Antithrombotic Therapy in Coronary Artery Disease

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In the last two decades, improved treatment of electrical disturbances and cardiac pump failure have reduced mortality after the ultimate, irreversible myocardial event of patients suffering from coronary heart disease: myocardial infarction. However, the major challenge in this field, primary prevention of myocardial ischemia, remains unconquered. The traditional belief that myocardial infarction is due to coronary thrombosis might be challenged by the marginal benefit that anticoagulant, antiplatelet, and fibrinolytic agents have provided. However, the classic view linking the pathogenesis of myocardial infarction to thrombotic disorders is substantiated by recent findings based on objective arteriographic observations. Moreover, there is increasing evidence that coronary thrombosis also plays a pathogenetic role in sudden deaths in patients suffering from ischemic heart disease without myocardial infarction. In light of these considerations, the discrepancy between the formidable effort to reduce morbidity and mortality from myocardial infarction by various antithrombotic strategies and the results achieved is disappointing. But it is not surprising, perhaps, since thrombosis is multifactorial in origin, with a host of pathologic features and many complicated natural regulatory mechanisms. Considering the complexity of the problem, the progress to date must be regarded as promising, even if far from satisfying.

This article will review critically the history and present status of antithrombotic therapy in coronary artery disease. We are confident that new knowledge about the mechanisms leading to coronary thrombosis will in time render most present practices obsolete.

Anticoagulant Therapy

When a variety of coumarin derivatives became available during the 1940s and their role in suppressing the synthesis of Vitamin K-dependent clotting factors was recognized, their use as safe anticoagulants seemed a ready answer to a major clinical problem. It was widely believed that arterial thrombotic events, like venous thrombosis, were the result of "clotting in the wrong place" and that they could be influenced by anticoagulation. Similarly, the most common arterial accident, myocardial infarction, was thought to be caused by coronary thrombosis, which both contributed to the development of atherosclerotic plaques and also precipitated the acute event. It was expected that anticoagulant therapy would limit the growth of thrombi and prevent occlusion of coronary arteries; would reduce the frequency of mural thrombi and of embolization to the brain, kidneys, and limbs; and would prevent deep vein leg thrombosis and pulmonary embolism, which often result from restricted ambulation during convalescence after an acute myocardial infarction.

In 1948, Wright et al. reported less mortality with the use of heparin and dicumarol in the first 6 weeks after myocardial infarction. Although these conclusions were challenged because of an inadequate randomization of patients, they opened an era of enthusiastic clinical trials during the 1950s, most of which are considered deficient by modern study design criteria.

Critics attacked the consistent conclusion of these early studies that anticoagulation reduces mortality after myocardial infarction. As there developed an appreciation of the essentials of a satisfactory clinical trial, further studies provided a different picture. Flawed by retrospective analysis and inadequate randomization, and marked by undertreatment due to overestimation of anticoagulant effect, these studies could not substantiate the previous claims of fewer early deaths after myocardial infarction for patients given anticoagulants. On the other hand, this medication usually achieved a significant reduction of venous thromboembolic complications after acute myocardial infarction.
Doubts might be raised about the pessimistic conclusions of studies in which analysis was limited to the first 48 hours after the acute event, when dysrhythmias or pump failure may have accounted for most of the deaths or when undertreatment might have led to incomplete protection. However, such conclusions are not surprising today, when the pathogenetic events leading to coronary insufficiency are known to involve other processes in addition to thrombosis and when thrombosis itself is recognized to be "hemostasis in the wrong place" with an important platelet component, rather than simply an aberration in plasma coagulation. Moreover, even the most timely anticoagulant treatment cannot change the course of an established thrombotic coronary occlusion, a frequent cause of transmural infarction. The unknown contribution of ventricular mural thrombi to the total mortality of myocardial infarction makes it difficult even today to assess the value of anticoagulant therapy in reducing the size and frequency of such thrombi.

In 1969 and 1970 two milestones marked the controversial history of anticoagulation therapy in secondary prevention of myocardial infarction. An influential paper by Gifford and Feinstein criticized the accumulated literature, stating that only two of 32 clinical studies had satisfied more than half the criteria of adequate trial design and that methodological shortcomings had been especially serious in those studies claiming benefits from anticoagulation. A subsequent report of the International Anticoagulant Review Group (IARG) analyzed 2487 cases from the more promising long-term trials carried out between 1950 and 1965. The 20% reduction of mortality in men given anticoagulants was disappointing, especially as the protection seemed to be restricted to patients with a history of prolonged angina and/or previous infarction.

Despite the publication of later clinical studies, most of which claimed that long-term anticoagulation therapy was protective, the critique of Gifford and Feinstein and the IARG analysis marked the end of an era. The equivocal results of clinical trials that were often of questionable design, the reluctance to use anticoagulants because of uncertainties about the intensity of treatment and monitoring, and changing views of pathogenesis all led to reduced reliance on anticoagulants and increased use of antiplatelet agents. Anticoagulants now were used chiefly to prevent venous thromboembolism after myocardial infarction in patients at high risk because of a previous history of thromboembolism, severe heart failure, or complications requiring prolonged bed rest. Anticoagulants were also used on occasion in patients with preinfarction angina, but there was a pervasive mistrust of their effectiveness against the coronary thrombotic process.

In 1975, two important retrospective studies reopened the question of the effectiveness of anticoagulants in reducing mortality from myocardial infarction. A study of 2330 patients hospitalized in Israel revealed a highly significant reduction in the 21-day mortality rate in patients treated with anticoagulants (8.3%) as compared with those not receiving this therapy (27.3%). There was an inverse correlation between the intensity of the anticoagulant therapy and the case fatality rate in each of the 22 hospitals in the study.

Similarly, a Maryland survey of 1156 patients hospitalized for myocardial infarction showed an in-hospital mortality rate that was 2.5 times lower in patients given anticoagulants than in those who were not. These results were supported by the lower fatality rate in anticoagulated patients enrolled in subsequent randomized well-controlled studies. A new analysis in 1977 considered all previous studies that had included a control group and had recorded in-hospital mortality. These 32 trials were subdivided according to random or nonrandom allocation of patients and, among the latter, according to those using historical and those using simultaneous controls. Although, as expected, the difference in mortality between control and treated patients was less in randomized studies than in nonrandomized ones and less in those with simultaneous control groups than in those with historical controls, the effectiveness of anticoagulants was statistically significant in the combined analysis of the six randomized controlled trials with an estimated 21% reduction in total mortality.

Not surprisingly, there was soon criticism of this analysis and of its recommendation that, in the absence of specific contraindications, all patients hospitalized for myocardial infarction should receive anticoagulants. The pooling of data from different trials was criticized and the conclusions from such an analysis were considered of dubious value for current clinical practice since they were generated from studies done before the use of coronary care units, antiarrhythmic therapy, and early mobilization. Further investigations were in order, a need that was soon satisfied.

In 1979, an extension of a previous retrospective study analyzed the survival of patients with myocardial infarction who had been discharged from 20 hospitals in Baltimore during two time periods. Even after correcting for unbalanced variables that might have led to worse results in the control group, this study confirmed the protection given by anticoagulants administered soon after myocardial infarction (the in-hospital mortality rate was 18% for anticoagulated patients vs 31% for controls). Moreover, a 5-year follow-up study of hospital survivors indicated a persistent, statistically significant lower mortality rate for those treated with anticoagulants during hospitalization.

In the meantime, a controlled randomized double-blind study was carried out on 898 Dutch patients over 60 years of age who had received anticoagulants after a primary myocardial infarction at least 6 months before (mean interval, 5.9 years). One-half of these patients had been randomly chosen to con-
tinue the therapy or to receive a placebo. Both groups were followed for 2 years. Evaluation according to “intention to treat” (including patients who deviated from the protocol) revealed a nonsignificant reduction in mortality in anticoagulant patients (11.6%) vs the control group (15.7%). This difference, however, becomes significant if data are analyzed by “drug efficacy” criteria, which removes from the overall evaluation any major deviations from the protocol. A more impressive result of this study was a significant reduction of recurrent myocardial infarction in the anticoagulant group both with “intention to treat” analysis (11% vs 27%) and with “drug efficacy” evaluation (4% vs 24%).

This study strongly suggests that long-term anticoagulation actually has a long-term protective effect after myocardial infarction and that the effect of treatment is greater than that of short-term therapy. Both the original report and a subsequent analysis showed that, although the incidence of bleeding was higher in anticoagulant patients, this did not influence mortality. The fatal hemorrhages in anticoagulant patients (intracranial bleeding in 0.91%) were balanced by the more frequent occurrence of stroke in the control group, confirming previous reports.

Other studies have shown that anticoagulants have a protective effect on cerebral and peripheral embolization. For example, the Veterans Administration Trial found a significantly lower rate of vascular accidents and of embolization to the kidneys and legs in anticoagulated patients, even though there was an insignificant decrease in the overall mortality. In the past, such data have raised the question as to whether anticoagulation was useful only in the early postinfarction period by preventing complicating thromboembolism. The Sixty-Plus Reinfarction Study indicated that such protection was long-term, preventing embolization long after myocardial infarction and also lowering mortality by preventing reinfarction.

Although these recent studies cannot totally dispel 30 years of doubts and controversies, it seems reasonable to acknowledge some benefit from anticoagulants in the secondary prevention of myocardial infarction. An estimated overall reduction of 10% to 20% in the mortality rate by use of anticoagulants matches the protection ascribed to antiplatelet drugs. Results from further trials specifically comparing these treatments, however, may either support or reject this conclusion.

Since the earliest days of antithrombotic drug treatment of acute myocardial infarction, heparin has often been used in conjunction with oral anticoagulants, but rarely has its effect been analyzed separately. For example, in concluding that early anticoagulation treatment fails to significantly improve survival, but only reduces thromboembolic complications, researchers have not distinguished between oral anticoagulants and heparin. Once studies showed that heparin treatment would not induce ventricular dysrhythmias by increasing free fatty acid levels, several clinical studies addressed the question of preventing venous leg thrombosis by giving heparin after myocardial infarction. Although these studies demonstrated heparin’s protection against venous thrombosis, the number of patients studied was too small to determine the effect of heparin treatment on overall mortality. Moreover, studies to evaluate the therapeutic role of heparin’s nonanticoagulant properties in humans did not confirm the protective effect that large doses of heparin had shown on experimental myocardial injury in dogs.

There is no proof of heparin’s value in short-term treatment after myocardial infarction, but there are several encouraging reports of both primary and secondary prevention of myocardial infarction by heparin. In addition to its well-documented effect against deep vein thrombosis and pulmonary embolism, low doses of heparin have reportedly reduced postoperative myocardial infarctions. While low doses of heparin (5000 IU twice a day subcutaneously) failed to prevent myocardial infarction in patients with unstable angina, higher doses (5000 IU every 6 hours intravenously) alone or in combination with atenolol significantly decreased the rate of infarction not only during the week of heparin administration, but also during the subsequent 2 months, suggesting true prevention rather than merely a delay of the event. The aim of this trial was to assess the relative effectiveness of atenolol and heparin in an intermediate coronary syndrome. Unfortunately, a suboptimal schedule of atenolol administration clouds the apparent lack of effect of this drug. We do not know whether administration of heparin given with effective beta-blockers would improve the prevention of recurrent chest pain or of myocardial infarction.

Long-term heparin administration has shown encouraging results in the secondary prevention of myocardial infarction. Intermittent therapy (20,000 IU subcutaneously twice a week over a period of 2 and 6 years) significantly decreased cardiovascular mortality in two randomized, controlled trials, although recurrence of infarction was not dramatically reduced. Moreover, high doses of heparin provided greater reduction in mortality than oral anticoagulant therapy. Even mini-doses of heparin (5000 to 6000 IU subcutaneously daily) showed a statistically significant advantage over oral anticoagulants, although in this study, the nonrandom allocation of patients could have affected the results.

On the other hand, while poorly designed studies supported a beneficial effect of heparin in secondary prevention of myocardial infarction, two well-controlled trials did not show that intermittent heparin therapy was better than a placebo or oral anticoagulants. At any rate, the suggestion that heparin is beneficial needs better definition, and it is surprising that this issue has received so little notice.

Aside from the general impression that anticoagulant therapy is mildly helpful in coronary artery disease, the foregoing raises many questions.
studies are needed to identify the type of patients and the clinical situations in which anticoagulant agents are most useful, the optimal length and kind of treatment, the best dosages and the specific choice of agents. A better understanding of pathogenesis is also needed.

**Antiplatelet Therapy**

During the 1970s, there was a departure from the earlier prevailing view provided by a new understanding of the pathogenetic mechanisms of arterial thrombosis and arteriosclerosis and a new emphasis on the role of platelets as major participants in these processes. Because of the high shear rates involved in arterial blood flow, platelet adhesion (rather than fibrin formation) is the predominant component of hemostatic reactions occurring at the site of an endothelial injury.

The process may be activated by adenosine diphosphate (ADP), perhaps released from red cells after rupture of an atherosclerotic plaque; exposure of collagen fibers as a result of endothelial cell loss; or other less well-characterized stimuli. Activated platelets provide a self-amplifying system; they release powerful platelet-aggregating agents (ADP, serotonin, thromboxane A₂) and expose membrane lipoproteins for the adsorption and concentration of the coagulation factors Va and Xa. This catalytic function (formerly known as "platelet factor 3") accelerates the intrinsic coagulation pathway. The formation of thrombin further contributes to platelet activation, and the formation of fibrin adds to the growth and stability of the initial plug of aggregated platelets.

Moreover, like fibrin, platelets seem to be involved in the development of atherosclerotic plaques. A "platelet-derived growth factor" has been shown to promote the growth of smooth-muscle cells in culture, a phenomenon now regarded as a model of a possible pathogenetic event leading to the primary atherosclerotic lesion. Other mitogenic factors released by stimulated platelets have also been identified: low-affinity platelet factor 4 (LA-PF4) and platelet basic protein (PBS). With the development of this pathogenetic model came a new strategy for the prevention and therapy of arterial thrombotic and atherosclerotic disease: viz., a de-emphasis of the traditional dependence on anticoagulant drugs and an interest in the exploration and application of agents whose action was directed at altering platelet function.

This therapeutic development was facilitated by the immediate availability of several drugs that were already widely used for other indications, had been proven safe, and had suppressed platelet function (e.g., dipyridamole, a vasodilator; sulfinpyrazone, a uricosuric agent; and aspirin, an anti-inflammatory and analgesic agent). Furthermore, a series of timely discoveries led to even greater enthusiasm: the platelet-inhibitory effect of aspirin was shown to result from its interference with platelet arachidonic acid metabolism and soon after the active derivatives — the powerful platelet-aggregating and vasoconstricting prostaglandin (PG) endoperoxides and thromboxane (TX) A₂ — were identified. This was followed by the discovery of the antiaggregating and vasodilatory substance prostacyclin (PGI₂), produced by the vessel wall. It was proposed that there existed a hemostatic balance between TXA₂ and PGI₂, the prothrombotic activity of the former being offset by the opposite activity of the latter. The prospect of inhibiting platelet TXA₂ formation without suppressing, or while even increasing, PGI₂ production stimulated further pathological research and recent new clinical trials.

Although the primary roles of platelets in arterial thrombosis and of thrombosis in myocardial infarction are still disputed, many experimental and clinical observations support the hypothesis that platelets are directly involved in some of the clinical manifestations of ischemic heart disease. In fact, platelets might not only contribute their mass to occlusive thrombotic deposits, but also provide vasoactive products (thromboxane A₂, serotonin) that might lead to coronary vasospasm. Such considerations have generated an era of large clinical trials of the secondary prevention of myocardial infarction (i.e., prevention of recurrent infarction), which is generally a more satisfactory goal than primary prevention because of the large number of patients needed for a valid trial of the latter. Prior myocardial infarction is the most potent risk factor in identifying a high-risk group of patients in a general population. An ambiguity implicit in this choice, however, is that patients with previous damage to the myocardium can die from many causes other than thrombotic events, which may complicate the evaluation of agents that are tested as antiplatelet drugs.

The Anturane Reinfarction Trial (ART) suffered from this ambiguity. The data from this study of the effect of sulfinpyrazone (Anturane) in patients who had survived myocardial infarction showed not only a reduction of overall mortality and of cardiac deaths, but also a statistically significant fall in sudden deaths, mainly during the first 6 months of follow-up when death may be more frequent from causes other than thrombosis (e.g., arrhythmias or pump failure).

It is of interest that in this study the addition of beta blockers did not improve the efficacy of sulfinpyrazone, although in the placebo group, beta blockers reduced the incidence of cardiac deaths. Since there was no additional protection afforded by the combination of sulfinpyrazone and beta blockers, as compared with either drug alone, it seems possible that both treatments may inhibit the action of the same risk factor, ventricular arrhythmias. As an alternative to the alleged antiplatelet effect of sulfinpyrazone, the antiarrhythmic potential of this drug is suggested by its ability to prevent death in dogs with induced nonthrombotic myocardial infarctions and a high inci-
dence of ventricular arrhythmias. The use of dipyridamole (Persantine) did not have any benefits in the Persantine/Aspirin Reinfarction Study (PARIS). There was a trend toward reduction of total mortality, coronary deaths, and incidence of myocardial infarction for the combination of dipyridamole and aspirin compared with placebo, but this difference did not achieve statistical significance. Aspirin alone was as effective. This is not surprising since dipyridamole is known to inhibit phosphodiesterase, the enzyme that destroys cyclic AMP, a potent natural platelet inhibitor. Aspirin might reduce dipyridamole's potential effectiveness by preventing production of platelet PGD and vascular PGI, both of which otherwise stimulate platelet adenylyl-cyclase to form cyclic AMP. Although not widely accepted, it has been claimed that dipyridamole has a special role in potentiating the effect of vascular PGI on platelet function. This role may be confounded when phosphodiesterase inhibits the negative feedback effect of prostacyclin on further prostacyclin production by the vessel wall. In whole blood, dipyridamole inhibits platelet aggregation induced by either collagen or ADP, an effect not shown in platelet-rich plasma.

The antithrombotic effect of dipyridamole is best shown when it is given in combination with aspirin. Increased patency of aortocoronary bypass grafts occurred after both a short-term and a long-term follow-up in patients given the drug with aspirin. Aspirin alone did not offer the same protection in other studies, but it is possible that the difference may be due to the delay in giving aspirin in the latter studies rather than to the use of dipyridamole. Indeed in two studies, a combination of aspirin and dipyridamole given after the operation failed to provide any benefit.

The combination of aspirin and dipyridamole has been shown to prevent platelet deposition in femoropopliteal prosthetic grafts, although it had no effect on vein grafts. The effect of aspirin and dipyridamole on the long-term patency of human prosthetic grafts is in dispute.

Under some circumstances, dipyridamole may have an antithrombotic effect without aspirin: like aspirin, dipyridamole with an oral anticoagulant reportedly improves the effectiveness of anticoagulant therapy in preventing thromboembolic episodes in patients with prosthetic heart valves. Furthermore, platelet survival in patients with prosthetic heart valves is prolonged by dipyridamole alone, an effect that is potentiated by aspirin.

The negative results of the PARIS trial raise some doubt about the proposed mechanisms of action mentioned above and also about the alleged role of dipyridamole as a vasodilator as an inhibitor of platelet adhesion to subendothelium and collagen, as an agent for prolonging platelet survival, and as a drug that limits the extent of atherosclerotic intimal lesions. It is difficult to endorse the design of an ongoing PARIS II trial that tests prevention of deaths and
nonfatal recurrences of myocardial infarction by a combination of aspirin and dipyridamole compared with a double placebo. This trial is being conducted without any group receiving aspirin alone, although the beneficial trend in the PARIS I trial may be ascribed entirely to aspirin itself. The main purpose of the new trial is to verify data from the first study indicating a 50% reduction in mortality in a subgroup of treated patients who were enrolled within 6 months after myocardial infarction. Even if positive results are obtained, this trial will not elucidate the relative roles of dipyridamole and aspirin.

For historical reasons related to its widespread use,160-162 and because of exciting discoveries made since it was first reported to be a platelet-suppressant agent,107-108 aspirin is the most studied among the antiplatelet drugs. Five major myocardial infarction trials59,163-166 in the past decade, in addition to the PARIS trial, studied aspirin's effectiveness, and others have been undertaken recently.

As usual, these clinical studies differ from each other in many ways, both in design and results. None has provided clear endorsement of aspirin's use, but in the aggregate they strongly support the thesis that aspirin has a modest beneficial effect in this application. Some of the earlier trials59,163,164 were inconclusive because they studied too few patients, but they suggested a favorable trend with aspirin in dosages between 300 mg164 and 1500 mg daily164 in patients who had had a recent59 myocardial infarction, an earlier one,164 or both.163 A significant reduction in mortality was achieved in a subgroup of patients studied in the Medical Research Council Trial163 within 6 weeks of the acute event. The importance of this finding, given the high risk in early convalescence after myocardial infarction, led to a second trial163 among patients admitted during the first month after myocardial infarction (more than 90% enrolled within the first 2 weeks). Although there was some benefit from aspirin (a 20% reduction in mortality and greater reduction of all coronary events), the results were not statistically significant. Meanwhile, a German-Austrian study56 showed a reduction in sudden deaths in the aspirin group, reminiscent of the findings with sulfapyrazone in the ART study.

The Aspirin Myocardial Infarction Study (AMIS)166 is the largest study of aspirin in secondary prevention of myocardial infarction, but it is also the source of the greatest concern. Aspirin was associated with an increased occurrence of sudden deaths and an increased overall mortality. In this trial, patients were admitted to the study late, between 2 months and 5 years after the myocardial infarction. However, there was also no obvious benefit in a smaller subgroup of patients with recent myocardial infarction. Moreover, the only positive result, a reduction of recurrent fatal and nonfatal myocardial infarction consistent with that in most other trials, was interpreted as a consequence of selection due to the increased rate of sudden death in the aspirin group.

Thus, after over a decade of great effort and expense, the message seems disappointing: no definitive advantage has been proven for antiplatelet drugs in the secondary prevention of myocardial infarction. However, when the over 10,000 patients involved in these clinical studies are considered together, they provide a more encouraging conclusion. Together, these studies reported a reduction of around 20% for overall mortality.59 and this was even greater for cardiovascular morbidity. Although this seems a small effect, the general use of aspirin in secondary prevention of myocardial infarction might save several thousand lives every year. A recent tough-minded overall evaluation167 of 10 years of clinical studies arrived at a similar conclusion.

The failure of aspirin to achieve a more striking improvement may have several explanations. Since production of PGI2 by the vessel wall is inhibited by aspirin,168 there is a dilemma as to whether the suppression of such a powerful vasodilating antiaggregatory agent could offset the benefits of inhibition of platelet formation of TXA2, which is characterized by the opposite biological properties, thus limiting the antithrombotic effectiveness of aspirin.169 Attempts to resolve this dilemma through selective inhibition of platelet cyclooxygenase by a low dose of aspirin have given mixed results in vitro,170 in animal models,171 and in humans.172-174 The dosages (between 300 mg and 1500 mg daily) used in clinical trials that have thrombosis as an end-point have never provided clear evidence that aspirin's effectiveness is dose-related. One wonders how much aspirin's effectiveness might be altered by inactive salicylates accumulated after long-term treatment with high doses of aspirin, which might blunt its inhibition of platelet and vascular cyclooxygenase.175,176 Moreover, since there was daily administration of aspirin in all these clinical studies, one cannot assess the relative importance of the reported rapid recovery of PGI2 production by vascular endothelium,169 as compared with that of TXA2 by platelets, which are unable to resynthesize cyclooxygenase177 inhibited by aspirin even at the level of megakaryocytes.106,178 Also, researchers in some studies129,179 have observed a gender-related difference in the antithrombotic action of aspirin. It was claimed that aspirin gives men better protection against thrombotic accidents, and this could account for an underestimation of the efficacy of the drug in large clinical trials that included both men and women.

Although these considerations and other recently proposed pharmacological models160,161 suggest that there might be improved results with aspirin, we should probably not expect any dramatic improvement in the clinical effectiveness of this familiar drug. At best, we face a multifactorial problem with a limited pharmacological tool. Aspirin blocks only one of three known pathways to platelet activation (in addition to the arachidonic acid pathway blocked by aspirin at the level of the cyclooxygenase enzyme, there are pathways that include ADP and possibly platelet-activating factor (PAF) 1-0-alkyl-2-acetyl-sn-glycer-
yli-3-phosphorylcholine or PAF-acether). Even if we assume that platelets have a major role in coronary thrombosis, it is likely that vascular lesions also promote thrombin formation, which stimulates platelets and generates fibrin despite the presence of aspirin. Also, even if we accept thrombosis as the main cause of coronary events, other precipitating factors, such as spasm, may be important. Antiplatelet therapy may have a role in the latter case, since platelet TXA₂ and other vasoactive platelet products may contribute to coronary spasm. The Veterans Administration Cooperative Study showed a dramatic reduction of both mortality and myocardial infarction by aspirin in the treatment of unstable angina, in which transient limitation of blood flow may result from coronary spasm.

Other pathogenetic mechanisms, however, may account for the beneficial effect of drugs in inhibiting platelets, whose role in coronary disease is probably not confined to the vasoconstrictive action of platelet contents. Furthermore, platelets are probably not the only triggers of arterial spasm. Implication of TXA₂ in these events is controversial; despite the association between local release of TXA₂ and coronary ischemia, aspirin's inhibition of TXA₂ synthesis does not influence the frequency of anginal attacks. On the other hand, such episodes have reportedly been reduced by administering ticlopidine, an antiplatelet agent that does not inhibit platelet cyclooxygenase or coronary artery tone. Finally, there seems to be no evidence that aspirin prevents dysrhythmias or pump failure, which are frequent causes of early death after myocardial infarction. Indeed, the occurrence of sudden death was increased in patients receiving aspirin in both the PARIS and the AMIS studies. Perhaps it is time to abandon the search for a single antithrombotic panacea for the problem of coronary disease. Further progress requires not only development of improved antithrombotic drugs (which will demand advances in understanding of platelet physiology and coagulation pathways), but also greater insight into the pathogenetic events, so that the mechanisms of therapeutic interventions may be fully understood.

In the meantime, 50% increased protection against primary myocardial infarctions and 20% fewer recurring myocardial infarctions are sufficiently encouraging results to warrant testing antiplatelet drugs in combination with other measures, such as the administration of anticoagulants and beta-blockers. The combination of antiplatelet agents and anticoagulants has already proved effective in patients with prosthetic heart valves, in whom both dipyridamole and aspirin seem to improve the effectiveness of anticoagulants in preventing thromboembolic events. The same combination might also apply to other high-risk situations, such as aortocoronary bypass grafts. Since the hemorrhagic risk may be greatly increased by combined therapy, pilot studies are necessary to test whether lowering the dosage of aspirin and anticoagulants and closer monitoring of their effects (as recently proposed for heparin) might ensure the safety of this approach.

**Thrombolytic Therapy**

Since attempts to prevent myocardial infarction have yielded disappointing results, treatment of the acute event remains relevant. Advances in the management of electrical disturbances have considerably improved the outcome of acute myocardial infarction, but there is room for advances directly focused on the etiologic events: i.e., the coronary occlusive process. Although it has been claimed that coronary vasospasm has an important role in the pathogenesis of coronary occlusive disease, the prevailing opinion holds to an even stronger association between myocardial infarction — especially transmural myocardial infarction — and thrombotic coronary occlusion. Antemortem recanalization or spontaneous lysis of occlusive thrombi, as well as postmortem thrombolysis or clot retraction, might have generated the conflicting results of necropsy studies, which reported an incidence of coronary thrombosis associated with myocardial infarction ranging from 20% to 90%.

More recent arteriographic findings demonstrated total coronary occlusion in over 85% of cases during the first 4 to 6 hours after the onset of symptoms in transmural myocardial infarction. The occlusion persisted in two-thirds of the cases examined within the first 24 hours, but in the remaining patients it spontaneously resolved. Although this study did not address the question of the relative pathogenetic roles of coronary spasm and thrombosis, when viewed with previous findings, the results strongly suggest that thrombosis is a crucial determinant of the occlusive coronary lesion. In contrast with previous reports, observations that nitroglycerine failed to re-open occluded coronary arteries (which were then recanalized by thrombolytic agents) suggest the major role of thrombosis in coronary artery disease. This interpretation does not, of course, verify or refute the possible role of spasm.

If thrombotic obstruction is a major precipitating event in acute coronary insufficiency, thrombolytic agents might reverse the interruption of oxygen delivery and, to the extent that myocardial injury is reversible, restore the pumping function of the heart. The benefit of fibrinolysis might be limited if platelets, not fibrin, are the major constituent of the thrombi that obstruct the coronary arteries; but even so, the dissolution of a reinforcing fibrin network might favor dispersion of a mass of aggregated platelets. Based on such a theoretical background, clinical studies since have tested the efficacy of systemic thrombolysis in the acute management of myocardial infarction, by intravenously administering streptokinase (SK) or urokinase (UK) as plasminogen activators.
Streptokinase is derived from Group C β-hemolytic streptococci and forms a complex with plasminogen; this complex proteolytically converts further plasminogen to the fibrinolytic enzyme plasmin. The relationship between dosage and fibrinolytic SK activity is unpredictable because of this drug’s complex formation and its susceptibility to inhibition by anti-streptococcal antibodies, resulting from previous streptococcal infections. Moreover, since it is a foreign protein, SK can induce allergic reactions that frequently lead to fever and other symptoms. In contrast, because UK has a human origin, it seldom provokes allergic side effects. (It is produced by human renal cells grown in culture.) Unlike SK, UK is, itself, an esterase and directly converts plasminogen to plasmin. Its use has been limited by its cost, which is several times greater than the cost of SK. Indeed, among 18 trials of systemic thrombolysis in myocardial infarction, only three evaluated UK.

Other writers have previously summarized and reviewed the details of major clinical studies. When several trials address the same clinical question, divergent results may arise from differences in patient selection, in type of therapy, in dosage, in associated treatment and general care, in the interval between the onset of symptoms and interventions, in the length of follow-up, and in the choice and ascertainment of endpoints and their analysis. However, even these variables cannot completely mask the benefits from systemic fibrinolytic intervention in the early phase of acute myocardial infarction.

The largest number of trials have reported equivocal results with systemic SK and only five reported a significant reduction in mortality with the treatment. Among the latter only the Frankfurter and Austrian studies can withstand rigorous criticism of patient allocation and analysis of results. Some trials actually showed more deaths in the thrombolytic treatment groups. Pooled results from randomized trials suggested, however, that there was a reduction of about 20% in the mortality of patients treated with SK as compared with controls. Among trials testing the efficacy of UK, only the French study observed a benefit from intervention, and that was of borderline statistical significance.

Examination of these trials raises many questions. Patient groups were in many cases nonhomogeneous and included those with past as well as impending infarctions. Furthermore, the interval between the onset of symptoms and the administration of fibrinolytic agents was quite variable, ranging from 72 hours in early trials to 12 hours in more recent studies. The critical importance of this variable has become apparent recently as a result of the experience with early intracoronary instillation of SK, detailed below.

Another question concerns the role of general care associated with fibrinolytic treatment. Although the Austrian study showed the lowest mortality among patients treated with SK in coronary care units and the highest in a control group treated on general wards, trials performed exclusively in coronary care units reported no difference in mortality between treated and control groups. In the Frankfurt study, the benefit from SK treatment in general wards equaled that in coronary care units. However, no difference was found between control patients on general wards or in coronary care units. Thus, although there are suggestions that SK infusion adds little to the improved quality of care achieved in coronary care units, this is far from proven.

In 1979 a new approach, direct intracoronary infusion of SK, was introduced to increase the efficacy and reduce the risk of fibrinolytic treatment in myocardial infarction. It is now established that this approach results in rapid recanalization of the thrombosed artery in most patients with acute myocardial infarction. It was hoped that the dose of fibrinolytic agent required for this effect would be much lower than that needed for intravenous infusion and that this would eliminate the hemorrhagic side effects; however, a systemic lytic state does, in fact, occur in virtually all cases. The rationale for this approach was to concentrate the intervention where it was needed, producing a prompt, local thrombolysis and avoiding the consequences of widespread fibrinolysis. If successful, this approach would satisfy several conflicting hypotheses about the fibrinolytic system. A locally increased concentration of SK would be desirable if plasmin is generated inside the thrombus from the action on plasminogen adsorbed to fibrin, from the SK-plasminogen complex diffusing into the clot, or from the plasminogen diffusing into the clot to be acted upon by SK adsorbed to fibrin. On the other hand, if plasmin is generated in the circulation, where its activity is regulated by the balance between its relative affinity for plasma inhibitors (e.g., α-antiplasmin) and that for fibrin, systemic or local administration of SK should make no difference, since plasmin produced anywhere by the SK-plasminogen complex would bind antiplasmin and perhaps be released as a free active enzyme only in the vicinity of fibrin.

This arguable theoretical background notwithstanding, a number of groups have pioneered the use of intracoronary SK infusion in myocardial infarction, and the practice has now become widespread. Much of the available data is collected in two large registries: the United States Streptokinase Registry and the European Society of Cardiology Streptokinase Registry. The results emerging from these registries are impressive: the recanalization rate is about 76%, and the reopening of the thrombosed artery is usually achieved with less than 200,000 U SK and within 20 to 30 minutes of infusion. Mortality is dramatically reduced in patients with successful reperfusion as compared with those in whom recanalization fails or reocclusion occurs: in the former group, mortality was 2.5% in the U.S. Registry and 7.6% in the European Registry; in the latter group, mortality was 18% and 21%, respective-
ly. Bleeding and reperfusion arrhythmias seem to be the principal complications, and both have usually been easily managed. The major limitation of intracoronary SK is that its benefit depends on the interval between the onset of symptoms and the intervention: the longer the former, the less effective the latter.

Recent randomized controlled trials have begun to define the potential benefits of intracoronary SK in acute myocardial infarction. Many of the findings of previous uncontrolled trials have been confirmed, including a high reperfusion rate with early SK infusion (81%) and significant benefit in the radionuclide ejection fraction, echocardiographic wall motion, electrocardiographic changes, and thallium-201 myocardial imaging. A reduction of in-hospital mortality in the SK group (one death as compared to four in the control group) was not significant because of the small size of the trial (only 50 patients).

Another small study involving 40 patients had different results. Thrombolytic treatment still showed a trend toward a lower mortality rate than placebo treatment. However, measurements of ventricular function at the time of intervention, after 12 days, and after 5 months did not indicate any advantage from SK infusion. This was despite the fact that it was more effective than dextran infusion in achieving recanalization (60% vs 10%). The results did not demonstrate any significant difference between cases in which reperfusion was successful and those in which it failed. The conflicting conclusions of these two studies may be ascribed partly to earlier intervention in the former trial (the mean interval between onset of the pain and initiation of SK infusion was 4 hours vs 5.4 hours in the negative trial). Although such a small delay may not seem relevant, its importance is supported by previous clinical findings and by experimental studies suggesting that a delay of less than four hours may be required for successful intervention.

More recently, the Western Washington Intracoronary Streptokinase Trial, a large multicenter, randomized study involving 250 patients, showed a 30-day mortality significantly lower in the SK group than in the controls, although the intervention was delayed up to 12 hours and the rate of reperfusion (68%), similar to that achieved in previous studies utilizing relatively late interventions, was lower than that resulting from earlier infusions. All the 13 control patients who died failed to have reperfusion after catheterization. The five deaths in the SK group occurred among patients with either no recanalization of thrombosed coronary arteries or a severe residual stenosis of reopened vessels. Despite the decisive effect on mortality (persisting at the 6-month follow-up) intracoronary SK did not improve parameters of myocardial function among survivors.

It is difficult to interpret the findings of these recent controlled studies. It might be argued that the frequent failure of late intervention to achieve reperfusion affects the recovery of myocardial function more than the mortality rate, but most of the early deaths seem to be related to the persistence of coronary occlusion. The most successful results were reported in two trials that followed thrombolytic treatment with anticoagulants during hospitalization and then continued for 3 months, or those that used antiplatelet therapy. If prevention of rethrombosis in recanalized vessels is important in such patients, suspending anticoagulants in control patients and in those in whom coronary reperfusion had been unsuccessful might have led to a worse long-term outcome in one of these trials. The usefulness of anticoagulants and antiplatelet agents in preventing reclosure is, of course, also subject to debate.

Enzymatic kinetic studies after SK infusion generally indicate a marked increase in peak plasma levels of CPK, apparently as a result of increased wash-out after reperfusion of an injured area. No reduction of cumulative release of cardiac enzymes has been observed after SK infusion, even when the intervention is timely, the infusion is intracoronary, recanalization is achieved, and cardiac function is improved. Considered with radionuclide evaluations of ejection fractions in injured areas (which often indicate recovery of myocardial function) these findings suggest that thrombolysis cannot prevent irreversible myocardial damage but may limit the size of the infarcted area and improve collateral circulation, even when the restitution of patency of the obstructed vessel may be too late to be effective itself. Spontaneous reperfusion may occur as well, although although SK-induced recanalization appears to improve myocardial function more than spontaneous recanalization, perhaps because of the time of reopening of the vessel.

Many issues remain to be settled: the overall survival, the maximum interval after the onset of symptoms during which the intervention can be successful, the risks due to bleeding and reperfusion arrhythmias, and particularly the risk/benefit ratio of intracoronary infusion as compared with that of intravenous administration. Possibly, the advantage of more effective local administration is vitiated by the delay due to the more time-consuming procedure with its requirement for cardiac catheterization. Furthermore, the hope that local SK infusion might be conducted without induction of systemic fibrinolysis has not been realized. In recent observations, almost all patients receiving intracoronary SK developed systemic fibrinolysis, but this may not have influenced the outcome, since reperfusion was achieved with or without systemic fibrinolysis.

There is generally less bleeding after intracoronary SK although it may be more frequent than in control patients. This is also the case with the systemic approach. Although rare, major bleeding and fatal hemorrhaging have been reported with both intracoronary and systemic SK infusions, and an unusually high incidence of intracranial hemorrhage has been reported with intracoronary infusion.
Intracoronary UK seems to have thrombolytic efficacy equivalent to SK, but induces fewer systemic fibrinolysis and bleeding complications. Other complications of cardiac catheterization may also influence the choice of intracoronary fibrinolytic treatment. Disturbances of cardiac rhythm, usually easily manageable but sometimes fatal, have been reported. Fatal embolization of thrombi during intracoronary SK infusion has also been described.

A reassessment of early systemic fibrinolytic therapy is needed to guide the choice between this and intracoronary intervention in acute myocardial infarction. Such an evaluation should provide information about the rate of recanalization and the incidence of bleeding complications or other undesirable side-effects after systemic fibrinolysis; should indicate whether treatment improves myocardial function, and whether the effect correlates with or is independent of successful recanalization; should indicate how the persistent atherosclerotic narrowing of cleared coronary arteries influences the overall outcome; should define what dose of SK and degree of fibrinolysis are required for a therapeutic effect; and should indicate which parameters can be used for monitoring. For such a study, coronary angiography will be required for patients treated with intravenous agents as well as for those receiving the drug into the coronary arteries.

Although complicated by the possibility of spontaneous recanalization, preliminary observations suggest that early, short-term, systemic infusion of SK can achieve recanalization within 1 hour and improve myocardial function in more than one-half of patients undergoing the treatment. The clinical relevance of this promising result is being assessed by current trials.

One of the more attractive prospects for improved thrombolytic therapy is the use of human extrinsic (tissue-type) plasminogen activator (t-PA). Extracted from uterine tissue or from culture fluid of a cell-line derived from human melanoma, this naturally occurring activator specifically activates plasminogen that is associated with fibrin, thus localizing the formation of the fibrinolytic enzyme, plasmin, to the thrombus. It is thought that systemic plasminemia does not occur, and bleeding complications are expected to be infrequent. As compared with previous fibrinolytic approaches to the treatment of myocardial infarction, t-PA could easily overcome the problems of dosage, route of administration, hemorrhaging and monitoring of fibrinolytic activity, since its effect is specifically limited to the site of thrombus formation.

In addition to its successful use in experimental animal thrombosis, intracoronary or intravenous — t-PA has achieved complete coronary thrombolysis within 10 minutes in dogs and has restored myocardial blood flow without depletion of fibrinogen and plasminogen, as usually occurs with other activators. Tissue activator has already been tested successfully in venous thrombosis in humans. More recently, its use in patients with evolving myocardial infarction has been reported. In this study, t-PA, either intracoronary or intravenous, induced coronary thrombolysis and recanalization within 19 to 50 minutes without concomitant induction of a systemic lytic state. In one of seven patients, neither t-PA nor SK induced thrombolysis. Enthusiasm for this therapeutic approach to thrombolysis has been dampened by the unavailability of t-PA. Sufficient amounts for therapy have thus far been obtained principally from cell lines derived from a malignant tumor and, despite the absence of toxic side-effects, ethical problems have confined its use to patients with life-threatening thromboembolism when other therapeutic tools had failed. The problem of mass production of t-PA may soon be solved by using recombinant DNA techniques.

Another promising candidate as a selective thrombolytic agent is pro-UK, the single-chain pro-enzyme, precursor of UK. Pro-U K has been extracted from human urine and cell cultures, and has been detected in plasma. This precursor of UK resists inactivation by plasma inhibitors and is converted to the two-chain active enzyme by fibrin-stabilized plasmin. Such a mechanism of activation limits the generation of the intrinsic plasminogen activator to the site of a clot. Both in vitro tests and in vivo animal models have shown that pro-U K can induce a more effective and specific fibrinolysis than that provided by UK, avoiding defibrinogenation and bleeding complications following the use of the latter agent. Because of these properties, pro-U K may prove to be a useful therapeutic tool for coronary thrombolysis in humans.

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