Antithrombotic Agents in Coronary Artery Disease

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Each year in the United States there are about 1 million "heart attacks"—a term that includes both acute infarction and sudden cardiac death. Nearly 300,000 victims die before admission to the hospital, and about another 200,000 die in the first month, most of them in the first 24 h after the attack. Thus, the cumulative mortality during the first month is about 50%. During the next 6 months, the cumulative mortality increases another 7–8%, so that by 1 year, another 10% have died. This means that, of the 400,000–500,000 patients who survive the first months, about 10% (40,000–50,000) die during the first year following infarction, generally due to sudden death or recurrent infarction. After patients have survived a year, the reinfarction and death rate stabilizes at 3–5%/year. This rate is similar to that of patients with symptomatic coronary artery disease (ie, angina pectoris) but is significantly greater than that of a randomly selected, age-matched population without overt coronary artery disease that has a 1% yearly incidence for those events.

Ideally, one would like to intervene before AMI occurs. However, a level I primary prevention trial in an unselected population requires many thousand patient years of study to detect a clinically important reduction in mortality or infarction if the frequency of those events is about 1%/year. The cooperative trial that tested the efficacy of clofibrate in reducing the incidence of MI or sudden death is a good example of such a primary prevention trial. Apart from the enormous cost involved in a trial requiring thousands of patient-years, the design of a level I primary prevention trial to test the efficacy of antithrombotic drugs must also address the difficult question of drug safety. For example, one would clearly hesitate to subject 99% of a normal population to the hazards of anticoagulant therapy to prevent MI or sudden death in the remaining 1%.

Secondary prevention level I studies involving survivors of MI are more practical than primary prevention studies. Although these patients are late in their disease process, they have had a clear-cut marker event for future thromboembolic events. Because of the increased frequency of reinfarction or death, the number of patient-years required to detect a significant drug effect is substantially fewer than in primary prevention trials. Nevertheless, several thousand patient-years are still required to detect a 30–50% reduction in the frequency of events, necessitating multicenter trials.

Even within the relatively well-defined study population of postinfarction survivors, important points must be considered in designing and interpreting secondary prevention trials. The prognosis after discharge from the hospital can be dramatically different when patients are stratified based on the presence of certain factors. Patients at high risk of dying have LV dysfunction, complex ventricular ectopic activity, and an anterior infarction; their mortality for the first year is about 19%. Those in the low-risk group have none of these factors, and only about 3% die in the first year. Obviously, the groups under investigation need to be well matched with respect to these and other risk factors.

The mortality curves following discharge from the hospital of patients who have had AMIs clearly show increased mortality in the first 2 weeks to 6 months; after that time, the curve parallels that of patients with stable coronary artery disease. Fatalities in the first 6 months after MI are generally due to pump failure, sudden cardiac death or recurrent infarction. It is clear that a secondary prevention trial involving patients who had a MI more than 6 months previously selects individuals who have already survived the greatest period of risk, whereas a study that involves patients in the first weeks following infarction selects a population initially at higher risk. Therefore, the time of entry into a study is important in the evaluation of therapeutic agents in the secondary prevention of MI.

Effectiveness of Anticoagulant Therapy on Reducing Morbidity and Mortality in AMI

Few subjects have engendered as much controversy as the use of anticoagulants in AMI. Anticoagulant therapy was accepted enthusiastically in the treatment of AMI after the first large clinical trial report was published in 1948. This enthusiasm persisted for approximately 2 decades, during which time it would have been considered unethical not to use anticoagulants in patients with AMI. The popularity of anticoagulant therapy in AMI began to wane in the late 1960s and early 1970s, coincident with the publication of several large, randomized studies evaluating anti-
coagulant therapy in the treatment of AMI. Critical review of the evidence for the possible value of anticoagulant therapy in AMI suggests that neither the initial enthusiasm, nor its subsequent decline, are justified by the published reports.

Clinical trials have evaluated anticoagulants both for the early and the long-term treatment of AMI. In this review we discuss only the randomized trials that entered sufficient numbers to have a reasonable chance of demonstrating clinically important differences in mortality, reinfarction, or clinically relevant systemic or pulmonary embolism.

**Short-term Anticoagulant Therapy**

Since 1948, there have been over 30 reports on the use of anticoagulants in AMI. Three of the randomized trials were of sufficient size to have an 80% chance of demonstrating a mortality or morbidity reduction of 50%. None of the studies was sufficiently large to have a greater than 80% chance of demonstrating a 20% reduction, had that occurred. One study reported a statistically significant difference in mortality. Thus, of these 3 studies, 1 was a level I study and the other 2 were level II studies in regard to demonstrating mortality reduction and/or reinfarction. Since it is probable from the results of pooled analysis that the expected improvement in mortality or reinfarction attributable to anticoagulants is much less than 50% but could be 20%, all 3 studies lacked statistical power for demonstrating clinically important differences. Only the results of these 3 large, randomized, controlled trials, summarized in Tables 1–3, will be considered here. When these trials were performed, isoenzymes were not available, and therefore the diagnosis of reinfarction was not reliable.

**Medical Research Council Trial:** This study was a single-blind, controlled trial in which 1,427 patients with AMI were randomized into an anticoagulant therapy group or control over a 28-day period. Patients of all ages and both sexes were enrolled. More than 92% of the randomized patients had definite or probable MIs by clinical and ECG criteria. Patients were randomized as soon as possible after admission to either a high- or very low-dose anticoagulant group. The time intervals between onset of symptoms and randomization into the anticoagulant groups were not stated. Patients assigned to the high-dose anticoagulant group received 14 heparin in an initial 15,000-unit bolus followed by 10,000 units every 6 h for up to 5 doses. Phenindione therapy was begun at the same time, and both anticoagulants were administered for the first 36 h of hospital admission. Phenindione was adjusted to maintain the thrombostest level between 20% and 10% (INR = 1.6–2.1). The comparison group received no heparin but was given small homeopathic doses of phenindione. The groups were evenly matched for important prognostic variables. The total case fatality rates were 18% in the comparative group (low-dose anticoagulants) and 16.2% in the full-dose anticoagulant group (INR = 1.6–2.1). Reinfarction occurred in 13% of patients in the comparative group and 9.7% in the high-dose anticoagulant group. Both

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**Table 1—In-hospital Mortality in Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
<th>Level of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronx Municipal</td>
<td>Control (391) vs Phenindione (745)</td>
<td>.21</td>
<td>30 &lt;0.005</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>MRC (BMJ 1979)</td>
<td>Control (715) vs Phenindione (712)</td>
<td>.18</td>
<td>11 NS</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>VA Coop (JAMA 1973)</td>
<td>Control (496) vs Coumadin (500)</td>
<td>.112</td>
<td>14 NS</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2—Incidence of Stroke in Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
<th>Level of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Coop</td>
<td>Control (496) vs Stroke</td>
<td>.002</td>
<td>75 &lt;0.005</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>MRC</td>
<td>Control (715) vs Stroke</td>
<td>.005</td>
<td>55 .037</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Bronx Municipal</td>
<td>Control (391) vs Stroke</td>
<td>.023</td>
<td>24 NS</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

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of these outcomes were assessed within 28 days of admission. Thus, the combined end points of mortality and reinfarction occurred in 31% of patients in the comparative group and in 25.9% of patients in the high-dose anticoagulant group (a 16% reduction, which was not statistically significant). Patients receiving anticoagulants had a statistically significant lower incidence of clinically diagnosed pulmonary embolism (5.6–2.2%) and a significant reduction in stroke (2.5–1.1%). Hemorrhage was significantly more frequent in the anticoagulant group (5.1%) than in the comparative group (1.3%), but none of these hemorrhagic events was fatal.

**Bronx Municipal Hospital Center Trial.** In this study 1,136 patients of both sexes with AMI were randomized to either anticoagulants or placebo in a single-blind fashion within 24 h of hospital admission and followed up for an unspecified period. Sixty-one percent of the study patients were found to have evidence of AMI by the study criteria. Patients in the anticoagulant group received 200 mg of phenindione and 5,000 units of heparin IV. Heparin, 10,000 units subcutaneously, was then given every 8 h to a maximum of 5 doses, and the dose of phenindione was adjusted to keep the PT between 2 and 2.5 times control (human brain thromboplastin) (INR = 2–2.5). All control group patients received an identical placebo. The control and treatment groups were comparable with regard to clinically important prognostic variables. The case fatality rate was 21.2% in the control group and 14.9% in the group receiving anticoagulants, a statistically significant difference (p<0.05). On subgroup analysis, the effectiveness of anticoagulants appeared to be restricted to women. Reinfarction occurred in 13% of the control group and 11.8% of the treated group (NS). Pulmonary embolism (diagnosed clinically) occurred in 6.1% of patients in the control group and in 3.8% of those treated with anticoagulants (NS). Stroke occurred in 2.3% of control patients and 1.7% of those treated with anticoagulants, a nonsignificant difference. There was a significantly higher frequency of hemorrhage in the anticoagulant than control group, but none of these hemorrhagic complications was fatal.

**Veterans Administration Cooperative Study.** In this trial, 999 men with AMI admitted to the VA Hospitals throughout the United States were randomly allocated to treatment or placebo groups. Patients were entered within 72 h of the onset of symptoms. The anticoagulant-treated group received heparin, 10,000 units subcutaneously, with further dosage adjustments according to the clotting time. Warfarin therapy was begun at the same time, and heparin was discontinued when the PT (human brain thromboplastin) was >25 s or greater (INR >2). Warfarin therapy was continued for 28 days. The control patients received placebos similar in appearance to heparin and warfarin. The in-hospital mortality rates were 11.2% in the control group and 9.6% in the anticoagulant treatment group (NS). Reinfarction occurred in 4% of patients in the control group and 2% in the anticoagulant-treated group (NS). But there were marked, statistically significant differences in the frequency of pulmonary embolism and stroke between the control group and those treated with anticoagulants. Pulmonary embolism occurred in 2.6% of patients in the control group and in 0.2% of the group treated with anticoagulants, while stroke was reported in 3.2% of patients in the control group and in 0.8% of the group receiving anticoagulants.

**Retrospective Studies:** Support for the use of anticoagulant therapy to reduce hospital mortality was provided by 3 retrospective analyses carried out in the 1970s that reported a 2- to 3-fold reduction in mortality in patients treated with anticoagulants compared with nontreated controls. Because of their methodologic difficulties, these studies can be considered, at best, to be only suggestive.

Further support for the use of anticoagulant therapy to reduce mortality was presented by Chalmers and associates, who reanalyzed the results of adequately designed, randomized studies of AMI and concluded that when the data were pooled there was an overall reduction in mortality of 21%. Despite the methodologic problems associated with pooling, these findings, plus the trends in case fatality rates in 2 of the 3 large studies and the significant reductions in mortality in the third, suggest that anticoagulants may produce a modest reduction (approximately 20%) in early mortality in patients with AMI.

**Rationale for the Short-Term Use of Anticoagulants**

The theoretical rationale for the early use of anticoagulants in patients with AMI is: (1) to prevent extension of coronary artery thrombosis with the expectation that this might reduce mortality by limiting infarction size and prevent reinfarction; (2) to prevent systemic emboli that arise from mural thrombi, a frequent complication in patients with transmural anterior MI; and (3) to prevent the development of venous thrombosis and pulmonary embolism.

The primary end points of studies of the early use of anticoagulants in patients with AMI were in-hospital mortality and reinfarction. It is now clear from the results of recent studies of coronary angiography performed in patients with AMI that 70–80% of patients entered into these trials of short-term anticoagulant therapy would have had an occlusive thrombus before anticoagulant therapy began. Even if anticoagulants prevent extension of coronary artery
Table 3 - Thromboembolic Complications of Acute Myocardial Infarction*

<table>
<thead>
<tr>
<th>Thromboembolic Complications</th>
<th>Heparin (n = 105)</th>
<th>Placebo (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombosis</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Mural thrombosis (autopsy)</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

*Steffensen 1969. Double-blind study of sc heparin, 10,000 bid, 212 patients (level I).

Table 4 - Thromboembolic Complications at Autopsy*

<table>
<thead>
<tr>
<th>Autopsy Findings</th>
<th>Anticoagulant (371 Patients, 85 Dead, 84 Autopsies)</th>
<th>No Anticoagulant (427 Patients, 109 Dead, 92 Autopsies)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>4/54</td>
<td>5%</td>
<td>26/92</td>
</tr>
<tr>
<td>Mural thrombosis</td>
<td>20/54</td>
<td>24%</td>
<td>53/92</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>3/84</td>
<td>4%</td>
<td>54/92</td>
</tr>
<tr>
<td>Estimated mortality from thromboembolism</td>
<td>5/371</td>
<td>1.4%</td>
<td>17/427</td>
</tr>
</tbody>
</table>


Thrombosis, it is unlikely that they would modify infarction size, thereby influencing the major determinant of early mortality of patients who are admitted to a hospital with AMI. It is possible, however, that anticoagulants could be of benefit, were they to reduce the frequency of rethrombosis in coronary arteries that have spontaneously recanalized, thus decreasing the rate of reinfarction. In fact, anticoagulants were highly effective in reducing the frequency of stroke (presumably due to systemic embolism) and pulmonary embolism, findings that are supported by other studies (see below). These 2 complications of MI, however, are relatively uncommon causes of serious morbidity or mortality and therefore have only a minor influence on mortality.

**Effectiveness of Short-term Anticoagulants in AMI**

**Mortality**

Most in-hospital deaths in patients admitted with AMI are from cardiac failure caused by extensive myocardial damage or from acute dysrhythmias. A relatively small proportion (approximately 10%) are caused by systemic embolism (usually stroke) and an even smaller proportion by pulmonary embolism. It is not surprising, therefore, that clinical trials have reported only a modest reduction in mortality except 1 study in which mortality in females was significantly reduced.

**Systemic Embolism**

Cerebral embolism occurs in 2–4% of untreated patients following MI. Approximately 7% of these embolic events lead to death or serious morbidity (Table 2). Systemic embolism to other organs such as kidney, spleen, and extremities, is more difficult to diagnose, and causes morbidity in only a very small proportion of patients with AMI. There is good evidence based on 2 level I studies and 1 level II study that less intense anticoagulant therapy (INR = 2.0, equivalent North American thromboplastin ratio, 1.3–1.5) reduces the frequency of stroke due to presumed cerebral embolism. Supporting evidence is based on 1 level I study and 1 level III study (Tables 3 and 4), demonstrating that anticoagulant therapy reduces autopsy evidence of both mural thrombosis and systemic embolism. In the 3 large randomized studies, there was a statistically significant reduction in stroke in 2 and a nonsignificant trend in the third (Table 2). The relative risk reduction for stroke in the anticoagulant treated group in these 3 studies was 55% for the MRC Study (p < 0.01), 24% for the Bronx Municipal Hospital Center Study (NS) and 75% for the Cooperative Veteran Administration Trial (p < 0.001). Thus, 2 of the 3 level I studies demonstrated a significant reduction in stroke in the patients treated with anticoagulants. The results of these 3 large clinical trials are supported by findings in smaller studies and by the results of autopsy studies (Tables 3 and 4) as well as by more recent reports.

There have been 6 published reports since 1982 on the risk of systemic embolism in patients with AMI (Table 5). Four of the studies identified the embolic risk in anterior MI and 3 reported on the frequency of associated mural thrombosis detected by echocardiography. Only 2 of the studies included sufficient numbers of patients to provide narrow confidence intervals on the observed rates. On the basis of these 2 studies, the risk of stroke is likely to be between 1% and 3% for all infarctions and between 2% and 6% for patients with anterior MI. Two-dimensional echocardiographic studies have shown that left ventricular mural thrombus rarely occurs with inferior MI, but will develop in 35% of patients with AMI. Thrombi are more likely to form with large infarctions or when LV function is poor. Mural thrombi tend to occur early after MI, even during the first 24 h, but may not occur until after 1 or 2 weeks. Clinically overt systemic thromboembolism, usually manifesting as stroke, will occur in about 20% of patients who have LV thrombus after MI.

Mural thrombus will develop in about 40% of
patients with apical akinesis or dyskinesis demonstrated by the initial echocardiogram after AMI.\textsuperscript{38,41-43} Left ventricular thrombus is almost always accompanied by apical wall motion abnormality. A mural thrombus that is protruding into the LV cavity, is freely mobile, or protrudes and is also freely mobile is more likely to embolize.\textsuperscript{44,45} Two-dimensional echocardiography is 77–92% sensitive and 84–94% specific in the diagnosis of LV thrombus.\textsuperscript{38-40} The major limitation is the technical quality of the echocardiograms that may be inadequate in up to 20% of cases.

Three studies have been published that examined the frequency of systemic embolism during anticoagulant therapy vs no treatment in patients with acute myocardial infarction and mural thrombosis.\textsuperscript{35,39,40} All were retrospective studies (level V), and all were far too small to provide reliable information, although their conclusions were that anticoagulants protected patients from systemic embolism (Table 6).

The intensity of anticoagulant therapy required to prevent arterial embolism is uncertain, but most studies used full doses of heparin followed by less intense warfarin (INR, 2.0–2.5). In 1 study (level I) a moderate dose of heparin (10,000 units subcutaneously twice daily for 16 days) reduced the frequency of arterial embolism (see Table 3).

Most studies demonstrate that systemic embolism is an early occurrence following AMI, usually within two months of the acute event.\textsuperscript{35,41} More recently, Stratton et al\textsuperscript{69} reported a 13% incidence of systemic emboli occurring throughout a 4-year period in patients with associated poor LV function (EF av = 0.3).\textsuperscript{49}

Although most studies support the effectiveness of anticoagulant therapy in preventing systemic emboli,\textsuperscript{35,38,50,51} some have questioned this.\textsuperscript{52,54} One reason for incomplete protection might be the lack of adequate anticoagulation immediately following AMI. Thus, initial IV heparin therapy should begin early and be maintained until oral warfarin, begun at the same time, establishes therapeutic anticoagulation.

Patients at high risk of systemic embolism are those with anterior infarction, especially in the presence of wall motion abnormalities.\textsuperscript{35,38,41} In this group of patients the prevalence of LV thrombosis is approximately 30–40% (Table 5).\textsuperscript{35,50-54} Other risk factors are large infarction size, presence of a dilated and poorly functioning left ventricle, AF, cardiac failure, and acute ventricular aneurysm. Patients with inferior infarctions are at a low risk for systemic embolism. Most systemic thromboembolic events occur within the first 3 months of acute infarction.

The role of 2-dimensional (2D) echocardiography in predicting the risk of systemic embolism is uncertain for several reasons. The relationship between the presence or absence of mural thrombosis or wall motion abnormalities (detected by 2D echocardiography) and systemic embolism has not as yet been assessed by a prospective cohort study of adequate size. Although the results of several small studies suggest that the risk of systemic embolism is low in the absence of mural thrombosis detected by 2D echocardiography,\textsuperscript{55} it would be premature to accept these preliminary observations and to limit anticoagulant therapy to patients with anterior MI who have demonstrable mural thrombus. This is because 2D echocardiography may fail to detect up to 20% of mural thrombi\textsuperscript{55,56} and because the presence of LV thrombus depends on the timing of the 2D echocardiographic study. Finally, it has not yet been unequivocally demonstrated that patients with AMI but without 2D echocardiographic evidence of mural thrombus have a very low risk of systemic embolism.

It is recommended, therefore, that anticoagulant treatment for the prevention of systemic embolism after anterior AMI be maintained for 3 months; for

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**Table 5—Embolism/Stroke and Acute Myocardial Infarction—Recent Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% All MI</th>
<th>% Anterior MI</th>
<th>% Mural Thrombi†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinreich et al (1984)</td>
<td>261</td>
<td>1.7</td>
<td>4.0</td>
<td>22</td>
</tr>
<tr>
<td>Ezekowitz et al (1984)</td>
<td>41</td>
<td>7.3</td>
<td>14.0</td>
<td>20</td>
</tr>
<tr>
<td>Komrad et al (1984)</td>
<td>740</td>
<td>2.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Johannessen et al (1983)</td>
<td>54</td>
<td>5.5</td>
<td>9.4</td>
<td>—</td>
</tr>
<tr>
<td>Keating et al (1983)</td>
<td>49</td>
<td>4.0</td>
<td>6.8</td>
<td>43</td>
</tr>
<tr>
<td>Friedman et al (1982)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*BRAIN embolism within 28 days of MI, except Keating et al and Friedman et al, who included brain and systemic embolism.
†Patients with mural thrombi detected by echocardiography who did not receive anticoagulants.

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**Table 6—Acute Myocardial Infarction, Mural Thrombi, and Embolism**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up Period, mo</th>
<th>Nonanticoagulated</th>
<th>Anticoagulated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Embolism</td>
<td>N</td>
</tr>
<tr>
<td>Weinreich et al 1984</td>
<td>4</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Keating et al 1983</td>
<td>3</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Friedman et al 1982</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Aggregate (%)</td>
<td>4</td>
<td>27</td>
<td>14 (52)</td>
</tr>
</tbody>
</table>

*Retrospective studies of consecutive patients, selection of anticoagulation was nonrandomly done. Mural thrombi were detected by echocardiography; includes brain and systemic emboli.
patients in congestive heart failure or in whom LV function is significantly reduced, anticoagulant treatment should continue long-term.

Since thromboembolic stroke is frequently disabling, it is preferable to start anticoagulant therapy before a thrombus develops. The decision to begin anticoagulant drugs in patients with AMI could be made on the basis of apical wall motion abnormality demonstrated by 2D echocardiography, or, if unavailable, by the presence of a large anterior MI, particularly if associated with AF, cardiac failure, dilated left ventricle, or an acute LV aneurysm.

Thrombus is very commonly associated with chronic LV aneurysm (48–66% in surgical studies).\textsuperscript{57,58} However, systemic arterial emboli are infrequent (4–5% by preoperative history). In a retrospective study of 89 patients with LV aneurysm, 20 were treated with anticoagulants for 40 patient years and 69 were not so treated for 288 patient years.\textsuperscript{59} Only one patient, who was not receiving anticoagulants, had a clinical embolic event, an incidence of 0.35/100 patient years. On the basis of this study, therefore,\textsuperscript{59} chronic LV aneurysm, even if it contains thrombus, does not justify chronic anticoagulant therapy.

Venous Thromboembolism

The risk of clinically diagnosed pulmonary embolism was reduced in all 3 of the large randomized studies of anticoagulants in AMI. The incidence was reduced, 5.6–2.2%, in the British MRC study (p<0.01),\textsuperscript{13} 6.1–3.8% in the Bronx Municipal Center Study (NS),\textsuperscript{14} and 2.6–0.2% in the Veterans Administration Cooperative Trial (p<0.005).\textsuperscript{15} The clinical diagnosis of pulmonary embolism is notoriously unreliable and subject to bias, and, therefore, the results of these studies cannot be considered definitive. Nevertheless, the findings of these 3 studies are supported both by autopsy data (Tables 3 and 4)\textsuperscript{32,33} and by the results of several studies using \textsuperscript{18}F fibrinogen leg scanning to detect venous thrombosis in patients with AMI.

Hemorrhagic Complications

Hemorrhagic complications were recorded in the 2,348 patients who were randomized into anticoagulant therapy in the 3 large trials.\textsuperscript{13-15} Minor bleeding occurred in 7% of patients, major bleeding in 1.5%, CNS bleeding in 0.05%, and fatal bleeding in none.

Low-Dose Heparin in the Prevention of Venous Thrombosis Following MI

Three studies have assessed the efficacy of low-dose heparin following MI. In 1978, Marks and Teather\textsuperscript{60} reported the results of a level I study in which 81 postinfarction patients were randomized to receive low-dose heparin (7,500 units subcutaneously twice daily) or to serve as a control group. Thrombi (detected by fibrinogen leg scanning) occurred in 14 patients in the control group and in 2 in the low-dose heparin group, a statistically significant difference. Similar results were reported by Warlow et al in 1973.\textsuperscript{61} In contrast, Handley,\textsuperscript{62} in a level II study, randomized 50 patients to heparin (7,500 units subcutaneously every 12 h for 7 days) or to a control group. Venous thrombosis (detected by fibrinogen leg scanning) developed in 29% of the controls and in 23% of the treated patients, a statistically nonsignificant difference. Possible reasons for the differences between the results of this study and the studies previously reported include the small number of patients entered into the Handley study (a total of 50 among both groups) and the design of the study. Patients were monitored for 2 weeks but received heparin only for 1 week.

Therapeutic Doses of Heparin in the Prevention of Venous Thrombosis Following MI

In most early studies, the diagnosis of venous thrombosis or pulmonary embolism was made using subjective criteria. These studies will not be summarized here. Three groups of investigators assessed the effectiveness of “therapeutic” doses of heparin followed by oral anticoagulants,\textsuperscript{63-65} using objective end points. All reported a significant reduction in the incidence of venous thrombosis.

There is good evidence, therefore, that low-dose anticoagulant therapy (heparin 5,000–7,500 units subcutaneously twice daily) is effective in reducing venous thromboembolism in patients with AMI.

Risk and Benefits of Short-Term Anticoagulant Therapy

Approximately 600,000 patients are admitted to coronary care units in the United States each year with AMI. If death due to pulmonary embolism or systemic embolism occurs in 2% of these patients and anticoagulant therapy reduces this mortality by 50%, then 6,000 lives/year could be saved. Additionally, if 1% of patients suffer a nonfatal but disabling cerebral embolus, and anticoagulants are 50% effective in preventing cerebral embolism, an additional 3,000 patients could benefit from anticoagulant therapy.

The major risk of short-term anticoagulant therapy is hemorrhage. In the 3 large trials,\textsuperscript{13-15} there were no hemorrhagic deaths reported in approximately 2,000 patients. Thus, there is less than a 5% chance that the true rate of fatal hemorrhage would be 0.15% or greater, a finding that would not negate the potential benefits of anticoagulant therapy in reducing mortality and serious morbidity from thromboembolism.

None of the studies performed to date demonstrated a reduction in total mortality of 20%. It is highly unlikely that a study with a sufficiently large sample
size will ever be performed, since it would require over 10,000 patients to demonstrate a statistically significant difference of 8 of 10 times, if the true reduction in mortality is 20%.

In summary, therefore, if all patients with AMI were treated with anticoagulants for 3 months, over half a million patients would require such therapy to prevent death or major morbidity in 7,000–10,000 patients.31

Reduction in mortality from pulmonary embolism may be achieved with low-dose heparin during hospitalization. A reduction of morbidity or mortality from stroke can be achieved with full doses of anticoagulants for the first few months after AMI. It would be reasonable, therefore, to limit the longer course of full-dose anticoagulant therapy to patients who are admitted to hospital with acute transmural anterior MI; low-dose heparin should be given the remaining patients with inferior or nontransmural anterior MI.

**Long-term Anticoagulant Therapy After AMI**

Since the introduction of long-term anticoagulant therapy for survivors of AMI in the late 1940s, many observational studies and clinical trials have been performed. Because the incidence of death and reinfarction greatly lessens once patients are discharged from hospital, long-term trials require even larger numbers of patients than the short-term trial to detect true differences at conventional levels of statistical significance. Most studies evaluating long-term anticoagulant therapy have been methodologically inadequate.32 Three trials were large enough to have an 80% chance of demonstrating a 50% difference in death or reinfarction at a 5% probability level.33,34 None was large enough, however, to be able to demonstrate a 20% difference. The 3 trials were the Medical Research Council Trial,31 the Veterans Administration Cooperative Trial,32,33 and the German/Austrian Multi Centre Clinical Trial.34

**Medical Research Council Trial.**31 This randomized trial performed between 1955 and 1962 included 325 men and 58 women aged 40–69 years. Patients were recruited approximately 4–6 weeks after hospital admission for acute transmural MI. It should be noted that nearly all had received anticoagulant therapy while hospitalized before entry into the study; 195 patients were randomly allocated to receive high-dose anticoagulant therapy (N = 195), adjusted to maintain the PT using human brain thromboplastin 2–2.5 times the control (INR 2.0–2.5). The control group of 188 patients received a daily dose of 1 mg of phenindione (equivalent to 0.1 mg of warfarin) too small to influence blood coagulation. There were 8 participating centers, and the patients in the 2 treatment groups were well matched for important prognostic variables. The trial continued for a 3-year period of follow-up (Table 7). During this time, there was a 30% reduction in the case fatality rate in the treated group, which was not statistically significant. The benefit appeared most marked during the first 6–12 months following hospital discharge and tending to disappear over the remaining 2 years of follow-up. There was a significant reduction in recurrent MI, 39.9% in control patients compared with 20.5% in the anticoagulant-treated group (p < 0.001) during the 3-years of follow-up. Thromboembolic episodes (mainly systemic embolism) also occurred significantly less frequently in patients who received full-dose anticoagulants, while hemorrhagic events were significantly more frequent in those receiving full-dose anticoagulants.

**Veterans Administration Study.**32,33 This clinical trial, 1957–64, consisted of 747 male patients randomized within 21 days of hospital admission for AMI in 15 VA Hospitals to receive either long-term anticoagulant therapy or placebo. All received anticoagulant therapy during their initial hospital phase and were then randomized to receive either warfarin or placebo after discharge from hospital. The dose of warfarin was adjusted to maintain the PT (human brain) within 2–2.5 times control (probable INR 2–2.5). The patients

<p>| Table 7—Effect of Long-term Anticoagulant Therapy on Case Fatality Rates in Myocardial Infarction |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
<th>Level of Study</th>
</tr>
</thead>
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<tr>
<td>MRC [BM 1964]</td>
<td>Control (185) vs AC (195)</td>
<td>.213</td>
<td>Death</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>German-Austrian (Ca 1980)</td>
<td>Phenindione control (309) vs AC (320)</td>
<td>.149</td>
<td>Death</td>
<td>-6-66</td>
<td>NS</td>
</tr>
<tr>
<td>VA Coop (JAMA 1969)</td>
<td>Phenprocoumon control (350) vs AC (385)</td>
<td>.12</td>
<td>Death over trial</td>
<td>-65-30</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Bishydroxycoumadin (or warfarin)</td>
<td>.31</td>
<td>period</td>
<td>(-16-25)</td>
<td></td>
</tr>
</tbody>
</table>
were followed for 7 years. The mortality rate was significantly less at 3 years in the group treated with anticoagulant therapy (p<0.01), but after 3 years the mortality rates were relatively similar. At the end of 7 years of follow-up the mortality rates were almost identical (42% in the control group and 40% in the anticoagulant-treated group). There was a 25% reduction in the rate of recurrent myocardial infarction in the group treated with anticoagulants (NS). Stroke and other thromboembolic episodes were reported more frequently in the control group (p<0.05).

**German-Austrian Center Clinical Trial.** This clinical trial evaluated 2-year case fatality rates in patients with AMI who were randomly assigned to phenprocoumon (n=320), acetylsalicylic acid (n=317), or placebo (n=309) therapy between 1970 and 1977. Men and women aged 45–70 years were recruited within 30 and 42 days after MI. The dose of phenprocoumon was adjusted to maintain the thrombotest between 1.2 and 5% or the PT between 25–15% of control (INR 2.5–5.0). Patients treated with acetylsalicylic acid received 1.5 g daily, while those patients in the placebo group received no active drug. The 3 groups were well matched for prognostic variables, with no significant differences in case fatality rates, fatal or nonfatal recurrent MI, or coronary mortality rates, although there were trends in favor of aspirin use in both the case fatality rate and recurrent myocardial MI in both the aspirin and phenprocoumon groups. There was a nonsignificant trend for a reduction in fatal and nonfatal recurrent MI rates. There was a nonsignificant trend for a reduction in fatal and nonfatal recurrent MI in both the aspirin and phenprocoumon group. There was a nonsignificant reduction in thromboembolic complications and a significant increase in hemorrhagic complications in the group treated with phenprocoumon.

The results of the three studies for case fatality rates are summarized in Table 7. There was a nonsignificant difference in case fatality rate in 1 study (approximately 30%). The case fatality rates were almost identical in the treated and control groups in the other 2 studies. All 3 studies showed a reduction in recurrent MI in the anticoagulant-treated group. This reduction was substantial and significant in the MRC study and nonsignificant in the other 2. Unfortunately, the criteria for recurrent AMI were not clearly described. Combining the end points of mortality and recurrent infarction, there was a significant reduction in the MRC study, due mainly to a reduction in infarction, and nonsignificant and minimal trends in favor of anticoagulants in the other 2 studies. All 3 studies combined pulmonary embolism and systemic embolism under the heading of thromboembolic complications. There was a reduction in thromboembolic complications in all 3 studies, and in 2 this reduction was statistically significant.

The majority of systemic emboli in patients with AMI who are in sinus rhythm arise from a LV mural thrombus. The risk of systemic embolism from a LV mural thrombus appears to be greatest during the first 3–4 months after AMI, and there seems little justification, as a routine, in continuing anticoagulant therapy beyond this period. Thus, the benefits of long-term anticoagulant therapy in survivors of AMI are at best equivocal. On the other hand, the rate of hemorrhagic complications is considerably greater in the patients treated with anticoagulants than in the control group. Most of the hemorrhagic complications were minor, and few of the major hemorrhagic complications were fatal. Nevertheless, the side effects (1% for major hemorrhage), inconvenience, and cost of long-term anticoagulant therapy would justify the use of such treatment only if it were clearly of benefit in reducing major end points.

In 1970 an International Anticoagulant Review Group attempted to overcome the problem of inadequate numbers by pooling data from 9 controlled, long-term anticoagulant trials involving 2,205 men and 282 women. Using the pooled data, it was concluded that mortality was reduced by 20% in men given long-term anticoagulants, but the benefit appeared to be restricted to patients with prolonged angina or previous infarction on admission to the trial. The same difficulties about data pooling discussed with respect to the short-term trials also apply to this analysis.

### Table 8—Sixty-Plus Reinfarction Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Anticoagulant</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>439</td>
<td>439</td>
<td></td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Time since first infarct</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total deaths within 2 yr</td>
<td>69</td>
<td>51</td>
<td>p = 0.017</td>
</tr>
<tr>
<td>Sudden deaths</td>
<td>20</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Total intracranial</td>
<td>20</td>
<td>12</td>
<td>p = 0.16</td>
</tr>
<tr>
<td>Hemorrhagic intracranial</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Nonhemorrhagic intracranial</td>
<td>13</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Not identified</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total recurrent infarct</td>
<td>64</td>
<td>29</td>
<td>p = 0.0005</td>
</tr>
<tr>
<td>Fatal recurrent infarct</td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

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In 1980 the Sixty-Plus Reinfarction Study\textsuperscript{67} (Table 8) from the Netherlands revived the issue of the value of long-term anticoagulation in survival of AMI. Ambulatory patients over 60 years of age from 6 centers were studied; all were receiving anticoagulants following documented MI that had occurred at least 6 months earlier. This study sought to determine whether continuation of well-controlled oral anticoagulant therapy targeted to an INR of 2.7–4.5 would result in a decrease in mortality or recurrent infarction over 2 years. Eligible patients were randomized to continue anticoagulants or to receive a placebo. The double-blind character of the trial was maintained by having both groups continue with the same pattern of hospital visits for blood tests; “dosage adjustments” were made in both groups. Patients were followed up for 3 years, even when they had deviated from the protocol. In addition to death and reinfarction, intracranial hemorrhagic and nonhemorrhagic episodes were recorded. Analysis was carried out by “intention to treat” as well as by “clinical efficacy” guidelines, ie, exclusion of patients who deviated from the protocol for more than 28 days.

A group of 439 patients received placebo, and another 439 patients received oral anticoagulant therapy. The average age of the patients was 67.6 years; the mean interval since the initial infarction was 6 years. Total deaths and sudden deaths were not significantly different within 2 years between the placebo and the anticoagulation groups. Although hemorrhagic intracranial events were more frequent in the treated group, nonhemorrhagic intracranial events were markedly reduced in patients who received anticoagulant therapy. As a result, there was no significant difference in total intracranial events between the control and the treated groups. There was an unequivocal and dramatic 55% reduction in the incidence of fatal and nonfatal recurrent MI in the group that received anticoagulants.

This well-designed and well-conducted study demonstrated that anticoagulant therapy in patients with a history of MI can produce a significant reduction in recurrent infarction, a process that is thrombosis dependent. The time between the first infarction and entry in the trial (median, 6 years) is of some concern, since it is possible that all but those patients for whom anticoagulant therapy was beneficial may have been eliminated. Also, the study does not address the question of efficacy of long-term anticoagulant therapy in patients under 60 years of age. Nevertheless, together with recent evidence confirming the importance of thrombosis in AMI, the Sixty-Plus Reinfarction Study suggests that anticoagulants are effective in preventing recurrent MI. Furthermore, this study demonstrates that the bleeding risk associated with long-term anticoagulation need not detract from the beneficial effects of the drugs in preventing recurrence of MI.

Despite the impressive results reported by this study, it is unlikely that clinicians will be very enthusiastic about using anticoagulants in patients with MI (see chapter on risk benefits). Competing therapeutic alternatives such as \(\beta\)-adrenergic and calcium ion-blocking drugs\textsuperscript{68,69} which are in many ways easier to administer for both patient and physician, appear to be preferred at present. It has yet to be established, however, whether patients who benefit from anticoagulants are the same as or different from those who are protected by \(\beta\) blockers or calcium ion-blocking drugs.

**Angina**

There have been no appropriately designed trials of anticoagulants in patients with chronic stable angina and only a very limited number of trials of anticoagulants in patients with unstable angina.

Patients with stable exertional angina have an annual mortality of 4% and an annual incidence of AMI of 5%.\textsuperscript{70} Data from the early 1970s indicated that unstable angina was associated with a 1-year mortality of approximately 16%, a 3-month mortality of 8%, and an infarction rate of 21%.\textsuperscript{71} Results of more recent studies, however, show a 1-year mortality of approximately 10%, a 1–4-month mortality of approximately 5%, and an infarction rate of 8–10%.\textsuperscript{72}

Support for the use of anticoagulants in patients with unstable angina was provided by Wood in 1961.\textsuperscript{73} In this unblinded study, randomization was aborted after the first 40 patients, and the study was then continued as a cohort study with 100 treated patients and 50 controls. The last 30 control subjects were selected because of the presence of a contraindication to anticoagulants. This is, therefore, a level III study and cannot be used to draw valid clinical conclusions. In 1981 Telford and Wilson\textsuperscript{74} performed a randomized study of heparin plus atenolol vs atenolol therapy alone in patients with unstable angina. They reported a marked reduction in mortality and frequency of infarction in patients assigned to heparin plus atenolol. Unfortunately, almost 50% of the 400 patients randomized were subsequently removed from the trial, so this would have to be considered at best a level III study, and the interpretation of the results remains in doubt.

A new randomized placebo-controlled (not blinded) clinical trial by Williams et al\textsuperscript{75} provides some support for treating unstable angina with anticoagulant therapy. Half of 102 randomly assigned patients were treated with heparin for 48 h and with warfarin for 6 months. Patients found after entry to have AMI at baseline were withdrawn and each patient’s treatment assigned to the next patient to enter the study. At six months
the treated group had 2 Mls and 1 death compared with 3 Mls and 4 deaths in the control patients. Unstable angina recurred in 3 treated patients and in 10 of the controls. Only when all events, including recurrent unstable angina, were considered, was the advantage of treating patients with anticoagulants statistically significant (p = 0.05).

With only 102 patients in the trial, it was not surprising that there was imbalance at baseline. In fact, more control patients received β-adrenergic blocking drugs before entry because of the severity of angina. The small size of this study and the inhomogeneity of the treatment groups at baseline make this a level III study, the results of which are suggestive but not conclusive.

Zwerner et al.75 however, conducted a randomized study of 8 days of IV heparin with standard therapy or of standard therapy alone, in 61 patients with unstable angina pectoris. They found no difference between the heparin-treated and the control groups in the frequency of chest pain, or the rates of MI, need for intra-aortic balloon pumping, coronary angioplasty, mortality, or hemorrhage. The study was, unfortunately, too small to rule out a significant effect of IV heparin on the occurrence of major events, and it is therefore a level II study.

In a recent study comparing heparin, heparin plus aspirin, and placebo, Theroux and associates reported a marked reduction in MI in 18 of 239 (placebo group) and that all 3 treatment groups were more effective than placebo. In the 239 patients randomized in the heparin group there were only 3 episodes of MI compared to 18 episodes in the 239 patients randomized in the placebo group (p > 0.01).76,77

On the basis of these limited studies, it is concluded that the effectiveness of anticoagulants in patients with unstable angina is uncertain, but that such therapy could be effective. Additional trials are needed, however, before any firm recommendation is possible.

Fibrinolytic Therapy in Patients with Unstable Angina Pectoris

Several uncontrolled studies of fibrinolytic therapy in small numbers of patients with unstable angina have reported results varying from dramatically beneficial to discouraging (also see Cairns, p 125).77-96 In addition Lawrence et al.81 performed a randomized but not blinded study of IV streptokinase in 40 patients with unstable angina. At 6 months there were 4 Mls and 4 sudden deaths in the control patients and no infarctions and 1 sudden death in the treated patients. Gold et al.85 performed a randomized blinded trial of rtPA in 24 patients with unstable angina. Subocclusive coronary arterial thrombus persisted in 8 of 11 control patients and in none of the treated patients. Unstable angina continued in 6 of 11 control patients but in only one of 12 rtPA patients. Niclas et al.82 conducted a randomized, blinded trial of rtPA in 40 patients with unstable angina. Angiography showed only a nonsignificant trend towards reduced stenosis and no clinical advantage in preventing recurrent chest pain or AMI. In the same patients, Topol et al.84 reported no difference in the need for scheduled or emergency myocardial revascularization.

PLATELET ACTIVE DRUGS IN PATIENTS WITH CORONARY ARTERY DISEASE

Rationale for Using Antiplatelet Drugs

Recent clinical and experimental studies have provided insight into the pathogenesis of the acute manifestations of coronary artery disease (MI, unstable angina pectoris, and sudden death) that supports the use of platelet active drugs in the treatment of coronary artery disease.85 Patients with unstable angina have an increased risk of AMI and death.71 Unstable angina has been shown to be associated with limitations of coronary blood flow and with enhanced platelet reactivity.85-89 Increased concentrations of platelet products and products of prostaglandin synthesis are found in the coronary sinus blood in these patients.88,91 In the last few years, acute and serial coronary arteriographic studies have demonstrated that unstable angina is associated with the rapid progression of coronary artery disease and with complicated stenoses manifesting eccentric lesions, overhanging edges, and intraluminal filling defects.88,92 At autopsy these findings are associated with ruptured and raised atherosclerotic plaques, intimal flaps, and intraluminal thrombosis.84 These findings have been confirmed by direct visualization by coronary angiography.85 In the more recent studies of unstable angina pectoris, thrombus was found in more than half of the cases.77,80,96,97

It has been suggested since 1966 that rupture of the atherosclerotic plaque with aggregation of platelets at the site of the exposed subendothelium is the usual initiating event in AMI.98,99 Recent studies have confirmed that intracoronary thrombus occurs in almost all cases with AMI.90 Unstable angina may be at one end of a continuum in degrees of intracoronary thrombotic obstruction initiated by plaque rupture, and platelet aggregate formation.100,101 Acute Q-wave MI is associated with total occlusion, unstable angina with hemodynamically important thrombotic stenoses, and non-Q-wave infarction is in between them, sometimes with subtotal obstruction or with total obstruction and an adequate collateral blood supply.102-104 Sudden death, typically manifesting as ventricular fibrillation, is associated with similar lesions, ruptured plaque and thrombus, and with platelet aggregates embolizing to the coronary microvasculature.105,106

The underlying atherosclerotic stenoses associated with thrombotic occlusions of a coronary artery in
AMI need not be unduly severe.107 Coronary artery spasm can be the cause of unstable angina pectoris, and also of AMI in certain cases; more often, however, it is a contributing factor.108 Folts et al109 showed that when experimental coronary artery stenoses of 60–80% were induced in dogs, cyclic flow with reductions to near zero resulted. If the dogs were sacrificed when the coronary flow was near zero, platelet clumps were found obstructing the vessel. If the dogs were pretreated with aspirin, cyclic flow could not be induced. Plaque fissuring permits platelet aggregation to occur, and AMI, sudden death, and unstable angina pectoris may all follow.110

The acute manifestations of ischemic heart disease, MI, unstable angina pectoris, and sudden death, have, therefore, a similar pathogenesis.111 Atherosclerotic coronary artery disease is a chronic process subject to sudden changes both clinically and pathologically. Disruption of the coronary artery endothelium followed by platelet aggregate formation that initiates intraluminal thrombosis forms the basis for most acute events. The fundamental role of platelets in this process suggests that aspirin could have great benefit for the prevention and treatment of acute coronary events.

**AMI: Short-term Aspirin Therapy**

There is now convincing evidence that aspirin is effective in reducing mortality following acute myocardial infarction.

The ISIS-2 pilot study was a trial of 619 patients with suspected AMI randomized to streptokinase, 1.5 million units IV over 1 h, or a placebo, to aspirin 325 mg, on alternate days for 28 days, or a placebo, and to heparin, 1,000 units/hour for 48 h, or no heparin.112 Streptokinase therapy was associated not only with a nonsignificant early and late decreased mortality, but also with an early increase in nonfatal reinfarctions. Strokes were significantly decreased. Aspirin treatment was associated with a significant decrease in early mortality and a nonsignificant decrease in reinfarctions and strokes. Heparin therapy was associated with a nonsignificant decrease in nonfatal infarctions and an nonsignificant increase in strokes. The numbers studied, however, in this pilot study did not provide reliable information about the effects of aspirin or heparin following streptokinase treatment for AMI. The excess of nonfatal reinfarction seen when streptokinase was used alone in the ISIS-2 pilot study is consistent with the findings of marked platelet activation after IV streptokinase in patients with AMI.113

Verheugt et al114 conducted a randomized trial of 49 patients to evaluate 100 mg/day of aspirin vs placebo for 3 months after IV streptokinase therapy for anterior AMI. There was a statistically significant reduction in the frequency of left anterior descending coronary artery occlusion in the patients receiving aspirin.

The Second International Study of Infarct Survival (ISIS-2)115 was a randomized, placebo-controlled, double-blind trial of acute therapy with IV streptokinase, oral aspirin 160 mg daily for 1 month, both, or neither, in 17,187 patients with suspected AMI. In addition to showing a 23% reduction in the 5-week vascular mortality in those given streptokinase, it demonstrated a 21% reduction (11.4–9.2% mortality) in those given aspirin and a 40% reduction when the combination of streptokinase and aspirin was given. The results were statistically highly significant. Aspirin reduced nonfatal reinfarction by 51% and nonfatal stroke by 47%. An excess of early nonfatal reinfarction found when streptokinase was used alone, was entirely absent when aspirin was added. The early reduction in mortality with aspirin persisted when the patients were followed up for a mean of 15 months. Aspirin was not associated with any significant increase in major bleeding, including hemorrhagic stroke. There was, however, a small increase in minor bleeding, from 1.9 to 2.5%.

ISIS-2 demonstrated clear benefit of aspirin in the therapy of AMI, revealed that the benefit was additive to thrombolytic therapy, and showed that these benefits could be achieved with an aspirin dosage of 160 mg/day. Though associated with increased minor bleeding, aspirin therapy was not associated with any increase in hemorrhagic stroke.

**Unstable Angina Pectoris: Short- and Long-term Aspirin Therapy**

Two controlled studies have been performed to evaluate platelet active drugs in patients with unstable angina (Table 9). Lewis et al116 conducted a multicenter, double-blind, placebo-controlled randomized trial of aspirin treatment (324 mg in buffered solution once daily) for 12 weeks in 1,266 men with unstable angina. In this VA Cooperative Study unstable angina was defined as new onset or sudden worsening of angina without increased activity, and manifested by a frequency of 1 or more episodes per day, a duration longer than 15 min, or an occurrence at rest or during minimal activity. The frequency of death or AMI was reduced by 51% in the aspirin group compared with a placebo group; 31 patients (5.0%) compared with 65 control (10.4%) (p = 0.0005). Similarly, the observed reduction in mortality in the aspirin group was 51%, 10 patients (1.67%) compared with 21 (3.4%) in the placebo group (p = 0.054).

This striking observed benefit of aspirin has been corroborated by an independent Canadian study.117 This randomized double-blind, placebo-controlled trial compared the effects of aspirin (325 mg 4 times/day) and sulfinpyrazone (200 mg four times/day), either singly or in combination, with respect to the incidence of subsequent myocardial infarction or cardiac death.
Male and female patients were followed for up to 2 years (mean, 19 months), and the primary analysis of efficacy was based on eligible patients who had not stopped taking medication for more than 28 consecutive days preceding an outcome event. There was no observable benefit of sulfinpyrazone. Among patients receiving aspirin, however, there was an observed 55% risk reduction in MI or cardiac death, compared with patients not receiving aspirin (p = 0.004); the corresponding risk reduction for all deaths was 70% (p = 0.005). On an intent-to-treat basis, there as a 43% risk reduction for all deaths (p = 0.036). Observed benefits were similar for males and females. The life-table for the aspirin treated and control patients continued to separate throughout the 2 years of study, demonstrating the value of continued treatment.

These 2 studies, provide therefore, compelling evidence that aspirin is highly effective in the treatment of patients with unstable angina pectoris.

**Post-MI—Long-term with Platelet-active Therapy**

Three drugs have been evaluated in post-MI patients: aspirin, sulfinpyrazone, dipyridamole, and a combination of aspirin and dipyridamole.

Six long-term secondary prevention studies have been performed with aspirin181-183 (Table 10). None of these studies entered sufficient numbers of patients to have an 80% chance of demonstrating a statistically significant reduction (at the 0.05% level) in mortality and reinfarction or fatal reinfarction of 20%. The studies, therefore, were all level II.

Elwood et al181 reported a randomized, double-blind study of aspirin (1 300-mg tablet daily) in 1,239 men who had had recent MI. There was an observed risk reduction of 22% in total mortality after 1 year, but this was not statistically significant. For men whose qualifying infarction occurred less than 6 weeks before entry to the study, however, there was a statistically significant reduction in mortality, from 13.2% in the placebo group to 1.8% in the aspirin group. The corresponding mortality rates in men with less recent MIs were 8.3% and 8.8%, respectively.

The Coronary Drug Project Research Group119 studied 1,529 men who had had MI at least 7 years previously. Patients who had participated in 2 other secondary prevention studies that had terminated prematurely were randomized to aspirin (324 mg 3 times/day) or placebo groups. There was a 30% risk reduction in total mortality, from 8.3% in the placebo group, to 5.8% in the aspirin group, but this was not statistically significant.

Breddin et al180 randomly allocated 946 patients (80% males) within 6 weeks of their MI to aspirin (500 mg 3 times/day), a placebo (making the assessment of the benefit of aspirin double-blind), or to phenprocoumon, and followed them for up to 2 years. There was an 18% difference in total mortality. The coronary death rate, however (sudden death or fatal MI), was 4.1% in the aspirin treated-patients vs 7.1% in the placebo group (NS).

Elwood and Sweetnam181 randomly allocated 1,682 patients (85% males) to aspirin (300 mg 3 times/day) or placebo within 1 week of their qualifying infarction. Total mortality was reduced by 17% in the aspirin group, a mortality of 12.3% vs 14.8% in the placebo group. The corresponding reduction for total mortality or nonfatal MI was 25% and for ischemic heart disease mortality 22%. None of these reductions is statistically significant.

The Aspirin Myocardial Infarction Study Research Group (AMIS)184 conducted a multicentered, double-blind, randomized trial which recruited 4,524 patients (89% males) who had a documented MI 2–60 months previously, and followed them for up to 3 years. The total mortality was 10.8% in the aspirin (500 mg twice daily) group and 9.7% in the placebo group. There were fewer nonfatal MIs in the aspirin group, and the coronary incidence (coronary heart disease mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Lewis et al (1983)</td>
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<td>.101 vs .05</td>
<td>51 vs 0.005</td>
<td>0.0005</td>
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<tr>
<td>Cairms et al (1985)</td>
<td>Control (285) vs ASA (267) (325 mg qid)</td>
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<td>55 vs 0.004</td>
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</table>

### Table 9—Unstable Angina

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<th>Study</th>
<th>Regimens (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
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Six long-term secondary prevention studies have been performed with aspirin181-183 (Table 10). None of these studies entered sufficient numbers of patients to have an 80% chance of demonstrating a statistically significant reduction (at the 0.05% level) in mortality and reinfarction or fatal reinfarction of 20%. The studies, therefore, were all level II.

Elwood et al181 reported a randomized, double-blind study of aspirin (1 300-mg tablet daily) in 1,239 men who had had recent MI. There was an observed risk reduction of 22% in total mortality after 1 year, but this was not statistically significant. For men whose qualifying infarction occurred less than 6 weeks before entry to the study, however, there was a statistically significant reduction in mortality, from 13.2% in the placebo group to 1.8% in the aspirin group. The corresponding mortality rates in men with less recent MIs were 8.3% and 8.8%, respectively.

The Coronary Drug Project Research Group119 studied 1,529 men who had had MI at least 7 years previously. Patients who had participated in 2 other secondary prevention studies that had terminated prematurely were randomized to aspirin (324 mg 3 times/day) or placebo groups. There was a 30% risk reduction in total mortality, from 8.3% in the placebo group, to 5.8% in the aspirin group, but this was not statistically significant.

Breddin et al180 randomly allocated 946 patients (80% males) within 6 weeks of their MI to aspirin (500 mg 3 times/day), a placebo (making the assessment of the benefit of aspirin double-blind), or to phenprocoumon, and followed them for up to 2 years. There was an 18% difference in total mortality. The coronary death rate, however (sudden death or fatal MI), was 4.1% in the aspirin treated-patients vs 7.1% in the placebo group (NS).

Elwood and Sweetnam181 randomly allocated 1,682 patients (85% males) to aspirin (300 mg 3 times/day) or placebo within 1 week of their qualifying infarction. Total mortality was reduced by 17% in the aspirin group, a mortality of 12.3% vs 14.8% in the placebo group. The corresponding reduction for total mortality or nonfatal MI was 25% and for ischemic heart disease mortality 22%. None of these reductions is statistically significant.

The Aspirin Myocardial Infarction Study Research Group (AMIS)184 conducted a multicentered, double-blind, randomized trial which recruited 4,524 patients (89% males) who had a documented MI 2–60 months previously, and followed them for up to 3 years. The total mortality was 10.8% in the aspirin (500 mg twice daily) group and 9.7% in the placebo group. There were fewer nonfatal MIs in the aspirin group, and the coronary incidence (coronary heart disease mortality

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**Table 9—Unstable Angina**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimens (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al (1983)</td>
<td>Control (641) vs ASA (625) (324 mg/day)</td>
<td>.101 vs .05</td>
<td>51 vs 0.005</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cairns et al (1985)</td>
<td>Control (285) vs ASA (267) (325 mg qid)</td>
<td>.13 vs .06</td>
<td>55 vs 0.004</td>
<td>0.005</td>
</tr>
</tbody>
</table>
or definite MI) was 14.1% in the aspirin group vs 14.8% in the placebo group. Unfortunately, despite random allocation, there was a much greater preponderance of cardiovascular risk factors among patients in the aspirin-treated group, which may contribute in part to the lack of effect of aspirin in this study.

The Persantine-Aspirin Reinfarction Study Research Group recruited 2,206 patients (87% males) with a documented MI 2–60 months previously, who were followed up for 41 months on average. These patients were randomly allocated to receive aspirin (324 mg 3 times/day), aspirin (324 mg 3 times/day) plus dipyridamole (75 mg 3 times/day), or placebo, with twice as many patients in each of the active-treatment groups. The total mortality, coronary heart disease mortality, cardiovascular mortality, and coronary incidence (coronary death or nonfatal MI) were similar in the 2 active-treatment groups, and consistently lower than in the placebo group; in none of these outcomes was the difference statistically significant. In the subgroup of 447 patients entered within 6 months of their qualifying infarction, mortality was 51% lower in the aspirin group and 44% lower in the aspirin plus dipyridamole group compared with the placebo group (comprising only 95 patients). In contrast, for patients enrolled more than 6 months after their MI the observed mortality differences were very small.

Thus, 6 studies have assessed the efficacy of aspirin alone in the treatment of patients following AMI. Five studies, incorporating a range of doses of 300 mg–1.5 g daily, reported trends in favor of aspirin therapy with respect to several important outcomes. In contrast, the Aspirin Myocardial Infarction Study (AMIS) demonstrated no statistical effect of aspirin on any outcome, including total coronary incidence, although there was a decreased tendency for MI to recur.

If the results of these studies are pooled, the risk

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**Table 10—Effect of Aspirin or Aspirin and Dipyridamole on Case Fatality Rates in Survivors of Acute Myocardial Infarction (MI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (No. of Patients)</th>
<th>Events</th>
<th>% Relative Risk Reduction (95% Confidence Limit)</th>
<th>p Value</th>
<th>Level of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC I</td>
<td>Control (624) vs ASA (615)</td>
<td>.098</td>
<td>22 (-10–54)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(BMJ 1974)</td>
<td>(300 mg/day)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI 10 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC II</td>
<td>Control (850) vs ASA (832)</td>
<td>.148</td>
<td>17 (-5–39)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(Lancet 1979)</td>
<td>(300 mg/day)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI 1 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDPG</td>
<td>Control (771) vs ASA (758)</td>
<td>.063</td>
<td>30 (-1–61)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(J Chron Dis 1976) post-MI &lt;5 yr</td>
<td>(324 mg tid)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>German-Austrian</td>
<td>Control (309) vs ASA (317)</td>
<td>.10</td>
<td>18 (-26–62)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(Hemostasis)</td>
<td>(500 mg tid)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI 4–6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMIS</td>
<td>Control (2257) vs ASA (2267)</td>
<td>.097</td>
<td>-11 (-30–7)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(JAMA 1980)</td>
<td>(500 mg bid)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI mean 25 mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARIS I</td>
<td>Control (406) vs ASA (810)</td>
<td>.108</td>
<td>-18 (-12–48)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(Circ 1980)</td>
<td>(324 mg tid)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI 8 wk–5 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARIS I</td>
<td>Control (406) vs ASA (810)</td>
<td>.128</td>
<td>16 (-14–46)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(Circ 1980)</td>
<td>(324 mg tid)</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-MI 8 wk–5 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paris II*</td>
<td>Control (1,505) vs ASA 325 mg tid</td>
<td>.107</td>
<td>-9 (-14–46)</td>
<td>NS</td>
<td>II</td>
</tr>
<tr>
<td>(1985) post-MI 4 wk–4 mo</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Published as abstract.*
reduction with aspirin is 16% for cardiovascular deaths (p<0.01) and for the outcome of reinfarction, fatal or nonfatal, the pooled estimate of risk reduction with aspirin is 21% (p<0.001).184

Peto184 pointed out that very large trials, involving 5,000–10,000 patients per group, would be required to ensure that an actual risk reduction of 10–20% could be observed with statistical confidence. In the absence of trials of such size, he suggested that data from several properly randomized trials be pooled to provide the best guide to the effects of the therapeutic agent being considered. There are many potential problems with such an approach, but Peto reasoned that these potential dangers may be less important than those of not pooling and so failing to recognize a medically important effect about which reliable evidence can thereby be obtained. Not all clinical epidemiologists, however, agree.

The Antiplatelet Trialists’ Collaboration performed a meta-analysis of all 25 randomized trials of prolonged antiplatelet treatment for patients with a history of TIAs, occlusive stroke, unstable angina, or MI.185 The trials included 29,000 patients, among whom there were 3,000 deaths. The analysis demonstrated that antiplatelet therapy reduced vascular mortality by 15%, stroke or MI by 30%, and overall vascular events by 25%. There was a similar reduction of MI in patients with previous infarction or with cerebrovascular disease. There was an equivalent reduction in vascular mortality in patients manifesting cardiac or cerebral disease. No apparent effect on nonvascular mortality was seen. There was no significant difference in the reduction of vascular events among patients given doses of aspirin that varied from 300 mg to 1,500 mg/day.

The Anturane Reinfarction Trial Research Group186 reported the initial findings of a trial in which patients were randomly allocated to sulfipyrazone (200 mg 4 times/day), or placebo 25–35 days after MI. The authors claimed a statistically significant annual reduction cardiac mortality, from 9.5 to 4.9%. Patient access was stopped at that time, but the trial was continued until all 1,558 eligible patients (87% males) had completed at least 1 year of follow-up. When the patients had been followed for 16 months on average, a second report appeared187 in which an overall reduction of 32% in cardiac mortality was reported (p = 0.06). The reduction was almost entirely due to a 75% reduction in sudden death over the first 6 months of treatment (p = 0.03). No further benefit of treatment could be deduced thereafter.

The analysis of the Anturane Myocardial Reinfarction Study has been criticized on 2 grounds: departures from the protocol, and the classification of sudden death.188-190 Patients were excluded from the analysis after randomization on the basis of a number of prospectively defined criteria, including: (1) end points occurring within the first 7 days of randomization; (2) the discovery that patients were ineligible after they had been randomized; and (3) end points being reached more than 7 days after the prescribed treatment was stopped. If the analysis had been performed on the basis of an intention to treat, there would have been 60 deaths in the placebo group and 41 in the sulfipyrazone, a difference that is not statistically significant (Table 11). We have therefore classified this as a level II study. This is because in each group there were 16 deaths in patients who met 1 of the 3 criteria outlined above. When these patients were removed from the analysis, the number of deaths in each group was 44 and 25, a much greater difference that approached statistical significance.

The second problem related to the definition of sudden death vs MI. It was suggested, for example, that some of the patients classified as sudden death should have been included with the MI group. Since the differences found between the sulfipyrazone and placebo groups were almost exclusively in the sudden death category, reclassifying patients from the sudden death category into the MI group could remove part of the impressive difference found for sulfipyrazone using sudden death as the end point.

The FDA did not approve the claim by the pharmaceutical company that sulfipyrazone is effective in preventing sudden death in the first 6 months after infarction.190 The principal criticism documented in the FDA report was that the criteria for classifying the causes of death were illogical and inconsistently

<table>
<thead>
<tr>
<th>Table 11—Effect of Sulfipyrazone on Case Fatality Rates in Survivors of Acute Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Art II (NEJM 1980)</td>
</tr>
<tr>
<td>Aris (Lancet 1982)</td>
</tr>
</tbody>
</table>

|     |     |     |     |     |     |
|     |     |     |     |     |     |

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applied. The FDA was also concerned about 2 potential sources of bias: (1) the exclusion from the primary analysis of patients who had been considered to be improperly enrolled because they were ineligible, and (2) the practice of classifying certain deaths as unanalyzable after the deaths had occurred. Because of this, the Policy Committee decided to check both the consistency and the objectivity of the original classification by external and independent reviewers. Since the Policy Committee had remained blinded with respect to treatment assignment, it also undertook a complete reclassification of all deaths using the same material as that used by the external reviewers. Essentially similar results were obtained.

A second Anturane Reinfarction Trial was reported by an Italian group. This was a study of 727 patients randomized in a double-blind trial to sulfipyrazone and placebo groups. The design was similar to the Anturane Reinfarction Trial except that patients were withdrawn from the study if any thromboembolic event occurred. A thromboembolic event was defined as a MI, stroke, or a TIA. Treatment with sulfipyrazone did not significantly affect the total mortality or the sudden death rate (Table 11), but it did reduce the incidence of reinfarction and of all thromboembolic events over an average period of 19 months. The effect was cumulative and did not show the pattern of early benefit reported in the Anturane Reinfarction Trial. The patients in the Italian study had a lower prevalence of prior MI, and fewer patients had cardiac failure. The overall mortality in the first 6 months of the study was much lower in the Italian trial than in the Anturane Reinfarction Trial.

Thus, although the 2 trials of sulfipyrazone showed beneficial effects, these effects were not consistent. In the Anturane Reinfarction Trial it was a change of the early incidence of sudden cardiac deaths effected, while in the Italian study a change in reinfarction and total thromboembolic events occurred, but total or sudden cardiac deaths were the same.

In the Persantine-Aspirin Reinfarction Study (PARIS) a trend in favor of either aspirin or of the combination of aspirin and dipyridamole for the reduction of overall total and coronary artery-related mortality was reported at 36 months. No statistically significant difference was shown between the combination and aspirin alone. Subsequent analysis indicated that a subgroup of patients receiving the combination of aspirin and dipyridamole or aspirin alone who were entered less than 6 months following MI had a significant reduction in the 3-year coronary mortality throughout the 3 years of the study. Because the effects on overall mortality were not conclusive, a new prospective study enrolling patients between 3 weeks and 6 months following MI was initiated.

In the Persantine-Aspirin Reinfarction Study Part II (PARIS II), 3,128 persons who had recovered from MI sustained 4 weeks to 4 months previously were randomized into 2 groups, dipyridamole plus aspirin (75 mg and 325 mg, respectively, given together 3 times/day; n = 1,563) and placebo (n = 1,565). The average length of follow-up was 23.4 months. Results for the 6 prespecified primary outcome events were: total mortality, 9% lower in the treatment group compared with the placebo group at 1 year, and essentially no difference for the total follow-up period; coronary mortality, 20% lower at 1 year and 6% lower overall; incidence of definite nonfatal MI plus fatal acute coronary disease, 30% lower at 1 year and 24% lower overall. The coronary incidence differences were statistically significant by study criterion at 1 year and at the end of study.

Since no aspirin-only group was included in the study, it is not possible to assess the relative effectiveness of the combination vs aspirin only in achieving this result. Thus, there is no conclusive evidence yet that dipyridamole adds to the benefit of aspirin for the secondary prevention of MI.

Primary Prevention

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial of 325 mg of aspirin every other day, and β-carotene on alternate days as primary prevention of cardiovascular disease and cancer, respectively. Entered into the trial were 22,071 apparently healthy male physicians aged 40–84 years. The aspirin component of the trial was stopped prematurely after an average of 4.8 years of follow-up because of a statistically significant 47% reduction in the risk of MI (relative risk, 0.53 with 95% confidence limits 0.42–0.67; p = 0.0001). There were 104 patients with MI in the aspirin group vs 189 in the control group. There was no statistically significant difference in mortality. Because of the unexpectedly low mortality rate in the participating physicians (only 12% of that expected), there was no prospect of acquiring definitive data on mortality until well beyond the scheduled termination of the trial. There were 15% more strokes in the aspirin group (80 vs 70), with significantly more moderate to severe or fatal hemorrhagic strokes in the aspirin group, based on a small number of events (10 vs 2).

In contrast, the British aspirin primary prevention study was a randomized, but not placebo controlled, trial of 500 mg aspirin daily for 6 years undertaken in 5,139 apparently healthy male physicians. There was no statistically significant difference in the incidence of nonfatal MI or of stroke in the treated and control groups, although the confidence intervals did not exclude a 25% reduction by aspirin. The mortality was 10% lower in the aspirin group, but was not statistically significant. Disabling strokes were some-
what more common in the aspirin-treated patients.

An overview of the 2 primary prevention studies, when considered together, demonstrates a significant reduction in nonfatal MI of about \( \frac{1}{3} \) \( (p = 0.0001) \), no significant difference in strokes overall, but an increase in disabling strokes.\(^{136}\) Neither the American nor the British study had sufficient power to assess mortality.

**Aspirin Therapy—Conclusion**

Aspirin therapy has been shown to decrease both MI and mortality in patients with unstable angina pectoris and AMI. Reinfarction following AMI or in those with previous MI is decreased, as are recurrent TIAs and minor strokes. In addition, aspirin decreases the incidence of MI in apparently healthy middle-aged men. Its effectiveness has been easier to demonstrate in patients at higher risk of death and MI. In short, aspirin is effective in preventing the acute complications of atherosclerotic coronary artery disease.

The benefit of aspirin therapy relative to the risk of continued therapy is greater in patients at high risk of coronary events. On the basis of benefits demonstrated in those with AMI treated for 1 month, aspirin would be expected to prevent about 250 deaths/1,000 patient-years of treatment. On the basis of demonstrated benefits in patients with unstable angina treated for 3 months, aspirin would be expected to prevent about 60 deaths/1,000 patient years of treatment. Similarly, long-term aspirin therapy for patients with coronary artery disease would be expected to prevent about 10 deaths/1,000 patient years, and for primary prevention, perhaps 1 death/1,000 patient-years of aspirin treatment. The possible risk of less than 1 death/1,000 patient years of aspirin treatment is of less concern when deciding whether to treat patients with aspirin who have known coronary artery disease, particularly if acute manifestations are present. The small risk must be weighed carefully against the expected benefits of aspirin for primary prevention in low-risk patients. The odds in favor of aspirin for primary prevention can be increased by selecting patients at higher risk because of associated coronary risk factors.

Aspirin therapy is indicated for AMI and for unstable angina pectoris. It should be given as soon as it is evident that the patient has an acute myocardial ischemic event, provided that aspirin is not contraindicated, because of potential bleeding problems. In the ISIS-2 trial,\(^{118}\) the first aspirin tablet, which was enteric-coated, was chewed to achieve therapeutic blood levels rapidly. Thereafter, aspirin therapy should be continued indefinitely.

Long-term aspirin therapy is indicated for secondary prevention in patients with other prior MI, and, because of the similar pathogenesis of the acute manifestations, probably also in patients with other evidence of coronary artery disease. Definite stable exertional angina pectoris is usually an indication that coronary artery disease is present, as is a positive exercise test or coronary arteriographic study.

In spite of the evidence of benefit for primary prevention, aspirin therapy is not recommended for all middle-aged men because of the possible risk of cerebral hemorrhage. Aspirin therapy should be considered only for those of both sexes in whom coronary risk factors are present. For example, a middle-aged man with diabetes mellitus or a postmenopausal woman with a high plasma cholesterol level and a family history of coronary artery disease are both at sufficiently increased risk of an acute coronary event that aspirin for primary prevention should be considered. On the other hand, caution is needed when the coronary risk factor is systemic hypertension, since in such individuals the risk of cerebral hemorrhage may be significant. It is uncertain whether old age itself is a risk factor for cerebral hemorrhage when aspirin is being prescribed. In the ISIS-2 study, short-term therapy with aspirin, even in association with streptokinase given to those of advanced age, did not result in an increased frequency of cerebral hemorrhage.\(^{115}\) Atherosclerotic peripheral vascular disease, often associated with coronary artery disease, should be considered a strong coronary risk factor and long-term aspirin therapy given unless contraindications are present.

Aspirin therapy should not be considered to replace measures to control smoking, systemic hypertension, and hyperlipidemia, or for the proper management of diabetes mellitus.

Whether for primary or secondary prevention, aspirin therapy should be started only on the advice of a physician.

**Aspirin Dose**

The meta-analyses of antiplatelet trials revealed no difference in the effectiveness of aspirin dosages that varied from 300 mg to 1,500 mg/day.\(^{140}\) Higher dosages were associated with more GI adverse effects. The successful use of aspirin in doses of 160 mg/day for AMI and 325 mg every other day for primary prevention suggests that such doses should be effective for patients who have other manifestations of coronary artery disease. Since decreased compliance might occur with alternate-day dosing, and a 160-mg preparation of aspirin is not readily available in the United States, 325 mg/day is recommended to protect against MI and death. An enteric-coated preparation is associated with fewer GI adverse effects.

**Summary and Recommendations**

**Acute Myocardial Infarction**

1. It is strongly recommended that all patients with
2. Aspirin therapy, 325 mg/day, should be considered for all individuals with evidence of coronary artery disease and in those with risk factors for coronary artery disease. This grade B recommendation is made on the basis of 1 level I study of primary prevention.134

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