative study (67). The clinical diagnosis of pulmonary embolism is often difficult, but two autopsy studies comparing pulmonary embolism in the presence and absence of anticoagulant therapy are supportive of the findings of these three trials. (81,82) Three recent trials that looked for venous thrombosis in the lower extremities with radioisotope scanning techniques are also supportive of a protective effect of anticoagulants. The presence of thrombi in the veins of the leg was reduced significantly in two of the studies (83,84) and reduced, but insignificantly so, in the third (85,86). Modern coronary care emphasizes early ambulation of the patient following MI. The incidence of deep venous thrombosis is reduced as a result. (87) Therefore, pulmonary embolism today probably occurs less frequently than in 5% of patients and is more prevalent in patients at high risk for venous thrombosis, such as patients with heart failure, shock, preexisting venous disease or history of venous thromboembolism, obesity, and patients requiring bed rest for more than 3 days. Nevertheless, there is a strong **consensus** that patients with acute myocardial infarction should receive anticoagulation, with at least low-dose heparin (5,000 units intravenously or subcutaneously every 12 hours until fully ambulatory). The majority of the experts appear to favor application to all patients with acute infarction (1,79). Some prefer to restrict it to patients at high risk for venous thrombosis (61).

The hemorrhagic risks of short-term anticoagulation after MI in the groups outlined above appears to be acceptably low enough in light of the demonstrated benefits. The ACCP-NHBLI consensus panel combined the results of the three above-noted randomized trials of short-term anticoagulation after MI. In the 2,348 patients who received anticoagulant therapy, minor bleeding occurred in 7%; major bleeding occurred in 1.5%; and bleeding into the central nervous system occurred in 0.05%. There were no deaths attributed to bleeding.

Long-term Anticoagulation In Survivors of MI to Prevent Reinfarction and Death

The statistical demands of trials to show a beneficial effect on mortality and morbidity in survivors of MI are formidable. (1,61) The death rate and reinfarction rate drop substantially following the hospital phase of MI and continue to drop exponentially for about a year. From a year after MI, the mortality rate returns to a rate identical to patients with stable chronic coronary heart disease without MI. Many trials with oral anticoagulants long-term commencing in the first few weeks after MI have been performed, but only three had an 80% chance to demonstrate a 50% difference in death or reinfarction at the 5% probability level. No such trial has been performed with a power of demonstrating a 20% difference.

The MRC trial was a trial of 383 people who had survived an MI 4-6 weeks before entry into the trial. (88) All of these subjects had been treated with anticoagulant therapy during the hospital phase of their illnesses. They were randomly allocated to receive either full or homeopathic doses of phenindione. The patients were followed for three years. The death rate was decreased 30%, from 21.3% to 14.9% (NS). Recurrent MI was reduced from 39.9% to 20.5% ($P<0.001$).

The VA Cooperative study was a trial of 747 male patients who were enrolled within 21 days of hospital admission for acute MI. (74,75) They were randomly assigned to either placebo or warfarin and were followed for 7 years. At three years of follow-up, mortality was significantly reduced ($P<0.01$), but by the end of the 7-year follow-up, the death rates were virtually identical. Recurrent MI was reduced by 25%.

The German-Austrian Centre Clinical Trial was a trial of placebo vs. aspirin vs. phenprocoumon. (76) (The results with aspirin are discussed below.) Three-hundred and nine patients were randomly allocated to placebo treatment and 320 were assigned treatment with phenprocoumon. They were enrolled 30-42 days after MI and were followed for 2 years. The relative risk of death was increased 18%, from 10% to 12% (NS). There was a non-significant reduction in the rate of recurrent myocardial infarction.

A fourth trial, the Sixty-Plus Reinfarction Study (89), requires discussion although it does not fit precisely into this section, because the 878 subjects had sustained an MI 6 or more months before entry into the study. In fact, the mean time from infarction was 6 years. All of the patients were over 60 years of age and all had received oral anticoagulant therapy since the time of their infarction. They were randomly assigned to placebo or oral anticoagulant therapy. After two years of follow-up, there was no difference in death rates, but recurrent myocardial infarction was reduced by 55%.

Because of the low statistical power of the available studies, an international pooling group has combined the results of nine studies. (77) The results of this effort suggest that mortality was reduced by 20% in men given long-term anticoagulants, with the benefit limited to patients with prolonged angina or previous MI on admission to the trial.

Last year, the results of a trial of low-dose, subcutaneous heparin in survivors of MI was reported from Italy. (90) It was a prospective, randomized, controlled trial of heparin, 12,500 units daily, in 728 patients who had sustained a Q-wave infarction 6-18 months before enrollment. After two years of follow-up, the mortality rate was decreased by 48% ($P<0.05$),(drug efficacy analysis) or 34% (NS),(intention to treat analysis). Recurrent infarctions were decreased by 63%, from 3.56% to 1.32% ($P<0.05$).

Bleeding complications, not unexpectedly, were common in most of these trials. Most of the hemorrhagic episodes were minor, however. In general, the incidence of stroke was reduced, implying a decrease in embolic and thrombotic strokes that outweighed any increase in hemorrhagic strokes.

The absence of more compelling evidence of benefit than demonstrated thus far, the risk of bleeding, and the practical difficulties associated with long-term oral anticoagulation make this therapy hard to recommend as routine therapy after MI. The reduction in mortality and reinfarction does not appear to be any greater than with anti-platelet therapy, which is much simpler, associated with fewer hemorrhagic complications, and presumably has a similar mode of cardiac protection, namely an antithrombotic effect. The incidence of thromboembolism, however, appears to be reduced. [Reviewed in (1)] Therefore, a **consensus** has developed that oral anticoagulant therapy should not be recommended routinely after MI. (1) A **parallel consensus** has developed, however, that survivors of MI should be treated long-term with oral anticoagulants if any of the following risk factors for systemic or pulmonary embolism are present: atrial fibrillation, previous systemic embolism, venous thromboembolism, or severe heart failure. (1)

ANTICOAGULANT THERAPY FOR UNSTABLE ANGINA PECTORIS - SECONDARY PREVENTION

From 1948 to 1964, there were several trials of anticoagulation in patients with unstable angina. The results were contradictory and the trials are not entirely satisfactory when judged by today's standards for clinical trials. There is only one recent study of anticoagulation in unstable angina. (13). Heparin therapy was associated with a statistically significant ($p<0.024$) reduction in progression to transmural infarction. The study design has been criticized by some and there was a high dropout rate, so that the precise degree of protection conferred by heparin remains uncertain. The protective effects of antiplatelet therapy in unstable angina are much more convincing than the effects of anticoagulation (see below). Therefore, a **consensus** has developed that anticoagulants should not be used routinely in unstable angina. (1) Nevertheless, a few patients with unstable angina will require urgent coronary artery bypass surgery. .Aspirin therapy is associated with increased perioperative bleeding following coronary bypass surgery. (This is discussed further in the section on antiplatelet therapy to protect coronary artery bypass grafts.) Many cardiac surgeons are reluctant to perform bypass surgery on patients who have received aspirin in the week before surgery. Therefore, a **consensus** has developed that patients with unstable angina who are likely to require urgent coronary artery bypass surgery should receive heparin therapy prior to the surgery instead of aspirin.

ANTIPLATELET THERAPY FOR MYOCARDIAL INFARCTION AND UNSTABLE ANGINA PECTORIS - SECONDARY PREVENTION

Antiplatelet Therapy for Unstable Angina

Two prospective, randomized, placebo-controlled trials of antiplatelet therapy in unstable angina pectoris have shown remarkably similar and highly protective effects. The principal end point in both studies was myocardial infarction or coronary death.

The VA Cooperative study randomly assigned 1,338 male patients to 324 mg of aspirin in a buffered solution or placebo for 12 weeks, beginning within 51 hours of hospital admission. Death or nonfatal MI were reduced 51%, from 10.1% to 5% ($p<0.0005$). Analysis by intention to treat showed a 41% reduction in this end point

($p<0.004$). The protective effects were maintained at one year after entry into the study. (11)

In the Canadian multicenter trial, a total of 555 patients, including 27% women, were randomly allocated to placebo-controlled treatment within 8 days of hospitalization of aspirin (325 mg 4 times daily), sulfinpyrazone (200 mg 4 times daily), both, or neither. Treatment lasted for 2 years. When the study ended, mean follow-up was 18 months. Active treatment with a regimen including aspirin was associated with a 51% reduction in myocardial infarction or death, from 13 to 6% ($p<0.005$). Analysis by an intention to treat analysis showed a reduction of this end point by 30% ($p<0.07$). Sulfinpyrazone treatment alone was not protective. Women as well as men benefited. (12)

There is a **consensus** that patients with unstable angina should be treated with aspirin for two years at 325 mg per day. (1) Because some reports have suggested that women are less responsive to the protective effects of aspirin therapy against cardiovascular events and because the one study that included women administered high-dose aspirin, some physicians prefer to use doses of about a gram per day in female patients with unstable angina.

Antiplatelet Therapy for Acute Myocardial Infarction

Until this year, there were very few data regarding a protective effect of antiplatelet therapy given to patients early during acute myocardial infarction. One small study, supported by the MRC, utilized a single 300 mg dose of aspirin given within the first day of admission. (91,92) There was a 7% decrease in mortality at the time of hospital discharge. (NS) The huge ISIS-2 trial reported its findings at the meeting of the American College of Cardiology this spring and a report of the study was published just 12 days ago, in Lancet. (93) This trial was a randomized, placebo controlled trial of aspirin (160 mg chewed as soon as possible after entry and then 160 mg daily) and streptokinase given within the first 24 hours after the onset of acute myocardial infarction. A total of 17,189 patients were randomly assigned to receive aspirin alone, aspirin plus streptokinase, streptokinase alone, or both active drugs. The primary end points were vascular and total mortality 5 weeks after the infarct. Aspirin therapy significantly reduced mortality, by 21%, from 11.5% to 9.3%. The effects of aspirin were additive to the effects of thrombolytic therapy. There was a 23% reduction in mortality with aspirin therapy in patients who received active streptokinase (i.e. aspirin plus streptokinase *vs.* streptokinase plus aspirin placebo, $P<0.0003$). This effect was as prominent as the 19% reduction in mortality demonstrated in the patients who received aspirin alone (i.e. aspirin plus streptokinase placebo *vs.* aspirin placebo plus streptokinase placebo, $P<0.0001$). Because these data are so new, it would be premature to suggest that a consensus has developed favoring routine use of aspirin in the acute phase of MI. Nevertheless, I expect such a consensus will develop quickly in view of these data, and the protective effects that have been demonstrated in patients with unstable angina (see above) and in patients who have survived MI (see below). The effect presumably is due to prevention of new thrombus and platelet plugging following spontaneous or streptokinase-induced fibrinolysis.

Long-Term Antiplatelet Therapy In Survivors of Acute Myocardial Infarction

Ten large, randomized, placebo-controlled long-term secondary prevention studies have been performed with antiplatelet agents in survivors of myocardial infarction. Eight were carried out with aspirin, either alone (6 studies) or in combination with dipyridamole. Two were carried out with sulfinpyrazone.

The first MRC trial was a randomized, double-blind study of aspirin, 300 mg once daily, in 1,239 men who had sustained a myocardial infarction within 10 weeks of enrollment. Follow-up was one year. Mortality was reduced 22%, from 9.8% to 7.6%. (NS). The reduction was much more prominent in men who were enrolled within 6 weeks of infarction. In that case, mortality was reduced from 13.2% to 7.8%. (92,94)

The Coronary Drug Project Research Group (CDP) randomly assigned 1,529 men with MI within 5 years of enrollment to aspirin (324 mg three times daily) or placebo. Total mortality was reduced 30%, from 8.3% to 5.8% (NS). (95,96)

The German-Austrian Trial randomly allocated 946 patients within six weeks of MI to aspirin (500 mg three times a day), placebo, or oral anticoagulation (see above). Follow-up was 2 years. Total mortality was reduced 18%, from 10% to 8.5% (NS). The coronary death rate was reduced more markedly, from 7.1% to 4.1% (NS). (97,98)

The second MRC trial randomly assigned 1,682 patients to aspirin (300 mg three times daily) or placebo within one week of MI. Total mortality was reduced 17%, from 14.8% to 12.3%. The risk of the combined end point of total mortality plus nonfatal MI was reduced from 28% to 22% (NS). (92,99)

The Aspirin Myocardial Infarction Study (AMIS) randomly assigned 4,524 patients with an MI 2-60 months previously and followed them for up to 3 years. Total mortality was increased 11%, from 9.7% to 10.8%. There were fewer nonfatal MIs in the aspirin group and the combined incidence of coronary heart disease mortality or nonfatal MI was reduced from 14.8% to 14.1%. (100,101) In spite of its size and randomization, the aspirin group received a disproportionately large share of patients with cardiovascular risk factors which may have affected the study outcome. (1)

The first Persantine-Aspirin Reinfarction Study (PARIS) randomly allocated 2,206 patients with MI 2-60 months previously to therapy with aspirin (324mg three times daily), the same aspirin regimen plus dipyridamole (75mg three times daily), or placebo. The average follow-up was 41 months. The active groups had twice as many patients as the placebo group. Total mortality was reduced 18% by aspirin alone, from 12.8% to 10.5%. It was reduced 16% by the combination of aspirin and dipyridamole, from 12.8% to 10.7% (NS). Patients who were entered into the trial within six months of their infarction appeared to have the majority of the beneficial effects of antiplatelet therapy. (102-104)

The results of these six trials were analyzed in an editorial in Lancet in 1980. It was pointed out that a trial of 5,000-10,000 patients would be required to detect with confidence a 10-20% end point reduction. The author of this editorial pooled the data of these six trials and concluded that the risk reduction with aspirin is 16% for cardiovascular death ($P<0.01$) and the combined end point of fatal and nonfatal MI is reduced by aspirin by 21% ($P<0.001$). (105)

The PARIS group carried out a second study, enrolling patients earlier than their first study, 4 weeks to four months after MI. They randomly assigned 3,128 people to the same aspirin plus dipyridamole regimen that they used earlier or to placebo. The groups were of the same size. The follow-up period averaged 23.4 months. At one year, total mortality was reduced 9% and coronary mortality was reduced 20%. (NS) At the conclusion of the study, the differences were much less striking. Nevertheless, the combined end point of coronary mortality plus nonfatal infarction was reduced significantly at one year and at the conclusion of the study. (106)

Based upon these studies, the Food and Drug Administration approved aspirin as an effective treatment following myocardial infarction for reduction of death and reinfarction.

Two randomized, placebo-controlled studies of sulfinpyrazone after myocardial infarction have been performed, one in North America and the other in Italy. Both trials studied the effects of 200 mg of sulfinpyrazone four times daily. The North American trial demonstrated a reduction in mortality of 24%, from 10% to 8% (NS). Total mortality in the Italian study was reduced 26%, from 5% to 4%.(NS). The sulfinpyrazone trials created a lot of controversy about some of the techniques of data analysis. Furthermore, there were some inconsistencies between the two studies in benefits on cardiac death and reinfarction. As a result, the Food and Drug Administration did not approve sulfinpyrazone as effective therapy following MI. (1)

Earlier this year results were published, from an enormous reanalysis of the available data from virtually all of the clinical trials of antiplatelet agents in stroke, myocardial infarction, and unstable angina, by the Antiplatelet Trialists Group. (107) They pooled and reanalyzed all of the above 9 trials, plus the Micristin study, a randomized trial in West Germany of aspirin, 1500 mg/day, *vs.* placebo in 1340 people. Pooling these ten antiplatelet trials in survivors of MI, they calculated an odds reduction of 25% for stroke, myocardial infarction, or vascular death ($p<0.0001$), an odds reduction of 31%: for non-fatal myocardial infarction ($p<0.0001$), and an odds reduction for all vascular deaths of 13% ($p<0.005$).

The ACCP-NHLBI consensus panel concluded late in 1985 (1) that individual clinical judgments should determine whether to use aspirin in survivors of MI. Since that panel made their recommendations, the full report of PARIS-II has appeared, the analyses of the pooled results from the Antiplatelet Trialist Group has been published, and the beneficial effects of aspirin in the acute phase of MI have been published by ISIS-2. Furthermore, the Food and Drug Administration has approved aspirin therapy post MI as effective for prevention of further coronary events. Low-dose aspirin should be effective and, therefore, side-effects will be minimized. Therefore, I believe that a **consensus** has developed in recent months that survivors of MI should be treated with low-dose aspirin for at least 1-2 years following MI.

ANTITHROMBOTIC THERAPY FOR STABLE ANGINA PECTORIS - PRIMARY PREVENTION

There are no data available now on the value of long-term antithrombotic therapy in patients with stable angina pectoris in preventing myocardial infarction and cardiac death.

ANTIPLATELET THERAPY IN SUBJECTS AT RISK FOR CORONARY EVENTS - PRIMARY PREVENTION

In January of this year, some results were published from two studies, one in the USA and the other in the United Kingdom, of aspirin administration to apparently healthy physicians. (108,109) Entry was restricted to males, aged 40-84 years, to select a group at high risk for the development of coronary heart disease end points. The principal investigator in each trial was a co-investigator in the other. There were 5,139 British physicians and 22,071 American physicians enrolled. The Americans were randomly assigned to 325 mg aspirin every other day or placebo. This trial also included random assignment to beta-carotene or its placebo. In the British trial, the physicians were randomly assigned to aspirin or aspirin-avoidance.

It was not a placebo controlled study; the dose was 500 mg daily; and there was no beta-carotene limb of the study.

In the American study, the risk of fatal or non-fatal MI was reduced by 47% ($p<0.00001$). This observation, along with the extraordinarily low mortality of American physicians, led to premature termination of the study. The combined end point of either nonfatal MI, stroke, or cardiovascular death was also reduced, by 23% ($p<0.006$). The incidence of stroke was increased, by 15% (NS), but the risk of moderate to severe or fatal hemorrhagic stroke was substantially increased ($p<0.02$). There were 10 such events in the aspirin-treated physicians and 2 in the placebo-treated group.

No protective effect against MI was demonstrated in the British trial. There was a 10% lower total mortality in the aspirin group (NS). Vascular deaths were reduced by 6% (NS). There was a significant reduction in transient ischemic attacks, but an increase in the number of strokes. The aspirin-treated group had more disabling strokes.

More analyses and comparisons of these studies are yet to come. A **consensus** on the role of aspirin in primary prevention of coronary events in asymptomatic middle-aged and elderly men cannot yet be formed. The burden of increased disabling strokes may outweigh potential benefits for coronary events when very long-term treatment is involved, especially for subjects at particularly low risk for coronary events. For the time-being, it has been recommended that long-term aspirin administration for primary prevention of coronary events be a matter of individual judgment for each subject, weighing carefully the risks for coronary events alongside the possible risks of aspirin therapy. (110,111)

ANTIPLATELET THERAPY FOR PROTECTION OF CORONARY BYPASS GRAFTS

Prevention of closure and stenosis of the inverted veins used in coronary bypass surgery is a complicated topic that has been extensively investigated in man and in experimental models. (61) Antiplatelet therapy might influence the state of the graft by several mechanisms, including prevention of early thrombosis, prevention of the development of intimal hyperplasia, prevention of the development of graft atherosclerosis, and prevention of thrombosis in grafts that are stenosed as a result of atherosclerosis. There has been considerable **controversy** on this topic, because the results of clinical trials have been contradictory, with both positive and negative results. Chesebro and Fuster and their colleagues at the Mayo clinic have studied this issue and have compared the results of many of the clinical trials based on when the antiplatelet therapy was started. (61) This comparison makes a compelling case that the results are highly dependent upon when the antiplatelet regimen is begun. The most positive results have been obtained when antiplatelet therapy is begun before the operation. (61,112,113) If therapy is begun more than 48 hours after operation, the protective effect is greatly diminished or absent. (61) The Mayo clinic studies utilized dipyridamole therapy, 100 mg 4 times daily, for 2 days before the operation. The same dose of dipyridamole was given orally 2 hours before the operation and one hour after the operation, by nasogastric tube. They gave the first dose of aspirin 7 hours post-operatively, by nasogastric tube, along with 75 mg of dipyridamole. Long-term therapy, begun one day after operation, was aspirin, 325 mg, plus dipyridamole, 75 mg 3 times daily. With this regimen including early therapy, a highly beneficial effect on graft patency was seen soon after operation and one year later. This regimen did not significantly increase peri-operative bleeding. Strong additional support for the importance of early

therapy has come in the last year from a large VA cooperative study. (114,115) This study evaluated 5 different antiplatelet treatment regimens: aspirin 325 mg daily, aspirin 325 mg 3 times daily, aspirin 325 mg plus dipyridamole 75 mg 3 times daily, sulfinpyrazone 265 mg 3 times daily, and placebo. Therapy was started 48 hours before operation except for the aspirin-treated groups, in which a single 325 mg dose of aspirin was given 12 hours before surgery. All of the antiplatelet regimens improved graft patency, both early and one year post-operatively ($p<0.005$). All of the aspirin treatment regimens significantly increased bleeding in the first 35 hours after operation. Sulfinpyrazone did not. Low-dose aspirin was as effective as high-dose aspirin or the aspirin and dipyridamole combination.

Anticoagulant therapy has also been found to provide protective effects for keeping bypass grafts open that is comparable to the effects of antiplatelet therapy. (61,116)

There is a strong **consensus** that antiplatelet therapy should be employed for patients undergoing bypass surgery and that treatment should be begun before the operation. There is no **consensus** yet on the ideal antiplatelet regimen. The most widely employed regimen now is probably the Mayo Clinic protocol of dipyridamole 2 days preoperatively, aspirin 7 hours post-operatively followed by long-term therapy with high-dose aspirin plus dipyridamole. Fuster has recently recommended modifying this regimen to dipyridamole preoperatively, aspirin 325 mg 7 hours post-operatively, and aspirin 325 mg daily for long-term therapy. (61) Anticoagulant therapy is an acceptable alternative for patients who cannot take an antiplatelet regimen.

ANTIPLATELET THERAPY FOR PREVENTION OF RESTENOSES FOLLOWING BALLOON ANGIOPLASTY (PTCA) OF CORONARY ARTERIES

Balloon angioplasty has emerged in recent years as an important alternative to coronary bypass surgery in well-selected cases. Restenosis, which occurs in 25-35% of cases, is a major limitation. Balloon angioplasty is a thrombogenic and atherogenic intervention. Success is probably always associated with intimal fractures, plaque fracture, medial disruption, and expansion of the external diameter of the vessel. Platelet deposition and thrombus formation are important causes of acute occlusion of the vessel soon after the procedure. The mechanisms of restenosis are less well understood. (117) Anticoagulant and antiplatelet therapies are rational in the immediate post-angioplasty phase of recovery. The role of long-term antiplatelet therapy has been **controversial**. (61) The results of a randomized placebo-controlled trial in 376 patients of antiplatelet therapy with aspirin 330 mg plus dipyridamole 75 mg 3 times daily were published earlier this year. (118) Therapy was begun 24 hours before the procedure. Intravenous dipyridamole replaced the oral agent for 24 hours beginning 8 hours before the procedure was to start. All patients were treated with a calcium blocker and anticoagulation. The incidence of transmural myocardial infarction during or soon after PTCA was markedly reduced (6.9% *vs.* 1.6%, $p=0.0113$), but the incidence of restenosis 4-7 months later was unchanged.

There is now a **consensus** that patients undergoing PTCA should receive heparin anticoagulation before the procedure and for a minimum 18-24 hours afterwards and that they should receive antiplatelet therapy with aspirin and dipyridamole before the procedure and for at least 48 hours afterwards. Long-term antiplatelet therapy remains **controversial**. Long-term antiplatelet therapy is still employed by many physicians following PTCA. Furthermore, many patients will

need long-term antiplatelet therapy because of recent unstable angina or myocardial infarction.

CONSENSUS AND CONTROVERSY IN THROMBOLYTIC THERAPY OF ACUTE MYOCARDIAL INFARCTION AND UNSTABLE ANGINA

The resurgence of thrombolytic therapy in the last few years for syndromes of acute myocardial ischemia has been reviewed by many authors recently (14,15,30,62,63,119-128) and at these exercises on March 17, 1988 by Dr. David Hillis. A comprehensive review of this topic is beyond the scope of this review, but several areas of current consensus and controversy deserve comment.

Consensus - Intravenous Thrombolytic Therapy Opens Thrombosed Coronary Arteries, Reduces Mortality, and Reduces Infarct Size

The reference standard for successful coronary thrombolysis is the result with intracoronary infusion of streptokinase or urokinase in patients with evolving transmural MI. Reviews of these studies demonstrate that the rate of successful reperfusion, when therapy is employed within 6 hours of the onset of symptoms, is 70-80%. The failure to achieve reperfusion in 20-30% of patients may be due to the presence of older clot. It is well known that coronary thrombosis in unstable angina and MI has layers of varying age. Wide-spread, timely application of intracoronary fibrinolytic therapy is, however, logistically and economically impractical. Trials of early intravenous thrombolytic therapy show that intravenous thrombolytic therapy can approach the patency rate achieved with intracoronary therapy.

The most important end point of fibrinolytic therapy is mortality. The evidence is now overwhelming that mortality is reduced in well-selected patients with acute MI who are treated in a timely way with intravenous thrombolytic agents.

The Netherland Interuniversity Cardiology Institute study was reported in 1985. (129) Initially this was a trial of intracoronary streptokinase. In the last 117 of the 533 patients, intravenous streptokinase was administered before intracoronary streptokinase. It was a randomized trial of thrombolytic therapy versus no thrombolytic therapy. Mortality was significantly reduced at 28 days. The benefits were maintained at one year follow-up.

The Gruppo Italiano Studio Della Streptochinasi Nell'Infarto Miocardico (GISSI) study was reported in 1986. (130) This trial was an unblinded study of intravenous streptokinase, 1.5 million units in one hour, versus no thrombolytic treatment in 11,806 patients in 76 Italian hospitals. Overall, there was an 18% reduction in mortality at 21 days follow-up, from 13% to 10.7% ($p<0.0002$). The benefit was time dependent. Mortality was reduced 23%, from 12% to 9.2%, when therapy was begun within 3 hours of pain and 47%, from 15.4% to 8.2%, when the infusion was begun within one hour.

The I.S.A.M. study group reported on the results of intravenous streptokinase therapy in 1741 patients in 1986. (131) Patients were treated within 6 hours of onset of symptoms and were randomly assigned to 1.5 million units of streptokinase or placebo. There was reduction in mortality from 7.1% to 5.2% overall (NS). The benefit was greater when therapy was given within 3 hours of symptoms, with reduction in mortality from 6.5% to 5.2% (NS).

The ISIS-2 study mentioned earlier in the discussion of aspirin also showed a highly beneficial effect on mortality with 1.5 million units of intravenous streptokinase administration, given within 24 hours of the onset of symptoms. (93) In the patients who did not receive aspirin, at the 35 day follow-up period there was a 25% reduction in mortality overall, from 12% to 9.2%. ($p<0.00001$) The effect was

additive to the effects of aspirin. The combination of streptokinase plus aspirin significantly reduced mortality at 35 days by 42:%. The effects were time dependent. Mortality reduction for streptokinase when given within 4 hours was 37%. ($p<0.0001$).

The European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator reported mortality results from their randomized trial of rt-PA versus placebo at the American College of Cardiology meeting in March of this year. The results will be published later this year in Lancet. (132) A total of 721 patients were enrolled. Active therapy was 100 mg of rt-PA given over 3 hours. All patients received low-dose aspirin and heparin. Patients were treated within 5 hours of onset of symptoms. Overall, mortality was significantly reduced by 51% at 14 days, from 5.7% to 2.8%.

The Thrombolysis in MI (TIMI) Phase I trial was not designed with mortality as a major end point. Nevertheless, they have just reported the mortality experience from that trial of intravenous streptokinase and rt-PA. (133) Patients with patent vessels 90 minutes after thrombolytic drug administration had a significant reduction in mortality compared to patients whose thrombosed coronary arteries were not patent at this interval.

The surrogate end point of infarct size, assessed by radionuclide perfusion studies, estimates of left ventricular contraction, and enzymatic estimates of infarct size are also valuable as end points for treatment efficacy although less so than mortality. Data supporting preservation of myocardium have come from several sources, including : thallium-201 perfusion studies and left ventricular angiograms from the Western Washington Intravenous Streptokinase Trial [Kennedy, JW , pp 64-70 in reference (126)], left ventricular angiograms from an intravenous streptokinase trial in New Zealand (134), left ventricular angiograms from the I.S.A.M.study (131), a study of rt-PA at Johns Hopkins (135) and the TIMI-Phase I trial (136), and enzyme analysis from the I.S.A.M. study and the European Cooperative trial of rt-PA (132)

In recent months a **consensus** has emerged that thrombolytic therapy should be administered to well-selected patients with no contraindications if therapy can be applied in a timely way. The time dependence of the benefit is remarkable. Therefore a parallel **consensus** has emerged that it is imperative that emergency departments and mobile intensive care unit facilities be sufficiently organized to provide rapid patient assessment and prompt institution of therapy. Dr. J. Ward Kennedy, who organized the Western Washington Streptokinase Trials, has set a goal of 15 minutes from patient reception to institution of therapy at the hospitals in the University of Washington program in Seattle. Selection of patients is **controversial** as is the time of the therapeutic window. These controversies are discussed briefly below.

Controversy - Patient Selection

Patients who need thrombolytic therapy the most appear to benefit the most. In the GISSI trial, patients with anterior infarcts benefited the most. In a reanalysis of their data, the GISSI group has found that the benefit is greater the more leads of the 12-lead electrocardiogram that have significant ST-segment elevation. Patients with evolving Q-wave infarctions are more apt to have persistent totally occlusive thrombus than are patients with evolving non-Q wave infarcts. The ISIS-2 trial found that the benefit was fairly uniform, regardless of infarct location and a large variety of other cardiac risk factors. I believe that a **consensus** is now emerging that all patients with evolving Q-wave anterior MI and any patient with an evolving Q-wave infarct

who has significant elevation of the ST-segments on more than 3 leads on the 12-lead ECG should receive thrombolytic therapy if there are no contraindications and if it can be administered in a timely way. For other patients, a careful risk-benefit analysis for each patient is probably the wisest recommendation.

Fibrinolytic therapy may also play an important role in stabilization of some patients with unstable angina. The hope is that patients who fail to respond to antianginal and antithrombotic agents can be stabilized by thrombolysis and allow revascularization therapy to proceed at lower risk when the patient has been clinically stable for a day or two. (135) There is a **consensus** that use of fibrinolytic therapy in unstable angina should still be confined to clinical research and should not be employed as part of routine clinical practice.

Controversy - How Long is the Therapeutic Window?

Based upon the findings in experimental animals that infarction is largely complete and irreversible after 6 hours of total occlusion, one would expect that the window for effective fibrinolytic therapy would be short. The remarkable time dependency of the efficacy of therapy to reduce mortality support that expectation. Until the ISIS-2 trial results were available, a **consensus** had emerged that the appropriate window was 4-6 hours after the onset of symptoms. The results of the ISIS-2 trial, which showed a beneficial effect of thrombolytic therapy on mortality, even when it was administered 13-24 hours after the onset of symptoms requires a reappraisal of that consensus. This findings also requires development of new hypotheses to explain them. Several hypotheses have been advanced. The first of these hypotheses is that it is better to have an open vessel than a closed one, even if infarct size is not reduced. An open vessel might reduce the incidence of post-MI sudden death and might lead to better scar formation with less likelihood of myocardial rupture or aneurysm formation. An alternative hypothesis is that late thrombolysis might still achieve myocardial salvage in patients who still have some perfusion in the zone at risk, because of non-persistent or non-totally occlusive thrombus or substantial collateral vessel flow. Most physicians will probably wish to limit thrombolytic therapy to the first 4-6 hours pending further appraisal of the ISIS-2 data. New studies of later thrombolytic therapy are now under consideration or planning.

Controversy - What is the Best Thrombolytic Agent?

There are advantages and disadvantages to all of the thrombolytic agents that are currently available or apt to be available in the near future. (62,63) In making choices for individual patients, the major variables to address are the expected patency rate, the effect on myocardial salvage, the effect on mortality, and adverse side-effects. Compare the effects of different fibrinolytic agents on patency, myocardial salvage, and mortality from different studies with considerable caution. Some or all of the apparent differences may be due to study design, patient characteristics, concomitant medications, etc. The most reliable data derive from direct comparisons in the same study. Currently, we have only limited direct comparisons, principally for patency and side-effects, from TIMI-Phase I and the European Cooperative Study Group. Patency of the involved vessels was significantly better with rt-PA infusion in both studies. There were no important differences in side-effects, including bleeding and stroke. Most of the mortality data are from treatment with streptokinase. The only direct comparison of mortality came from the TIMI-Phase I trial, which was not designed as a mortality trial. (133) The differences were not significant. Direct comparisons of mortality are now

underway by the GISSI group and the ISIS group. The GISSI group has already begun enrollment for GISSI-2 and enrollment is now beginning for ISIS-3..The results will probably be available, at least in preliminary form, in about 18-24 months. Direct comparisons of the surrogate end point of myocardial salvage are currently scant.

Comment is due on the issue of bleeding risk with thrombolytic agents. There is now a **consensus** among most experts in thrombosis and hemostasis that the principle cause of bleeding with fibrinolytic therapy is lysis of hemostatic plugs and failure to form strong hemostatic plugs, not fibrinogen depletion. The fibrin of hemostatic plugs will be lysed as readily by fibrin-selective agents as the fibrin of thrombus. Furthermore, the fibrin-selective agents cause partial degradation of fibrinogen that results in a fibrin web with less tensile strength than normal. Also, fibrinolytic agents may induce platelet defects and the effects of fibrin-selective agents may be as marked or even more marked than those of the non-fibrin-selective agents. (63) Bleeding complications, therefore, will probably be as frequent with fibrin-selective as with non-fibrin-selective drugs as long as both are given in doses that lead to equivalent fibrinolysis. Fibrinolytic therapy was given to patients in GISSI and ISIS-2 in a manner very similar to current clinical practice. The bleeding risks were acceptably low. Early trials necessarily had a high bleeding rate at the sites of vascular access. As long as patients are well selected and vascular punctures and surgical incisions are avoided, the incidence of hemorrhage from fibrinolytic therapy for MI will be low and probably no greater than the risk of hemorrhage with systemic anticoagulation.

Advantages and Disadvantages of Streptokinase

The principal advantages of streptokinase are the great amount of information known about it, and its proved value and very low cost. The time dependency of streptokinase is a disadvantage. It is highly effective if given within 3 hours of the onset of MI. After that, its effectiveness diminishes with increasing time. Concomitant administration of anticoagulants is not essential because of the systemic lytic state. The principal disadvantages are its antigenicity and occasional allergic reactions, hypotension with rapid administration, and plasminogen activation in the circulation with fibrinogen depletion. The later two disadvantages may also be advantages. The lowered blood pressure may have an unloading effect and reduce myocardial oxygen demand. The lowered fibrinogen level reduces plasma viscosity and may improve coronary perfusion as a result. The systemic lytic state may be protective against rethrombosis.

Advantages and Disadvantages of APSAC

The major advantage of APSAC over streptokinase is that it can be given as a rapid infusion. This will be particularly advantageous as thrombolytic therapy is introduced into earlier use in the field, e.g. in air transport and in mobile intensive care units. It may be more fibrin-selective than streptokinase, but this is uncertain. Otherwise, it has the same advantages and disadvantages as streptokinase except for cost. The price is not known now, but it is apt to be considerably more expensive than streptokinase.

Advantages and Disadvantages of Urokinase

The lack of antigenicity and a long experience with urokinase administration for other indications are advantages. If it is confirmed that it is effective when given as a very rapid injection, this will be an advantage. Fibrinogen depletion is usually

intermediate between that of streptokinase and fibrin-selective agents such as rt-PA. It remains to be determined with certainty if this is an intrinsic property of urokinase or due to contamination with single-chain urokinase. As with streptokinase, the fibrinogen depletion is potentially both an advantage and disadvantage. Concomitant anticoagulant therapy is not essential because of the systemic lytic state. The absence of FDA approval for intravenous administration and the lack of a large body of knowledge on the best regimen for intravenous use after MI are disadvantages that will probably be rectified in the not-too-distant future. The cost of this agent, intermediate between streptokinase and rt-PA, is a disadvantage.

Advantages and Disadvantages of rt-PA

The principal advantages of rt-PA are: the lack of any known antigenicity; greater degree of fibrin-selectivity and lesser degree of fibrinogen depletion than streptokinase and urokinase; and less time-dependency for clot lysis than streptokinase. Disadvantages include the necessity for a prolonged infusion and concomitant administration of anticoagulants and its extremely high cost.

Advantages and Disadvantages of scu-PA

The advantages and disadvantages of scu-PA are similar to those of rt-PA. Early reports with scu-PA suggest that it may be synergic with rt-PA and urokinase. (137) In fact, it may be necessary to use scu-PA along with other agents as there may be a lag phase for initiation of fibrinolysis when scu-PA is used alone.

REFERENCES

1. Resnekov L, Chediak J, Hirsh J, Lewis D. Antithrombotic agents in coronary artery disease. Chest 1986; 89:54s-67s.

2. Hirsh J, Deykin D, Poller L. "Therapeutic Range" for Oral Anticoagulant Therapy. Chest 1986; 89:11s-15s.

3. Hirsh J, Fuster V, Salzman E. Dose Antiplatelet Agents; The relationship among side effects, and antithrombotic effectiveness. Chest 1986; 89:4s-10s.

4. Willerson JT, Campbell WB, Winniford MD, Schmitz J, Apprill P, Firth BG, Ashton J, Smitherman TC, Bush L, Buja LM. Conversion from chronic to acute ischemic heart disease: Speculation regarding mechanisms. American Journal Cardiology 1986; 54:1349-1354.

5. Smitherman TC, Hillert MCJr, Narahara KA, Burden LL, Lipscomb KM, Shapiro W, Nixon JV. Evidence for transient limitations in coronary blood flows during unstable angina pectoris: Hemodynamic changes with spontaneous pain at rest versus exercise-induced ischemia following stabilization of angina. Clin Cardiol 1980; 3:309-316.

6. Oliva PB. Unstable angina with ST-segment Depression: Pathophysiologic considerations and therapeutic implications. Annual Intern Medicine 1984; 100:424-440.

7. Smitherman TC. Unstable Angina Pectoris: The first half century: Natural history, pathopysiology, and treatment. American Journal Medical Science 1986; 292:395-406.

8. Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986; 74:6-9.

9. Sherman CT, Litvack F, Grundfest W. Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med 1986; 315:913-919.

10. Ambrose JA, Winters SL, Arora RR, Haft JI, Goldstein J, Rentrop KP, Gorlin R, Fuster V. Coronary angiographic morphology in myocardial infarction: A link between the pathogenesis of unstable angina and myocardial infarction. J Am Coll Cardiol 1985; 6:1223-1238.

11. Lewis HDJr, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JEIII, Schnaper HW, LeWinter MM, Linares E, Puoget JM, Sabharwal SC, Chesler E, Demots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of A Veterans Administration Cooperative Study. N Engl J Med 1983; 309:396-403.

12. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, Jablonsky G, Kostuk WJ, Melendez LJ, Myers MG, Sackett DL, Sealy BJ, Tanser PH. Aspirin,

sulfinpyrazone, or both in unstable angina: Results of a Canadian multicenter trial. N Engl J Med 1985; 313:1369-1375.

13. Telford AM, Wilson E. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. Lancet 1981; 1:1225-1228.

14. Loffel GL, Braunwald E. Thrombolytic therapy: A new strategy for the treatment of acute myocardial infarction. N Engl J Med 1984; 311:710-711.

15. Willerson JT, Winniford MD, Buja LM. Thrombolytic therapy for patients with acute myocardial infarction. American Journal Medicine Science 1987; 292:473-482.

16. Jackson CM, Nemerson Y. Blood coagulation. Ann Rev Biochem 1980; 49:765-811.

17. Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. Science 1964; 145:1310-1312.

18. Rao LVM, Rapaport SI. Studies of a mechanism inhibiting the initiation of the extrinsic pathway of coagulation. Blood 1987; 69:645-651.

19. Esmon CT. Protein-C: Biochemistry, physiology, and clinical implications. Blood 1983; 62:1155-1158.

20. Stenflo J. A new vitamin K-dependent protein: Purification from bovine plasma and preliminary characterization. Journal of Biological Chemistry 1976; 251:355-363.

21. Esmon CT, Owen WG. Indentification of an endothelial cell cofactor for thrombin-catalyzed activation of protein C. Proc Natl Acad Sci USA 1985; 82:4673-4677.

22. Walker FJ. Regulation of activated protein C by protein S. The role of phospholipid in factor Va inactivation. Journal of Biological Chemistry 1981; 256:11128-11131.

23. Harris KW, Esmon CT. Protein S is required for bovine platelets to support activated protein C binding and activity. Journal of Biological Chemistry 1985; 260:2007-2010.

24. Ogura M, Tanabe N, Nishioka J, Suzuke K, Saitolt. Biosynthesis and secretion of functional protein S by a human megakaryoblastic cell line (MEG-01). Blood 1987; 70:301-306.

25. Stern D, Brett J, Harris K, Nawroth P. Participation of endotheilial cells in the protein C-protein S anticoagulant pathway: The synthesis and release of protein S. J Biol Cell 1986; 102 (5):1971-1978.

26. Comp PC, Esmon CT. Generation of fibrinolytic activity by infusion of activated protein C into dogs. J Clin Invest 1981; 68:1221-1228.

27. Sakata Y, Curriden S, Lawrence D, Griffin J, Loskutoff D. Activated protein C stimulates the fibrinolytic activity of cultured endothelial cells and decreases anti-activation activity. Proceedings of the National Academy of Sciences of the United States of America 1984; 82:1121-1125.

28. Van Hinsbergh V, Bertina R, van Wijngaarden A, van Tillburg N, Emris J, Haverkate F. Activated protein C decreases plasminogen activator-inhibitor activity in endothelial cell- conditioned medium. Blood 1985; 65:444-451.

29. Jaques LB. The premises involved in the clinical use of heparin. Blood 1978; 4:275-276.

30. Collen D. On the regulation and control of fibrinolysis. Thromb Haemost 1980; 43:77-89.

31. Sprengers ED, Kluft C. Plasminogen activator inhibitors. Blood 1987; 69:381-387.

32. Budzynski AZ, Marder VG, Parker ME, Shames P, Brizuela BS, Olexa SA. Antigenic markers on fragment DD, a unique plasmic derivative of human crosslinked fibrin. Blood 1979; 54:794-804.

33. Schafer AI. The hypercoagulable states. Ann Int Med 1985; 102:814-828.

34. Mannucci PM, Tripodi A. Laboratory screening of inherited thrombotic syndromes. Thromb Haemost 1987; 57:247-251.

35. Comp P, Doray D, Patton D, Esmon CT. An abnormal plasma distribution of protein S occurs in functional protein S deficiency. Blood 1986; 67:504-508.

36. Cosio FG, Harker C, Batard MA, Brandt JT, Griffin JH. Plasma concentrations of the natural anticoagulants protein C and protein S in patients with proteinuria. J Lab Clin Med 1985; 106:218-222.

37. Bauer KA, Weiss LM, Sparrow D, Vakonas PS, Rosenberg RD. Aging-asssociated changes in indices of thrombin generations and protein C activation in humans. J Clin Invest 1987; 80:1527-1534.

38. Taylor FB, Chang A, Esmon CT, Vigano-D'Angelo S, Blick KE. Protein C prevetns the coagulopathic and lethal effects of Esherichia coli infusion in the baboon. Clin Invest 1987; 79:918-925.

39. Moore KL, Andreoli SP, Esmon NL, Esmon CT, Bang NU. Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro. Clin Invest 1987; 79:124-130.

40. Stern DM, Rimon S, Scott T, Nawroth PP. Modulation of endothelial cell coagulant properties. Thromb Haemost 1987; 58:40.

41. Nawroth PP, Brett J, Steinberg S, Esmon CT, Stern DM. Endothelium and Protein S: Synthesis, release, and regulation of anticoagulant activity. Thromb Haemost 1987; 58:49.

42. Scmitz JM, Apprill PG, Buja LM, Willerson JT, Campbell WB. Vascular prostaglandin and thromboxane production in a canine model of myocardial ischemia. Circ Res 1985; 57:223-231.

43. Meade TW, Mellows S, Brozovic M, Miller SG, Chakrabarti RR, North WRS, Haines AP, Stirling Y, Imeson JD, Thomson SG. Haemostatic function and ischaemic heart disease: Principal results of the Northwick Park heart study. Lancet 1986; 2:533-537.

44. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardivascular disease: The Framingham Study. JAMA 1987; 258:1183-1186.

45. Kruskal JB, Commerford PJ, Franks JJ, Kirsch RE. Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery disease. N Engl J Med 1987; 317:1361-1365.

46. Breddin K. Detection of prethrombotic states in patients with atherosclerotic lesions. Semin Thromb Hemost 1986; 12:110-123.

47. Juhan-Vague I, Moerman B, DeCock F, Aillaud MF, Collen D. Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathologic conditions. Thromb Res 1984; 33:523-530.

48. Wiman B, Chmielewska J, Ranby M. A novel fast inhibitor of tissue plasminogen activator in plasma, which may be of great pathophysiological significance. Scan J Clin Lab Invest 1985; 177:430-47.

49. Kruithof EKO, Gudinchet AL, Tran-Thang C, Ransijn A, Bachmann F. Antiactivator levels in various disease states, in Davidson J.F., Donati M.B., Coccheri S. (eds). Progress in Fibrinolysis 1985; VII:130.

50. Hamsten A, Wiman B, DeFaire U, Blomback M. Increased levels of rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. N Engl J Med 1985; 313:1557-1563.

51. Hamsten A, Wiman B, DeFaire U, Blomback M, Svensson J, Szamosi A, Mettinger L. Haemostatic function in myocardial infarction. Br Heart J 1986; 55:58-66.

52. Almer LO, Ohlin H. Elevated levels of the rapid inhibitor of plasminogen activator (t-PAI) in acute myocardial infarction. Thromb Res 1987; 47:335-339.

53. Gram J, Jespersen J. A selective depression of tissue plaminogen activator activator (t-PA) activity in euglobulins characterises a risk group among survivors of scute myocardial infarction. Thromb Haemost 1987; 57:137-139.

54. Gram J, Jespersen J, Kluft Rijken DC. On the usefulness of fibrinolysis variables in the characterization of a risk group for myocardial infarction. Acta Med Scand 1987; 221:149-153.

55. Hamsten A, DeFaire U, Walldius G, Dahlen G, Szamosi A. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. Lancet 1987; 2:3-9.

56. Johnson O, Mellbring G, Nilsson T. Defective fibrinolysis in survivors of myocardial infarction. Int J Cardiol 1984; 6:1012-1017.

57. Vigano S, Mannucci PM, D'Angelo G, Gelfi C, Gensini GF, Rostagno C, Serneri GG. Protein C antigen is not an acute phase reactant and is often high in ischemic heart disease and diabetes. Thromb Haemost 1984; 52:263-266.

58. O'Connor NJT, Broekmans AW, Bertina RM. Protein C values in coronary heart disease. Br Med J 1984; 289:1192-1192.

59. Gram J, Jespersen J. On the significance of antithrombin-III, alpha-2-macroglobulin, alpha-2-antiplasmin, histidine-rich glycoprotein, and protein C in patients with acute myocardial infarction and deep vein thrombosis. Thromb Haemost 1985; 54:503-505.

60. Gonzalez R, Vincente V, Alegre A, Pabon P, Alberca I. Protein C and antithrombin III in acute myocardial infarction. Thromb Res 1986; 43:681-685.

61. Penny WJ, Chesebro JH, Heras M, Fuster V. Antithrombotic therapy in acute myocardial infarction and unstable angina. Curr Probl Cardiol 1988; 13:433-513.

62. Marder V, Sherry S. Thrombolytic Therapy: Current Status (first of two parts). N Engl J Med 1988; 318:1512-1585.

63. Marder V, Sherry S. Thrombolytic Therapy: Current Status (Second of Two Parts). N Engl J Med 1988; 318:1585-1595.

64. Wright IS, Marple CD, Beck DF. Report of the committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction. Am Heart J 1948; 36:801.

65. Wright IS, Marple CD, Beck DF. Assesment of short-term anticoagulant administration after cardiac infarction: report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Reasearch Council. Br Med J 1969; 1:335.

66. Drapkin A, Merskey C. Anticoagulant in acute myocardial infarction: relation of therapeutic benefit to patients age, sex, and severity of infarction. JAMA 1972; 222:541-548.

67. Drapkin A, Merskey C. Anticoagulants in acute myocardial infarction: results of a cooperative clinical trial. JAMA 1973; 225:724.

68. Lovell RR, Denborough MA, Nestel PJ, Gobel AJ. A controlled trial of long-term treatment with anticoagulants after myocardial infarction with 412 male patients. Med J Aust 1967; 2:97-104.

69. MacMillan RL, Brown KW, Watt DL. Long-term anticoagulant therapy after myocardial infarction. Can Med Assoc J 1960; 83:567.

70. Meuwissen OJ, Vervoorn AC, Cohen O, Jordan FL, Nelemans FA. Double blind trial of long-term anticoagulant treatment after myocardial infarction. Acta Med Scand 1969; 186:361-368.

71. Conrad LL, Kyriacopouloas JD, Wiggins CW, et al. Prevention of recurrences of myocardial infarction. A double-blind study of the effectiveness of long-term oral anticoagulant therapy. Arch Inter Med 1964; 114:348.

72. Wasserman AJ, Gutterman LA, Yoe KB, Kemp VE, Richardson DW. Anticoagulants in acute myocardial infarction: the failure of anticoagulant to alter mortality in randomized series. Am Heart J 1966; 71:43-49.

73. Wasserman AJ, Gutterman LA, Yoe KB, et al. Second report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council: an assesment of long-term anticoagulant administration after cardiac infarction. Br Med J 1964; 2:837.

74. United States Veterans Administration. Long-term anticoagulant therapy after myocardial infarction. JAMA 1965; 193:157.

75. Ebert RV, Borden CV, Hipp HR, et al. Long-term anticoagulant therapy after myocardial infarction. Final report of the Veterans Adminstration cooperative study. JAMA 1969; 207:2263.

76. Breddin D, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. Circulation 1980; 62 (suppl V):63-72.

77. International Anticoagulant Review Group. Collaborative analysis of long-term anticoagulant administration after acute myocardial infarction. Lancet 1970; 1:203.

78. Chalmer TC, Matta RJ, Smith HJr, Kunzer AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Engl J Med 1977; 297:1091-1096.

79. Hirsh J, Cairns JA. Antithrombotic therapy in acute myocardial infarction and unstable angina. J Intensive Care Med 1987; 2:299-312.

80. Wessler S, Cornfield J. Coumarin therapy in acute myocardial infarction: A Hobson's choice. Arch Inter Med 1974; 134:774.

81. Steffensen KA. Coronary occlusion treated with small doses of heparin. Acta Med Scand 1969; 186:519-521.

82. Hilden T, Iversen K, Raaschou F, et al. Anticoagulants in acute myocardial infarction. Lancet 1961; 2:327.

83. Marks P, Teather D. Subcutaneous heparin; a logical prophylaxis for deep vein thrombosis after myocardial infarction. Practitioner 1978; 220:425-427.

84. Warlow C, Beattie AG, Terry G, Kenmure AC, Ogston D. A double-blind trial of low doses of subcutaneous heparin in the prevention of deep-vein thrombosis after myocardial infarction. Lancet 1973; 2:934-936.

85. Handley AJ. Low-dose heparin after myocardial infarction. Lancet 1972; 2:623-624.

86. Handley AJ, Emerson PA, Fleming PR. Heparin in the prevention of deep vein thrombosis after myocardial infarction. Br Med J 1972; 2:436-438.

87. Miller RR, Lies JE, Carretta RF, Wampold DB, DeNardo GL, Kraus JF, Amsterdam EA, Mason DT. Prevention of lower extremity venous thrombosis by early mobilization: Confirmation in patients with acute myocardial infarction by I-fibrinogen uptake and venography. Ann Int Med 1976; 84:700-703.

88. Second Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. Br Med J 1964; 2:837.

89. Report of the 60+ reinfarction study research group. A double-blind trial to assess long-term anticoagulant therapy in elderly patients after myocardial infarction. Lancet 1980; 2:989-994.

90. Neri Serneri GG, Rovelli G, Gensini GF, Pirelli S, Carnovali M. Effectiveness of low-dose heparin in prevention pf myocardial re-infarction. Lancet 1987; 1:937-942.

91. Elwood PC, Sweetnam PM. Aspirin and second mortality after myocardial infarction. Lancet 1979; 2:1313-1315.

92. Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. Circulation 1980; 62:53-58.

93. Second International Study of Infarct Survival. Collaborative Group: Randomized trial of intravenous streplokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349-360.

94. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, Hughes SJ, Renton R. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. Br Med J 1974; 1:436-440.

95. The Coronary Drug Project Research Group. Aspirin in coronary heart disease. J Chronic Dis 1979; 29:625.

96. The Coronary Drug Project Research Group. Aspirin in coronary heart disease. Circulation 1979; 62:59-62.

97. Breddin K, Loew D, Lechner K, uberla K, Walter E. Secondary prevention of myocardial infarction. A comparison of acetylsalicylic acid, placebo and phenprocoumon. Haemostasis 1980; 9:325.

98. Breddin K, Loew D, Lechner K, uberla K, Walter E. The German-Austrian Aspirin Trial: A comparison of acetylsalicylic acid, placebo, and phenprocoumon in secondary prevention of myocardial infarction. Circulation 1980; 62:63-72.

99. Elwood PC, Williams WO. A randomized controlled trial of aspirin in the prevention of early mortality in myocardial infarction. J Ray Coll Gen Pract 1979; 29:413.

100. The Aspirin Myocardial Infarction Study Research Group. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243:661-669.

101. The Aspirin Myocardial Infarction Study Research Group. The Aspirin Myocardial Infarction Study: Final Results. Circulation 1980; 62:79-84.

102. The Persantine-Aspirin Reinfarction Research Group. Persantine and aspirin in coronary heart disease. Circulation 1980; 62:449.

103. The Persantine-Aspirin Reinfarction Study Research Group. Persantine-Aspirin Reinfarction Study: Design, Methods, and Baseline Results. Circulation 1980; 62:1.

104. The Persantine-Aspirin Reinfarction Study Research Group. The Persantine-Aspirin Reinfarction Study. Circulation 1980; 62:85-88.

105. Anonymous. Aspirin after myocardial infarction (Editorial). Lancet 1980; 1:1172-1173.

106. Klimt CR, Knatterud GL, Stamler J, Meier P. Persantine-Aspirin reinfarction study, part II:secondary prevention with persantine and aspirin. Journal of the American College of Cardiology 1986; 7:251-269.

107. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Br Med J 1988; 296:320-331.

108. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J 1988; 296:313-316.

109. The Steering Committee of the Physicians' Health Study Group. Preliminary report: Findings from the aspirin component of the ongoing physicians' health study. The New England Journal of Medicine 1988; 318:262-264.

110. Orme M. Aspirin all round?. Br Med J 1988; 296:6618-6619.

111. Hennekens CH, Hutchison GB. An overview of the British and American aspirin studies. N Engl J Med 1988; 318:923-924.

112. Chesebro JH, Clements I, Fuster V, et al. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 1982; 307:73-78.

113. Chesebro JH, Fuster V, Elveback LR, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. N Engl J Med 1984; 310:209-214.

114. Goldman S, Copeland J, Moritz T, et al. Effect of antiplatelet therapy on late graft patency after coronary artery bypass grafting: V A cooperative study #207(abstract). Journal of the American College of Cardiology 1988; 11:152A-152A.(Abstract)

115. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy. Circulation 1988; 77(6):1324-1332.(Abstract)

116. Gohlke H, Gohlke-Barwolf C, Sturzenhofecker P, et al. Improved graft patency with anticoagulant therapy after aortocoronary bypass surgery: a prospective randomized study. Circulation 1981; 64(suppl II):II-22-II-27.

117. McBride W, Lange R, Hillis R. Restenosis after successful coronary angioplasty: pathophysiology and prevention. N Engl J Med 1988; 318:1734-1737.

118. Schwartz L, Bourassa M, Lesperance J, Aldridge H, Kazim F, Salvatori V, Henderson M, Bonan R, David P. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 1988; 318:1714-1719.

119. Ross AM(ed). Acute Myocardial Infarction: Thrombolysis and Angioplasty: International Workshop. Circulation 1987; 76 (II):II-1-II-88.

120. Verstraete M, Collen D. Thrombolytic Therapy in the Eighties. Blood 1986; 67:1529-1541.

121. Mitchell JRA. Back to the future: So what will fibrinolytic therapy offer your patients with myocardial infarction?. Br Med J 1986; 292:973-978.

122. Rentrop KP. Thrombolytic therapy in patients with acute myocardial infarction. Circulation 1985; 71:627-631.

123. Smith B, Kennedy JW. Thrombolysis in the Treatment of Acute Transmural Myocardial Infarction. Ann Int Med 1987; 106:414-420.

124. Effert S, von Essen R, Hugenholtz PG, Uebis R, Verstraete M, (eds). Facts and Hopes in Thrombolysis in Acute Myocardial Infarction. New York: Springer-Verlag , 1986:1-227.

125. Sobel B, Collen D, Grossbard E, (eds). Tissue Plaminogen Activator in Thrombolytic Therapy. New York and Basel: Dekker, Inc., 1987:1-241.

126. Kakkar VV, Kennedy JW, Mettinger KL, (eds). Coronary Thrombolysis: Current Answers to Critical Questions. London: Current Medical Literature, Ltd., 1988:1-158.

127. Sherry S. Recombinant Tissue Plasminogen Activator (rt-PA) Is it the Thrombolytic Agent of Choice for an Evolving Acute Myocardial Infarction. Am J Cardiol 1987; 59:984-989.

128. Hugenholtz P. Acute Coronary Artery Obstruction in Myocardial Infarction: Overview of Thrombolytic Therapy. Journal of the American College of Cardiology 1987; 9:1375-1384.

129. Simoons M, Brand M, Zwaans C, Verheug FWA, Remme WJ, Serruys PW, Bars F, Res J, Krauss XH, Vermeer F. Improved survival after early thrombolysis in acute myocardial infarction. Lancet 1985; 2:578-581.

130. Gruppo Italiano Per lo Studio Della Stretochinasi Nell'Infarto Miocardio (GISSI). Effectivness of Intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1:397-401.

131. The I.S.A.M. Study Group. A Prospective Trial of Intravenous Streptokinas in Acute Myocardial Infarction. N Engl J Med 1986; 314:1465-1471.

132. European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator in Myocardial Infarction. Effects of thrombolytic therapy on post-MI mortality. Lancet 1988; (in press)

133. Dalen JE, Gore J, Braunwald E, Borer J, Goldberg R, Passamani E, Forman S, Knatterud G, TIMI Investigators. Six - and Twelve -Month Follow-up of the Phase 1 Thrombolysis in Myocardial Infarction. American Journal of Cardiology 1988; 62:179-185.

134. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987; 317:850-855.

135. Gold HK, Johns JA, Leinbach RC, et al. A randomized, blinded, placebo-controlled trial of recombinant human tissue-type plasminogen activator in patients with unstable angina pectoris. Circulation 1987; 75:1192-1199.

136. Sheehan F, Braunwald E, Canner P, Dodge H, Gore J, Van Natta P, Passamani E, Williams D, Zaret B. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) Trial. Circulation 1987; 75:817-829.

137. Collen D, Stump D, Van de Werf F. Coronary thrombolysis in patients with acute myocardial infarction by intravenous infusion of synergic thrombolytic agents. Am Heart J 1986; 112:1083-1084.