RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2

ISIS-2 (SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL) COLLABORATIVE GROUP*

Summary

17 187 patients entering 417 hospitals up to 24 hours (median 5 hours) after the onset of suspected acute myocardial infarction were randomised, with placebo control, between: (i) a 1-hour intravenous infusion of 1.5 MU of streptokinase; (ii) one month of 160 mg/day enteric-coated aspirin; (iii) both active treatments; or (iv) neither. Streptokinase alone and aspirin alone each produced a highly significant reduction in 5-week vascular mortality: 791/8592 (9.2%) among patients allocated streptokinase infusion vs 1029/8595 (12.0%) among those allocated placebo infusion (odds reduction: 25% SD 4; 2p <0.0001); 804/8587 (9.4%) vascular deaths among patients allocated aspirin tablets vs 1016/8600 (11.8%) among those allocated placebo tablets (odds reduction: 23% SD 4; 2p <0.0001). The combination of streptokinase and aspirin was significantly (2p<0.0001) better than either agent alone. Their separate effects on vascular deaths appeared to be additive: 343/4292 (8.0%) among patients allocated both active agents vs 568/4300 (13.2%) among those allocated neither (odds reduction: 42% SD 5; 95% confidence limits 34-50%). There was evidence of benefit from each agent even for patients treated late after pain onset (odds reductions at 0-4, 5-12, and 13-24 hours: 35% SD 6, 16% SD 7, and 21% SD 12 for streptokinase alone; 25% SD 7, 21% SD 7, and 21% SD 12 for aspirin alone; and 53% SD 8, 32% SD 9, and 38% SD 15 for the combination of streptokinase and aspirin). Streptokinase was associated with an excess of bleeds requiring transfusion (0.5% vs 0.2%) and of confirmed cerebral haemorrhage (0.1% vs 0.0%), but with fewer other strokes (0.6% vs 0.8%). These “other” strokes may have included a few undiagnosed cerebral haemorrhages, but still there was no increase in total strokes (0.7% streptokinase vs 0.8% placebo infusion). Aspirin significantly reduced non-fatal reinfarction (1.0% vs 2.0%) and non-fatal stroke (0.3% vs 0.6%), and was not associated with any significant increase in cerebral haemorrhage or in bleeds requiring transfusion. An excess of non-fatal reinfarction was reported when streptokinase was used alone, but this appeared to be entirely avoided by the addition of aspirin. Those allocated the combination of streptokinase and aspirin had significantly fewer reinfarctions (1.8% vs 2.9%), strokes (0.6% vs 1.1%), and deaths (8.0% vs 13.2%) than those allocated neither. The differences in vascular and in all-cause mortality produced by streptokinase and by aspirin remain highly significant (2p <0.001 for each) after the median of 15 months of follow-up thus far available.

Introduction

REDUCTIONS in mortality that are realistically moderate (eg, “only” 20-25%) are important, especially if produced by widely practicable treatments for common causes of death, but reliable assessment of them may require strict randomisation of several thousand patients. The Second International Study of Infarct Survival (ISIS-2) has randomly assessed, with placebo control, the separate and combined effects of intravenous streptokinase (a single infusion of 1.5 MU over about one hour) and of oral aspirin (160 mg/day for a month) in 17 187 patients with suspected acute myocardial infarction (MI).

Streptokinase

During the 1960s and 1970s several trials of fibrinolytic therapy (chiefly involving intravenous streptokinase) were conducted. These studies were so small—none involved more than 750 patients—that they yielded apparently conflicting results, but an overview of their findings indicated that fibrinolytic therapy could reduce mortality by about a quarter. The prolonged regimens previously tested were not particularly convenient, and so a rapid high-dose intravenous regimen known to dissolve coronary artery
thrombi and recanalise occluded coronary arteries was adopted by the two large trials (GISSI and the present study) conducted to test the results of the overview. Animal models for infarction suggest that fibrinolytic therapy might be of value only if started within a few hours after the onset of pain. But, evidence from the previous trials had indicated that mortality was reduced not only among patients treated early (eg, 0–6 hours after the onset of pain) but also among those treated later (eg, between 6–12 hours, or even after a delay of more than 12 hours). Many patients do not reach hospital until several hours after the onset of chest pain, so reliable information is needed about any ‘time window’ for benefit from fibrinolytic therapy. In ISIS-2, therefore, patients were eligible up to 24 hours from the onset of pain, though the aim was always to treat them as promptly as possible.

**Aspirin**

An overview of the ten randomised trials of long-term aspirin or other antiplatelet agents among patients with a history of previous MI found a 25% reduction in “serious vascular events” (reinfarction, stroke, or vascular death), and two trials in unstable angina produced similar results.3

There was, however, little direct evidence on antiplatelet therapy in acute MI, for the only randomised trial was small, and involved just one single aspirin tablet, with no further treatment. Aspirin is the most convenient and widely tested antiplatelet agent, and irreversibly inhibits cyclo-oxygenase-dependent platelet aggregation. Although 40 mg/day will eventually achieve virtually complete inhibition, larger doses (such as the 160 mg dose used in ISIS-2) are needed for a rapid effect on the first day of treatment. Much larger doses may have little or no additional antithrombotic effect, and are more gastrotoxic.9

ISIS-2 trial tablets were continued for only the first month, since previous trials had already shown that long-term antiplatelet therapy started after the first few weeks is beneficial.

**Streptokinase and Aspirin**

After fibrinolytic therapy, recanalised coronary arteries is particularly prone to reocclusion. So, in principle, any early benefits might not persist unless reocclusion can be avoided,4,11 perhaps by anticoagulants, by antiplatelet agents, or by angioplasty. But, both in the previous trials of prolonged fibrinolytic therapy and in the recent GISSI trial of high-dose intravenous streptokinase, fibrinolytic therapy appeared to reduce mortality even if anticoagulants were not used. Hence, no fixed rules about anticoagulation were made in ISIS-2 — instead, collaborators were merely asked at randomisation of each patient whether or not they planned to add anticoagulants to the trial treatments: streptokinase alone, aspirin alone, both, or neither. This does not assess the effects of anticoagulation, but merely determines whether streptokinase is equally effective whether or not anticoagulants are used. The “factorial” design adopted in ISIS-2 (see Methods) does, however, allow separate assessment of the effects of streptokinase and of aspirin (and can determine whether much of the increased risk of reinfarction observed following fibrinolytic therapy could be avoided by aspirin).

**Patients and Methods**

To encourage recruitment, the trial procedures were as simple as possible — randomisation involved only a telephone call and no forms, the use of ancillary treatments was not restricted, and follow-up after discharge involved only mortality, through government records wherever possible. As a result, 417 hospitals in 16 counties (see acknowledgments) randomised a total of 17,187 patients.

**Treatment**

A $2 \times 2$ factorial study design was used.14 Half of all patients were allocated randomly to receive streptokinase (1.5 MU of ‘Streptase’) and half to receive matching placebo (hepatitis-B-antigen-free albumin), infused intravenously over about 1 hour in 50-250 ml physiological saline, starting immediately. Half of all patients were also allocated randomly to receive oral aspirin (exact dose: 162.5 mg in enteric-coated tablets) and half to receive matching placebo (enteric-coated starch tablets), given daily for 2 to 4 months from the onset of symptoms of suspected MI, and to have no clear contraindication to, streptokinase or aspirin. (Absolute contraindications at the start of ISIS-2 were any history of stroke or of gastrointestinal haemorrhage or ulcer, although in retrospect this may have been too restrictive. Possible contraindications included recent arterial puncture, recent severe trauma, severe persistent hypertension, allergy to streptokinase or anticoagulants, or intravenous beta-blockers. If any pre-randomisation details were incomplete then randomisation was not to be issued, and such patients were not part of the trial. In Oxford and Lyon, the computer allocated treatment using a “minimisation” algorithm13 to help avoid any chance differences between the treatment groups in prognostic features recorded at entry. On Jan 24, 1986, a programming error led to more of the patients randomised at Oxford during a period of about 2 months being allocated to placebo infusion and placebo tablets. Correction of this programming error restored exact balance by Aug 31, 1986. (The apparent effects of streptokinase and of aspirin among patients randomised in Oxford between Jan 24 and Aug 31, 1986, were, however, the same as in all other patients.) After allocation of a specific treatment pack containing active or placebo trial treatments, the patient was irrevocably in the trial. Whether or not the treatment they considered necessary. For example, although physicians were asked to state, just before randomising each patient, whether or not they “planned” to add anticoagulants to the trial treatments for that particular patient, their plan could be altered if some contraindication developed.

**Eligibility**

Patients were eligible if they were thought to be within 24 hours of the onset of symptoms of suspected MI, and to have no clear indication for, or contraindication to, streptokinase or aspirin. (Absolute contraindications at the start of ISIS-2 were any history of stroke or of gastrointestinal haemorrhage or ulcer, although in retrospect this may have been too restrictive. Possible contraindications included recent arterial puncture, recent severe trauma, severe persistent hypertension, allergy to streptokinase or anticoagulants, or intravenous beta-blockers). If any pre-randomisation details were incomplete then randomisation was not to be issued, and such patients were not part of the trial. In Oxford and Lyon, the computer allocated treatment using a “minimisation” algorithm13 to help avoid any chance differences between the treatment groups in prognostic features recorded at entry. On Jan 24, 1986, a programming error led to more of the patients randomised at Oxford during a period of about 2 months being allocated to placebo infusion and placebo tablets. Correction of this programming error restored exact balance by Aug 31, 1986. (The apparent effects of streptokinase and of aspirin among patients randomised in Oxford between Jan 24 and Aug 31, 1986, were, however, the same as in all other patients.) After allocation of a specific treatment pack containing active or placebo trial treatments, the patient was irrevocably in the trial. Whether or not the treatment they considered necessary. For example, although physicians were asked to state, just before randomising each patient, whether or not they “planned” to add anticoagulants to the trial treatments for that particular patient, their plan could be altered if some contraindication developed.

**Randomisation**

Entry to the study was by a 24-hour telephone service, based in Berlin for Germany, Gent and Bruxelles for Belgium, Valencia for Spain, Bellinzona for Austria and Switzerland, Lyon for France, and Oxford for all other countries. Before randomisation some details were recorded (directly on a computer in Oxford and Lyon, or first on computer-generated randomisation lists elsewhere), including patient identifiers, age, systolic blood pressure, hours from onset of the episode of pain that led to admission, aspirin use during the week before entry, and “planned” treatment in hospital (ie, whether non-trial treatment was likely to include any aspirin, anticoagulants, or intravenous beta-blockers). If any pre-randomisation details were incomplete then randomisation was not to be issued, and such patients were not part of the trial. In Oxford and Lyon, the computer allocated treatment using a “minimisation” algorithm13 to help avoid any chance differences between the treatment groups in prognostic features recorded at entry. On Jan 24, 1986, a programming error led to more of the patients randomised at Oxford during a period of about 2 months being allocated to placebo infusion and placebo tablets. Correction of this programming error restored exact balance by Aug 31, 1986. (The apparent effects of streptokinase and of aspirin among patients randomised in Oxford between Jan 24 and Aug 31, 1986, were, however, the same as in all other patients.) After allocation of a specific treatment pack containing active or placebo trial treatments, the patient was irrevocably in the trial. Whether or not the treatment they considered necessary. For example, although physicians were asked to state, just before randomising each patient, whether or not they “planned” to add anticoagulants to the trial treatments for that particular patient, their plan could be altered if some contraindication developed.

**Discharge**

At discharge, a pre-randomisation electrocardiogram (ECG) and a simple single-sided form were returned to the trial office. This
"discharge form" provided further identifiers to assist central mortality follow-up after discharge, as well as brief details of compliance with study treatments in hospital, other drug use in hospital, any apparent side-effects of treatment, and major events in hospital (bleeding, cardiac rupture, reinfarction, cardiac arrest, stroke, and death). Each ECG was read "blind" of treatment by three observers (with adjudication by the trial coordinator if no two agreed). If bundle branch block was present (6% of ECGs) this alone was noted, otherwise the ECG categories (as in ISIS-1) were:

- Inferior ST elevation (29%). \( \geq 3 \text{ mm in the sum of } II + III + aVF; \)
- Anterior ST elevation (25%). \( \geq 6 \text{ mm in the sum of } V_1 + V_2 + V_3 \text{ and/or } (b) \geq 6 \text{ mm in } V_4 + V_5 + V_6 \text{ and/or } (c) \geq 2 \text{ mm in } I + aVL; \)
- Inferior and anterior ST elevation (2%). \( \text{Both of above;} \)
- ST depression (8%). \( \text{None of the above, but with ST depression as extreme as the ST elevations required above;} \)
- Other abnormality (27%). \( \text{None of the above, but with } (a) \text{ pathological Q-waves (16%) } \geq 2 \text{ mm in any lead other than } aVR \text{ or } V_1, \text{ or } (b) \text{ no Q-waves but T-wave inversion (11%) in any lead other than } aVR \text{ or } V_1, \text{ or } (c) \text{ any conduction defect (eg, atrioventricular block) or any arrhythmia (eg, atrial fibrillation, supraventricular tachycardia);} \)
- "Normal" (2%). \( \text{Any remaining electrocardiograms.} \)

**Follow-up**

The present report is of outcome by allocated treatment among all randomised patients, except those 206 (102 active SK vs 104 placebo infusion; 95 active aspirin vs 111 placebo tablets) for whom discharge forms had not yet been obtained by July, 1988. Discharge was at a median of 10 days, and mortality follow-up was for a maximum of 34 and a median of 15 months. The completeness of follow-up is 99% to discharge, 97% to week 5, and 96% to Jan 1, 1988. (About nine-tenths of all deaths in the first 5 weeks occur in hospital, so it is probable that more than 98% of the 5-week deaths among the 17 187 randomised patients are included in the present analysis.)

All deaths were reviewed blind of treatment allocation by the trial coordinator. Causes of death were subdivided into "non-vascular" (ie, definitely non-vascular) and "vascular" (ie, definitely or possibly vascular). The latter, as specified in the original protocol, includes all deaths attributed to cardiac, cerebral, haemorrhagic, other vascular, or unknown causes (ie, 9th International Classification of Disease categories 390–459, 530–535, or 797–799).

Those finally classified as non-vascular were not adversely associated with treatment (table i), so their addition to the analyses of vascular mortality to yield analyses of all-cause mortality would not weaken the apparent effects of treatment. For all reports of stroke on the discharge forms, further clinical details (including any relevant investigations, such as computerised tomographic [CT]...
those discharged alive in both active and placebo groups and should do likewise for those that were not. Among those discharged alive, the infusion was completed in 98% of patients allocated placebo and in 92% allocated streptokinase with the 8595 Allocated Placebo Infusion. Comparison of the 8592 Patients Allocated Intravenous Streptokinase with the 8595 Allocated Placebo Infusion.

continued their trial tablets throughout the hospital stay, when nine-tenths of five-unit mortality occurred (so, among those dying before week 5, compliance must have been 90-95%).

Comparison of the 8592 Patients Allocated Intravenous Streptokinase with the 8595 Allocated Placebo Infusion.

Effect on vascular mortality in first 5 weeks (figs 1a, 3a) and later (fig 2a).—During the first 5 weeks there were 791 (9-2%) vascular deaths in the streptokinase-grouped-allocated group compared with 1029 (12-0%) in the placebo group. This 25% SD 4 reduction in the odds of death in the streptokinase group is highly significant (2p < 0.00001) with 95% confidence interval ranging from 18% to 32%. Several years of further follow-up will be needed to see how long these early gains persist. Thus far, with median follow-up 15 months, there has been a slight and non-significant further divergence after day 35 (fig 2a). Hence, the overall divergence after day 35 (fig 2a). Hence, the overall
TABLE I—EFFECTS OF ALLOCATED TREATMENT ON CLINICAL EVENTS IN HOSPITAL AND ON NON-VASCULAR MORTALITY

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Streptokinase allocation</th>
<th>Aspirin allocation</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Streptokinase infusion</td>
<td>Placebo</td>
<td>Streptokinase &amp; Aspirin</td>
</tr>
<tr>
<td></td>
<td>Absolute reduction (%)</td>
<td>Absolute reduction (%)</td>
<td>Absolute reduction (%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>No randomised</td>
<td>8592</td>
<td>8595</td>
<td>8587</td>
</tr>
<tr>
<td>No with discharge form</td>
<td>8490</td>
<td>8491</td>
<td>8492</td>
</tr>
<tr>
<td>Renal failure</td>
<td>238</td>
<td>202</td>
<td>156</td>
</tr>
<tr>
<td>Any</td>
<td>-0.4%</td>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td>Any, discharged alive</td>
<td>155</td>
<td>-0.7%</td>
<td>83</td>
</tr>
<tr>
<td>Cardiac rupture</td>
<td>Any</td>
<td>0.0%</td>
<td>69</td>
</tr>
<tr>
<td>Any, discharged alive</td>
<td>6</td>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Any</td>
<td>74</td>
<td>7</td>
</tr>
<tr>
<td>Venticular fibrillation</td>
<td>607</td>
<td></td>
<td>690</td>
</tr>
<tr>
<td>Any, discharged alive</td>
<td>370</td>
<td></td>
<td>366</td>
</tr>
<tr>
<td>Bleed</td>
<td>“Major” (transfused)</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td>“Minor” (not transfused)</td>
<td>297</td>
<td></td>
<td>215</td>
</tr>
<tr>
<td>Stroke*</td>
<td>61</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>(a) Astology:</td>
<td></td>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Confirmed haemorrhage</td>
<td>7</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other, day 0-1</td>
<td>20</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Other, after 1 day</td>
<td>34</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>(b) Disability</td>
<td></td>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>Dead</td>
<td>24</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Disabled at discharge</td>
<td>17</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Not disabled</td>
<td>20</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Any, discharged alive</td>
<td>37</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>Non-vascular deaths</td>
<td></td>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td>Before wk 5</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>After wk 5</td>
<td>28</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Absolute reduction (%)</td>
<td></td>
<td></td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Transient ischaemic attacks lasting 24 h or less were not recorded routinely, and the 6 strokes reclassified on review as TIA are excluded (2 SK only, 2 aspirin only, 1 both, 1 neither). In addition to the 7 haemorrhages “confirmed” (by CT scan or necropsy), 3 “possibles” (2 SK only, 1 SK & aspirin) were reported. All 10 occurred on days 0-1. 9 died in hospital, and the 1 survivor (SK & aspirin, with CT confirmation) was severely disabled.

vascular death were 35% SD 6 (2p<0.00001), 16% SD 7 (2p=0.02), and 21% SD 12 (2p=0.08). The reduction is greatest in those randomised within 4 hours, but it is still significant (17% SD 6, 2p=0.004) in those randomised within 5-24 hours. If p-values are to be used at all to help decide whether, in a clearly positive trial, particular subgroups are also positive then 1-tailed p-values may be preferred: these are, however, simply half the cited “2p” values, eg, 1p = 0.002 instead of 2p = 0.004.) Within the early period, there was no evidence that benefit was substantially greater among patients randomised within 1 hour than among those randomised after 2-4 hours. Detailed subdivision of the effects of delay are provided in fig 3a, but the confidence intervals are too wide for the pattern to be clear without also using evidence from other trials (see Discussion).

Effect of streptokinase on other clinical events in hospital (tables I and II).—Hypotension and bradycardia were reported far more commonly in the streptokinase group than in its control (10.0% vs 2.0%), generally during the 60-minute infusion or very shortly after. The excess was not related to the initial blood pressure—indeed, even among the 631 with a systolic blood pressure below 100 mm Hg it was no greater than average. Reports of allergic reactions (4.4% vs 9.9%) were in most cases confined to shivering, pyrexia, or rashes, also generally during or just after the streptokinase infusion; on blind review, however, no reports of anaphylactic shock were confirmed. 22% of patients received prophylactic steroids but, as predicted on theoretical grounds, this strategy did not seem to alter the reported rate of allergic reactions (3.3% SD 0.5 excess with streptokinase among patients given prophylactic steroids and 3.6% SD 0.3 among those not). Bruising or “minor” bleeding (for example, oozing from puncture sites, microscopic haematuria, blood-streaked vomit or sputum) was reported more commonly among patients given prophylactic steroids (3.5% vs 1.0%), and there was also a small excess (0.3% SD 0.1) of bleeds requiring transfusion ("major" bleeds: 0.5% vs 0.2%; 2p<0.001). This excess appeared similar whether or not streptokinase was used with aspirin, and even the excess of minor bleeds caused by streptokinase appeared to be only slightly greater in the presence of aspirin (2.8% SD 0.3) than in its absence (2.3% SD 0.3). The excess of any bleeds caused by streptokinase did, however, depend on whether intravenous, subcutaneous, or no heparin use was planned (absolute excesses 5.3%, 2.6%, or 1.5%; table II), as did the excess of major bleeds (0.7%, 0.4%, or 0.0%; but, the lack of any excess of major bleeds in the absence of heparin involved only 8/2903 streptokinase vs 8/2907 control patients). There was no unusual excess of bleeds or of hypotension among the 401 who were aged 80 or over, or among the 178 with a systolic blood pressure of 200 mm Hg or more.

There was a significant excess (0.1% SD 0.3) of confirmed cerebral haemorrhage with streptokinase (7 vs 0; 2p<0.02), all occurring on the day of randomisation or the following day, and all followed by death (6 cases) or severe disability (1 case). During this early period there was also a slight but non-significant excess of “other” strokes (20 vs 13), some of which may also have involved cerebral haemorrhage. But, although streptokinase was associated with an excess of early strokes, there were fewer strokes in the streptokinase group after this early period (34 vs 54, 2p<0.05). Consequently, there was no increase in the
cerebral haemorrhage. There were significant reductions in tested. In particular, there was no significant excess of aspirin vs 0-4% placebo). Apart from a small absolute excess (0-6% SD 0-2; 2p < 0-01) of “minor” bleeds, there were no reported with a similar frequency in both groups (0-4% I)-Bleeds requiring transfusion (“major” bleeds) were both in the first 5 weeks and in the entire study period to Jan 1,1988.

There were fewer non-vascular deaths among aspirin-allocated patients (25 vs 39; NS: table I), so all-cause mortality was also significantly reduced (2p < 0-0001), both in the first 5 weeks and in the entire study period to Jan 1, 1988.

**Effect of aspirin on other clinical events in hospital (table 1)**—Bleeds requiring transfusion (“major” bleeds) were reported with a similar frequency in both groups (0-4% aspirin vs 0-4% placebo). Apart from a small absolute excess (0-6% SD 0-2; 2p < 0-01) of “minor” bleeds, there were no significant adverse effects of the low-dose aspirin regimen tested. In particular, there was no significant excess of cerebral haemorrhage. There were significant reductions in overall risk of stroke (0-7% streptokinase vs 0-8% control; NS) or in the risk of disabling/fatal stroke (0-5% vs 0-6%; NS).

Cardiac arrest was significantly less common among patients treated early and those treated late after the event. When this was done, aspirin was still associated with significant reductions in reinfarction (1-0% vs 2-0%) and in stroke (0-3 vs 0-6%).

**Comparison of the 4292 Patients Allocated the Combination of Streptokinase and Aspirin with the 4300 Allocated Neither**

Effect on vascular mortality in first 5 weeks (figs 1c, 3c, 4) and later (fig 2c).—Mortality among patients allocated the combination of both agents was significantly less than that among patients allocated both placebos (42% SD 5 reduction by the combination, with 95% confidence limits 34%-50%; 2p < 0-00001). Indeed, the combination was significantly (2p < 0-0001) better than either active treatment on its own. After the first 5 weeks there was no indication of any further convergence or divergence (fig 2c). Hence, the overall difference in vascular mortality, including both early and late deaths, remains highly significant (2p < 0-0001). Non-vascular deaths were slightly fewer among treated than among control patients, so all-cause mortality was also highly significantly reduced (2p < 0-0001), both in the first 5 weeks and in the entire study period to Jan 1, 1988.

The beneficial effects of streptokinase and of aspirin on mortality appear to be largely independent of each other (fig 4). Streptokinase significantly reduced 5-week vascular mortality both among patients who received aspirin and among those who received placebo tablets (reductions in the odds of death by streptokinase: 28% SD 6 and 23% SD 6 respectively; each 2p < 0-0001). Similarly, aspirin reduced mortality irrespective of whether patients were allocated streptokinase or placebo infusions (reductions in the odds of death by aspirin: 25% SD 6 and 21% SD 6, respectively; each 2p < 0-0001).
Fig 5—Subgroup analyses of the odds of vascular death in days 0–35.

Square sizes and 95% confidence intervals are as in fig 3. Asterisks denote subsidiary analyses that were prespecified in the protocol for aspirin (* and **) or for streptokinase (**). (The sum of the 26 \( \chi^2 \) tests for heterogeneity in the 26 different non-astrological subgroup analyses in fig 5(a) and 5(b) was 58.5 on 50 degrees of freedom, NS. If no real heterogeneity of effect existed then about 1 or 2 of these 26 heterogeneity tests would be expected to yield a p < 0.05 result by chance alone, and in fact only the 1 for aspirin and previous MI did so; all other heterogeneity tests, including that for streptokinase and ECG, were p > 0.05.)
onset of symptoms (odds reduction at 0-4, 5-12, and 13-24 hours: 25% SD 7, 21% SD 7, and 21% SD 12, respectively), while the effects of streptokinase appeared greatest among those treated earliest. So, when patients allocated the combination of both streptokinase and aspirin are compared with those allocated neither active drug, the odds of death were significantly reduced among patients randomised 0-4 hours (53% SD 8 reduction; 2p < 0-00001), 5-12 hours (32% SD 9 reduction; 2p < 0-0001), and 13-24 hours (38% SD 15 reduction; 2p = 0.01) after pain onset.

Effects of the combination of both agents on other clinical events in hospital (table 1).—As for streptokinase alone, the combination of streptokinase and aspirin was associated with a 0-3% SD 0-1 excess of “major” bleeds when compared with patients receiving neither active treatment. A 0-1% excess of cerebral haemorrhage was still observed, but this was offset by shortfalls of 0-3% in other strokes with death in hospital, of 0-1% in disabling strokes, and of 0-2% in other strokes with discharge alive. Overall, therefore, the combination of streptokinase and aspirin was associated with 0-5% SD 0-2 fewer strokes (0-6% vs 1-1%; 2p = 0-02). It was also associated with fewer reinfarctions, cardiac ruptures, and cardiac arrests in hospital, but most of these differences were among patients who died in hospital and so have already been accounted for in the mortality analyses.

Subgroup Analyses of the Effects of Streptokinase and of Aspirin on 5-week Vascular Mortality (fig 5): Results, with Discussion

Even in a trial as large as ISIS-2, reliable identification of subgroups of patients among whom treatment is particularly advantageous (or among whom it is ineffective) is unlikely to be possible. When in a trial with a clearly positive overall result many subgroup analyses are considered, false negative results in some particular subgroups must be expected. For example, subdivision of the patients in ISIS-2 with respect to their astrological birth signs appears to indicate that for patients born under Gemini or Libra there was a slightly adverse effect of aspirin on mortality (9% SD 13 increase; NS), while for patients born under all other astrological signs there was a strikingly beneficial effect (28% SD 5 reduction; 2p < 0-00001). It is, of course, clear that the best estimate of the real size of the treatment effect in each astrological subgroup is given not by the results in that subgroup alone but by the overall results in all subgroups combined. In different biological subgroups, however, the sizes of the effects of treatment may well really be somewhat different, but still the directions of the effects in the different subgroups may well all be the same, as long as patients with clear contraindications to treatment or with negligible risk of early death from infarction are excluded. If so, then the best estimate of the direction (but only of the approximate size) of the real effect of treatment in each different biological subgroup may be that suggested by the proportional risk reduction in all subgroups combined. Clearly significant overall results may therefore provide strong indirect evidence of benefit in subgroups where the results, considered in isolation, are not conventionally significant (or even, perhaps, slightly adverse).

“Lack of evidence of benefit” just in one particular subgroup is not good “evidence of lack of benefit”. Overall, for example, GISSI provided strong evidence that streptokinase reduces mortality,1 but inevitably the results were not conventionally significant in particular subgroups (eg, patients with inferior infarcts, those aged over 65 years, those with a previous infarct, those presenting more than 6 hours after pain onset, and so on). However, the overall GISSI result provided strong indirect evidence that fibrinolytic therapy has at least some effect in these subgroups, and ISIS-2 confirms this (figs 5a and 6). As would be expected if subgroup analyses were not particularly informative, some are discordant in different studies (eg, no apparent benefit from streptokinase in GISSI or ISIS-2 among patients with ST depression) and some are discordant (eg, in ISIS-2 streptokinase reduced mortality significantly [2p < 0-001] in patients with a history of MI, while in GISSI it did not). Of the aspirin subgroup analyses, two did indicate a degree of heterogeneity just about as great as that for astrology, but neither is supported by other evidence. First, the lack of apparent effect among diabetics is not conventionally significant, and a non-significant interaction in another trial has led to the opposite suggestion.21 Second, the lack of apparent effect of aspirin in people with a previous infarct is implausible, since in the present study aspirin significantly reduces reinfarction among such patients (38/1454 vs 66/1483, 2p < 0-01), and
long-term aspirin use after MI reduces both reinfarction and death (table III). All these subgroup analyses should, perhaps, be taken less as evidence about who benefits than as evidence that such analyses are potentially misleading. (Statistically valid methods for estimating the true effect of treatment in an "outlying" subgroup do exist,22 but do not include "analysis" just of that one subgroup on its own; instead, where there is little evidence of any real heterogeneity, as in the present study, they involve giving more weight to the overall result than to the data in the subgroup of interest.)

**Discussion**

The size of this trial ensures that the reductions in vascular mortality (or in all-cause mortality) that have been demonstrated for intravenous streptokinase and for oral aspirin are both definite. The benefits appeared to be largely independent of each other—that is, streptokinase reduced mortality by a roughly similar additional amount irrespective of whether aspirin was used or not, and vice versa. Consequently, the combination of both active drugs produced a reduction in the odds of death at 5 weeks that was far larger (42% SD 5 for both agents versus neither) than that produced by either drug alone, with such a narrow 95% confidence interval for this reduction (34%–50%) that the possibility of there being little real benefit is absolutely excluded. This does not, of course, guarantee that the risk reductions will be exactly the same size in each specific category of future patients, but it does provide strong indirect evidence that these treatments will generally reduce coronary mortality substantially. Generalising too far may lead to patients being treated inappropriately, for if streptokinase is used where it can confer no benefit then it may cause 1 or 2 unnecessary deaths per thousand. But so too may failing to generalise far enough, for if aspirin and streptokinase are not used where they could confer benefit then this may lead to about 50 avoidable deaths per thousand.

**Fibrinolytic Therapy**

The principal findings were that streptokinase improves 5-week survival, that this benefit persists for some years, and that (although the effects seem greatest among patients treated most promptly) fibrinolytic therapy appears to produce some benefit even among those treated up to 24 hours from pain onset.

The hypothesis that fibrinolytic therapy might be beneficial more than 6 hours after pain onset was generated by an overview1 of previous trials (fig 6). Among such patients in ISIS-2 streptokinase produced a reduction in overall mortality among 6477 patients, which compares favourably with the small number typically avoid about 15–20 early deaths among every 1000 patients, as hypotension, allergic reactions, or minor bleeding may be worrying but do not usually cause patients managed in hospital any serious problem, and the recent trials (ISIS-2, ISIS-2 pilot, GISSI, ISAM) have demonstrated that serious side-effects of the rapid high-dose iv streptokinase regimen are rare—only about 3 bleeds requiring transfusion and about 1 or 2 cerebral haemorrhages per 1000 patients, with no significant increase in the total number of strokes (ISIS-2 61 SK vs 67 placebo, GISSI 49 vs 40, ISAM 5 vs 0, ISIS-2 pilot 2/413 vs 5/206 [p = 0/005], other trials 1 vs 0: total 117 vs 112). On the other hand, the risk of coronary death in patients with suspected acute MI may be high, even among those without pronounced ST elevation on their ECG or among those admitted late after symptom onset. A reduction in mortality of "only" 14%, as suggested by the trial results for those presenting after 6 hours, would typically avoid about 15–20 early deaths among every 1000 patients, which compares favourably with the small number of serious complications that might be expected.

**Antiplatlet Therapy**

Reinfarction, stroke, and mortality are reduced by antiplatelet therapy used long-term in the months or years after a myocardial infarction or in patients with unstable angina (table III). But before ISIS-2 and its pilot, daily aspirin had not been tested in the acute phase of MI. The present trial indicates that one month of low-dose aspirin, started immediately in 1000 patients with suspected acute MI, would typically avoid about 25 deaths and 10–15 non-fatal reinfarctions or strokes, and that much of this benefit persists well beyond this short treatment period. Continuation of antiplatelet therapy for 2–3 years in 1000 post-MI patients would, moreover, typically prevent about a further 20 deaths and a further 30 non-fatal events.5

The optimum dose, and frequency of dosing, of aspirin remains uncertain. If the chief mechanism is inhibition of cyclo-oxygenase-dependent platelet aggregation, then any daily dose from about 40 mg upwards may suffice—as indeed, may less frequent doses. The definite reductions in vascular events observed with 160 mg/day in ISIS-2 resemble those observed with higher doses (300–1500 mg daily) in the long-term trials (table III). Higher doses of...
aspirin are several times more gastrotoxic than lower doses, but do not seem to be any more effective. At present, therefore, when long-term antiplatelet therapy is to be used after MI, unstable angina, transient cerebral ischaemia, or stroke, a dose of about 160 mg/day may be preferred.

The Combination of Streptokinase and Aspirin

This combination appears to have serious side-effects that are no more frequent than those of streptokinase alone. Yet the combination reduces the risk of disabling or fatal stroke and of reinfarction, as well as reducing mortality much more substantially than either agent does alone. For patients in ISIS-2 admitted early after the onset of pain, the combination seemed to reduce 5-week mortality by about one-half, and even when used after a delay of several hours it seemed to reduce mortality by about one-third. For example, among those entered 13–24 hours after the onset of pain the mortality reduction was 38% SD 15 (45/608 vs 71/614), with apparently equal contributions from aspirin and from streptokinase (fig 3). Only two-thirds of these patients treated up to 24 hours after pain onset, the combination reduced the odds of vascular death by 42% SD 5, with a lower confidence limit of 34%. The apparent effect of streptokinase is a little better in ISIS-2 than in some other trials (fig 6), but still the combination of streptokinase and aspirin is likely to reduce 5-week mortality by more than one-third for a wide range of patients, avoiding about 50 deaths (or more, if antiplatelet therapy is continued for a longer period) among every 1000 treated.

Platelet activity is increased in acute MI, and is increased still further by fibrinolytic therapy. But this increase can be avoided by the addition of aspirin.24 In ISIS-2, the increase in reinfarction—and hence, presumably, in reocclusion—produced by streptokinase alone was avoided if streptokinase was given in combination with aspirin. If fibrinolytic and antiplatelet therapies are combined, then it is not yet clear whether additional interventions to avoid reocclusion (eg, anticoagulants or angioplasty) will confer additional benefit. But it is clear that streptokinase and aspirin will reduce both reinfarction and death, even if other interventions are not used. This finding substantially simplifies the routine use of fibrinolytic therapy.

Research Implications

These results indicate what large simple randomised trials23 can offer, not only in acute MI but also in many other conditions. They also show what overviews of randomised trials can offer, for ISIS-2 was undertaken because of the benefits suggested by two overviews (one of which also engendered two studies of aspirin for primary prevention,28 and the other of which also engendered the GISSI1 study of streptokinase). Moreover, the fibrinolytic overview generated the hypothesis that treatment could be effective even if given to patients presenting late after pain onset. This influenced the design of ISIS-2, and the results for such patients could double the number of patients who benefit from treatment.

ISIS-2 has shown that fibrinolytic therapy and antiplatelet therapy both reduce mortality in many categories of patient. For any patients where uncertainty remains about the benefits of fibrinolytic therapy, this should encourage further randomisation between fibrinolytic and control treatment, as in EMERA26 and ISIS-3. Streptokinase is the most extensively studied fibrinolytic agent, and the present results indicate that the cost per life saved by it is only a few thousand pounds. Newer fibrinolytic agents such as tPA27,28 and APSAC29 are 5–10 times as expensive as streptokinase, and are now being tested, though only within 6 hours of pain onset. For neither, however, have the trials been large enough for indirect comparison even of an overview of them with the streptokinase results in hours 0–6 only (fig 6) to yield statistically reliable information (and, of course, selected comparisons just of single trial results with each other could be even less statistically informative). Hence, it is not known which, if any, of the fibrinolytic agents is most effective at averting cardiac death and which, if any, carries the greatest risk of cerebral haemorrhage or other serious side-effects.80 GISSI-2 and ISIS-3 will therefore involve direct large-scale randomised comparison between different fibrinolytic agents.

For antiplatelet therapy, the drug costs may be negligible—for example, perhaps just a few tens of pounds per life saved by aspirin—but, now that such treatments have been proved to avert death, some really large randomised comparisons are needed between different antithrombotic regimens (for example, one antiplatelet regimen versus another or aspirin alone versus aspirin plus anticoagulation).

Clinical Implications

The initial diagnosis of MI, and decisions about acute treatment, depend largely on the physician's judgment of the clinical history and of the admission ECG. Such decisions cannot, of course, take into account information available only later from cardiac enzyme estimation or coronary angiography. ISIS-2 is directly relevant to acute treatment, for the principal entry criterion was that the responsible physician suspected acute MI on the basis of the clinical presentation alone (although in practice 98% of patients had some ECG abnormality). The absolute mortality reductions appear to be greatest for patients at greatest risk of death (for example, women, older patients, hypotensive patients, patients with a previous MI or with an anterior infarct). Patients with systolic blood pressures below 100 mm Hg are at particular risk, and among them streptokinase appeared to produce a particularly large absolute benefit (while the incidence of hypotension due to streptokinase was no larger in them than in normotensives). Similarly, among the 3411 patients aged over 70 (fig 5a) streptokinase was associated with a significant reduction in mortality, and in absolute terms the 5-week survival benefit was somewhat greater among them than among younger patients (with no evidence that the risks of treatment, in particular cerebral haemorrhage or other bleeding, were related to age). But even though the absolute benefits produced by streptokinase and by aspirin may be largest among high-risk patients, they may still also be worthwhile in many categories of patients at below-average risk of cardiac death. Furthermore, the benefits of streptokinase may also outweigh the risks even among many patients who have some relative contraindication (eg, recent use of streptokinase or an old history of stroke or of gastrointestinal haemorrhage or ulcer).

For streptokinase, ISIS-2 does not support the suggestion3 that the benefit among those treated within the first hour is much greater than among those treated slightly later (fig 3a); but, a small decrease in the median time of treatment (eg, from 5 hours to 4 hours81) does produce a small improvement in the mortality reduction (eg, from 20% to 23%; fig 6). Worthwhile improvements might therefore be achieved by simple measures, such as encouragement of prompt hospital admission and starting treatment in the emergency room before transfer to...
coronary care. It might, however, be best to delay fibrinolytic treatment until hospital admission unless the patient is in shock or in need of urgent revascularization.

Aspirin does not require particularly careful monitoring, and its placebo, but otherwise the entire study was financed by Behringwerke, and Bellinzona, the computer department in Lyon, and the CTSU staff in

reinfarctions, and strokes could be avoided or substantially total with acute MI-then a few tens of thousands of deaths,

Aspirin does not require particularly careful monitoring,

...and its placebo, but otherwise the entire study was financed by Behringwerke, and Bellinzona, the computer department in Lyon, and the CTSU staff in

Aspirin does not require particularly careful monitoring,
REFERENCES


