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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; $2p < 0·00001$); 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; $2p < 0·00001$). 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.[1] The prolonged regimens previously tested were not particularly convenient, and so a rapid high-dose intravenous regimen known to dissolve coronary artery

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thrombi and recanalise occluded coronary arteries[2] was adopted by the two large trials (GISSI[3] 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.[4] But, evidence from the previous trials[1] 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.[5] There was, however, little direct evidence on antiplatelet therapy in acute MI, for the only randomised trial[6] 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.[7] 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[8] 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[10] might be 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[1] and in the recent GISSI trial of high-dose intravenous streptokinase,[3] 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 use anticoagulants. 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[3,12] following fibrinolytic therapy could be avoided by aspirin).

Patients and Methods

To encourage recruitment, the trial procedures were as simple as possible[13]—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 × 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 one month from a calendar pack, starting immediately with the first tablet crushed, sucked, or chewed for a rapid antiplatelet effect. Hence, there were 4 treatment groups: *streptokinase alone, aspirin alone, both, or neither.*

The trial treatments were to be interrupted only if this was thought to be clearly indicated by the responsible physician. In all other respects, physicians were free to use whatever additional therapy 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 aspirin, low risk of cardiac death, or some other life-threatening disease.) The fundamental criterion for entry was that the responsible physician was *uncertain* whether, for a particular patient, treatment with streptokinase or with aspirin was indicated. ECG changes at entry were not a requirement.

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" algorithm[15] 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 August, 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 treatments in the pack was actually given, patients remained in their originally allocated treatment group for an "intention-to-treat" analysis, and the few second entries were disregarded.

Discharge

At discharge, a prerandomisation 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 and at discharge, any apparent side-effects of treatment, and major events in hospital (bleeding, cardiac rupture, fibrillation, 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[16]) were:

Inferior ST elevation (29%).—≥3 mm in the sum of II + III + aVF;

Anterior ST elevation (25%).—*(a)* ≥6 mm in the sum of $V_1 + V_2 + V_3$ and/or *(b)* ≥6 mm in $V_4 + V_5 + V_6$ and/or *(c)* ≥2 mm in I + aVL;

Inferior and anterior ST elevation (2%).—Both of above;

ST depression (8%).—None of the above, but with ST depression as extreme as the ST elevations required above;

Other abnormality (27%).—None of the above, but with *(a)* pathological Q-waves (16%) ≥2 mm in any lead other than aVR or V_1, or *(b)* no Q-waves but T-wave inversion (11%) in any lead other than aVR or V_1, or *(c)* any conduction defect (eg, atrioventricular block) or any arrhythmia (eg, atrial fibrillation, supraventricular tachycardia);

"Normal" (2%).—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]

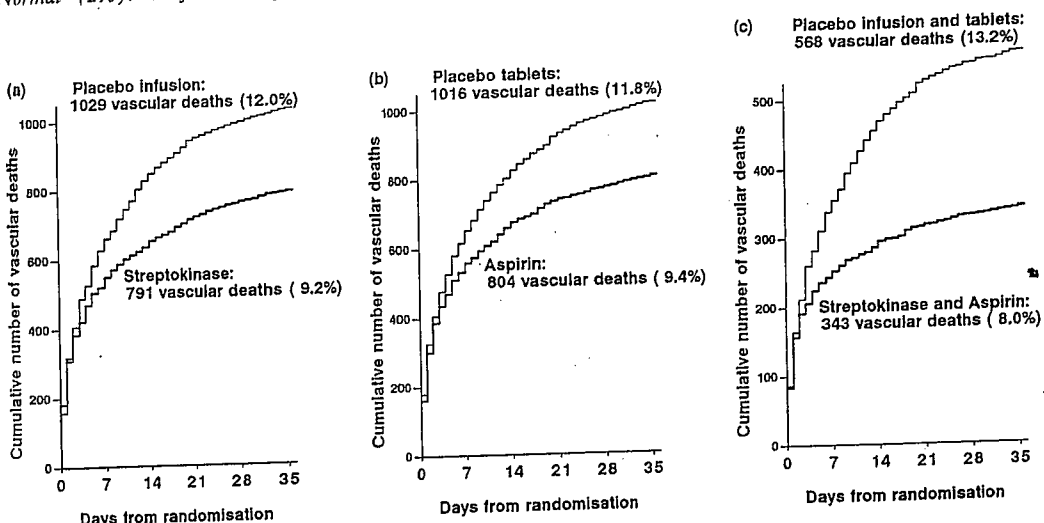

Fig 1—Cumulative vascular mortality in days 0–35.

(a) All patients allocated active streptokinase *vs* all allocated a placebo infusion; (b) all patients allocated active aspirin *vs* all allocated placebo tablets; and (c) all patients allocated both active treatments *vs* all allocated neither. (Statistical[5] tests to day 35—observed number of vascular deaths in active treatment group minus expected number, and the standard deviation of this difference: (a) −118·8 SD 20·2, (b) −105·3 SD 20·2, (c) −112·1 SD 14·3.)

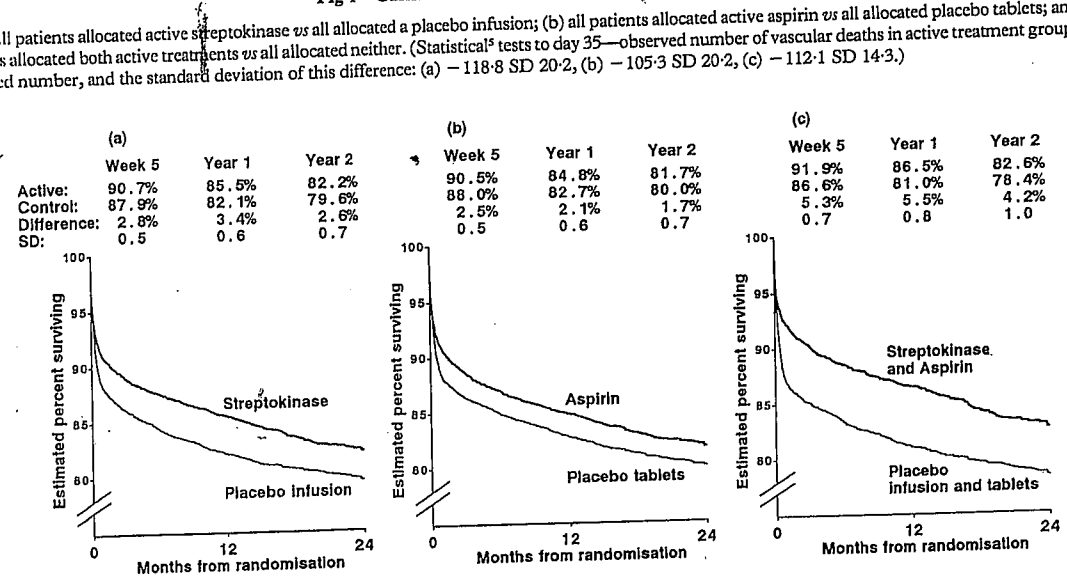

Fig 2—Life-table estimates of 12-month and 24-month survival.

Median follow-up 15 months, maximum 34 months. (Logrank[17] tests to Jan 1, 1988: (a) −133·5 SD 26·7, (b) −88·5 SD 26·7, (c) −110·7 SD 19·0.)

scans and necropsy reports) were requested. Confirmation or refutation of the stroke and its aetiology was based on "blind" review of these records by a neurologist. All strokes not confirmed by CT scan or necropsy as cerebral haemorrhages are described as being of "ischaemic or unknown" aetiology. For, while most probably were ischaemic, a few may have been due to undiagnosed haemorrhage. For each stroke, the "likely residual disability" was classified on the discharge form as non-significant (modified Rankin[9] grade 0–1), moderate (2–3), or severe (4–5); in the present report, the latter two categories are merged. The few reports of possible anaphylactic shock were also reviewed blind of treatment allocation.

Statistical Methods

The protocol specified three main analyses. These involved assessment of the effects of intravenous streptokinase on vascular mortality during (*a*) the first 5 weeks and (*b*) the entire period up to Jan 1, 1988 (ie, a median follow-up of 15 months), and of the effects of 1 month of oral aspirin on vascular mortality during the first 5 weeks (ie, days 0–35, the period of antiplatelet cover). It also specified one "most important subsidiary analysis", involving separate assessment of the effects of streptokinase on 5-week vascular mortality among patients randomised 0–4, 5–12, and 13–24 hours after the onset of symptoms, and six other subsidiary analyses (see Results).

Comparisons of survival to Jan 1, 1988, involve time-to-death analyses using logrank[17] methods (with exact variance calculations), but for events in hospital and deaths during the first 5 weeks comparisons involve simple analyses[5] of total numbers affected. Most results are presented in terms of changes in the *odds* of death: for example, a change from 10% dead (odds 10/90) to 8% dead (odds 8/92) involves an odds ratio of (8/92) ÷ (10/90), or 0·78, and is therefore described as a 22% reduction in the odds of death[5,18] (rather than as a 20% reduction in the risk of death). Odds ratios and reductions in odds are generally given with either 95% confidence intervals or ±1 standard deviation (SD). Two-sided p-values (2p) are cited, even in subgroup analyses where one-sided p-values (1p) might be more appropriate.[13,17]

During recruitment, interim results on events in hospital were reviewed about twice a year by an independent data monitoring committee. In the light of these interim analyses, and of any other evidence or advice they wished to seek, the data monitoring committee were to advise the chairman of the steering committee if, in their view, there was at any time proof beyond reasonable doubt that for all, or for some, types of patient either treatment was clearly indicated or clearly contraindicated. Otherwise, the steering committee, collaborators, and administrative staff (except those who produced the confidential analyses) would remain ignorant of the interim results. In January, 1987, the data monitoring committee reported that, among patients entered 0–4 hours after pain onset, there was clear evidence that mortality in hospital had been reduced by streptokinase.[19] Randomisation continued for those patients where, in the view of the physician actually responsible for the patient, substantial uncertainty remained about the appropriateness of treatment: this was still often the case not only for patients more than 4 hours after pain onset (for whom interim results were not made available during the trial), but also for some presenting earlier.

Results

17 187 patients were randomised between March 5, 1985, and Dec 31, 1987. This large size (and the use of "minimisation") ensured good balance between the treatment groups for the main prerandomisation prognostic features that were measured (see subgroup analyses below), 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. Since the fibrinolytic effect of an infusion that has been interrupted (usually because of some side-effect) may be substantial, effective compliance with streptokinase allocation is likely to be well over 92%. For aspirin, 94% of those discharged alive in both active and placebo groups

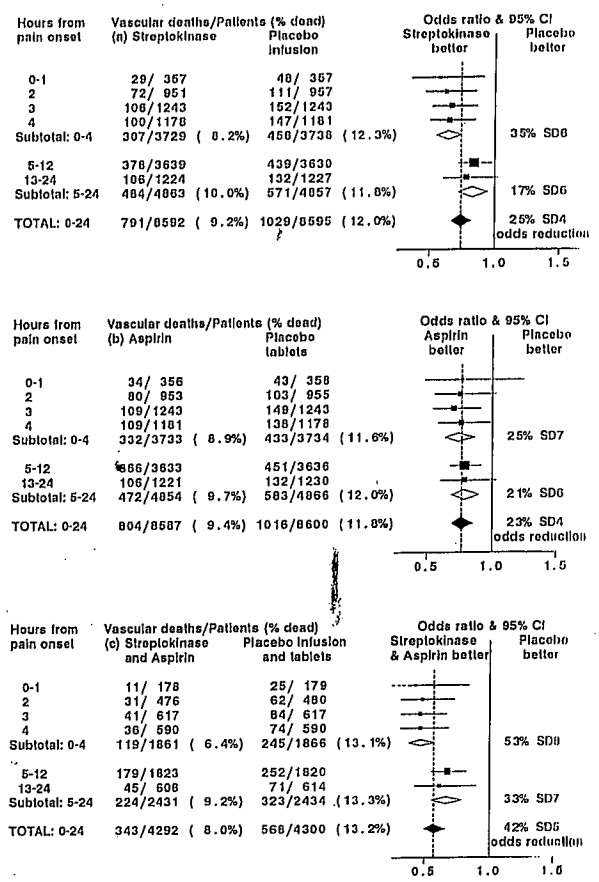

Fig 3—Reductions in odds of vascular death in days 0–35, subdivided by time from pain onset.

The sizes of the squares in figs 3, 5, and 6 indicate how much information is available,[5] and 95% confidence intervals are denoted by lines or by diamonds.

continued their trial tablets throughout the hospital stay, when nine-tenths of 5-week 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-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 difference, including both early and late vascular mortality, remains highly significant (2p < 0·00001). Non-vascular deaths were evenly distributed (32 *vs* 32: table I), 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.

Influence of delay from pain onset to randomisation on size of effect of streptokinase on 5-week vascular mortality (fig 3a).—Among patients randomised 0–4, 5–12, and 13–24 hours after the onset of pain, the reductions in the odds of

TABLE I—EFFECTS OF ALLOCATED TREATMENT ON CLINICAL EVENTS IN HOSPITAL AND ON NON-VASCULAR MORTALITY

Clinical event	Streptokinase allocation			Aspirin allocation			Combination therapy		
	Streptokinase	Placebo infusion	Absolute reduction (% Placebo −% SK)	Aspirin	Placebo tablets	Absolute reduction (% Placebo −% Asp)	Streptokinase & Aspirin	Both placebos	Absolute reduction (% Neither −% SK & Asp)
No randomised	8592	8595		8587	8600		4292	4300	
No with discharge form	8490	8491		8492	8489		4239	4238	
Myocardial infarction									
Any	238	202	−0·4%	156	284	1·5%	77	123	1·1%
Any, discharged alive	155	98	−0·7%	83	170	1·0%	46	61	0·4%
Cardiac rupture									
Any	74	76	0·0%	69	81	0·1%	31	38	0·2%
Any, discharged alive	6	6	0·0%	7	5	0·0%	2	1	0·0%
Cardiac arrest									
Any	687	796	1·3%	690	793	1·2%	311	417	2·5%
Ventricular fibrillation	370	425	0·6%	366	429	0·7%	160	219	1·4%
Other arrests	376	435	0·7%	381	430	0·6%	176	230	1·3%
Any, discharged alive	293	255	−0·4%	259	289	0·4%	133	129	−0·1%
Bleed									
"Major" (transfused)	46	18	−0·3%	31	33	0·0%	24	11	−0·3%
"Minor" (not transfused)	297	81	−2·5%	215	163	−0·6%	167	33	−3·2%
Stroke (excludes TIA)*									
Any	61	67	0·1%	47	81	0·4%	25	45	0·5%
(a) Aetiology:									
Confirmed haemorrhage	7	0	−0·1%	5	2	0·0%	5	0	−0·1%
Other, day 0–1	20	13	−0·1%	11	22	0·1%	7	9	0·0%
Other, after day 1	34	54	0·2%	31	57	0·3%	13	36	0·5%
(b) Disability									
Dead	24	26	0·0%	20	30	0·1%	12	18	0·1%
Disabled at discharge	17	23	0·1%	17	23	0·1%	9	15	0·1%
Not disabled	20	18	0·0%	10	28	0·2%	4	12	0·2%
Any, discharged alive	37	41	0·0%	27	51	0·3%	13	27	0·3%
Non-vascular deaths									
Before wk 5	4	4	0·0%	1	7	0·1%	1	4	0·1%
After wk 5	28	28	0·0%	24	32	0·1%	10	14	0·1%

*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* 0·9%) 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,[20] 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 streptokinase-allocated patients (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 0·03) 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

TABLE II—REPORTED SIDE-EFFECTS ASSOCIATED WITH STREPTOKINASE AND WITH PLACEBO INFUSION

Side-effect	Treatment allocation		Absolute *excess* with streptokinase (% SK–% Placebo)
	Streptokinase	Placebo infusion	
No randomised	8592	8595	
No with discharge form	8490	8491	
"Significant" hypotension and/or bradycardia	847 (10·0%)	173 (2·0%)	7·9%
Allergic reactions	374 (4·4%)	73 (0·9%)	3·5%
Any bleed	343 (4·0%)	99 (1·2%)	2·9%*
Gastrointestinal symptoms	100 (1·2%)	20 (0·2%)	0·9%
Arrhythmias	107 (1·3%)	28 (0·3%)	0·9%
Miscellaneous	99 (1·2%)	16 (0·2%)	1·0%
Patients with any of the above	1534 (18·1%)	383 (4·5%)	13·6%

*The bleeding caused by SK depended on whether the planned treatment involved iv heparin, sc heparin only, or no heparin (absolute excesses 5·3% SD 0·27, 2·6% SD 0·12, or 1·5% SD 0·14 respectively; $2p < 0·0001$ for trend).

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 allocated streptokinase, but this represented a reduction only in arrest with death in hospital. Hence, it does not represent any additional benefit over and above the reduction in total vascular mortality.

Reinfarctions in hospital were reported slightly more commonly among those allocated streptokinase (2·8% *vs* 2·4%; NS), the difference being in reinfarction with discharge alive, not in reinfarction with death in hospital. This overall excess of reinfarction was observed only if streptokinase was given in the absence of aspirin (3·8% among patients allocated streptokinase alone *vs* 2·9% of those allocated neither active drug), whereas among patients allocated the combination of streptokinase and aspirin there was no such excess (1·8% combination *vs* 1·9% aspirin alone).

Comparison of the 8587 Patients Allocated Oral Aspirin with the 8600 Allocated Placebo Tablets

Effect on vascular mortality in first 5 weeks (figs 1b, 3b) and later (fig 2b).—During the first 5 weeks there were 804 (9·4%) vascular deaths in the aspirin-allocated group compared with 1016 (11·8%) in the placebo control group. This 23% SD 4 reduction in the odds of death in the aspirin group is highly significant ($2p < 0·00001$), with 95% confidence interval ranging from 15% to 30%. As was the case for streptokinase, several years of further follow-up will be needed to see how long these early gains persist. Thus far, during a median follow-up of 15 months there has been a slight and non-significant convergence after day 35 (fig 2b), but the overall difference, including both early and late vascular mortality, remains highly significant ($2p < 0·001$). There were fewer non-vascular deaths among aspirin-allocated patients (25 *vs* 39; NS: table I), so all-cause mortality was also highly significantly reduced ($2p < 0·001$), 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 I)—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

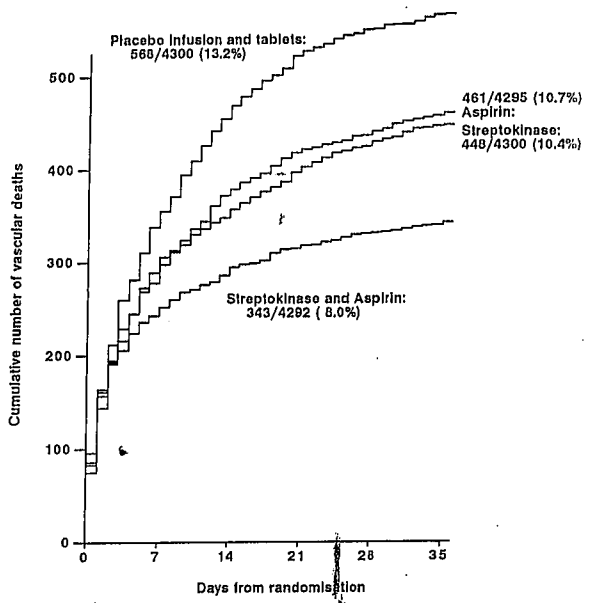

Fig 4—Cumulative vascular mortality in days 0–35.

Patients allocated (i) active streptokinase only, (ii) active aspirin only, (iii) both active treatments, and (iv) neither.

reinfarction ($2p < 0·00001$), in cardiac arrest ($2p < 0·01$), and in stroke ($2p < 0·01$), but there is a considerable overlap between early deaths and these events reported in hospital since some patients had both. To avoid double counting in the assessment of any effects of aspirin over and above those on mortality, attention may be restricted to patients discharged alive. 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 allocated aspirin and among those allocated 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 $2p < 0·001$).

Aspirin produced similar-sized reductions in mortality among patients treated early and those treated late after the

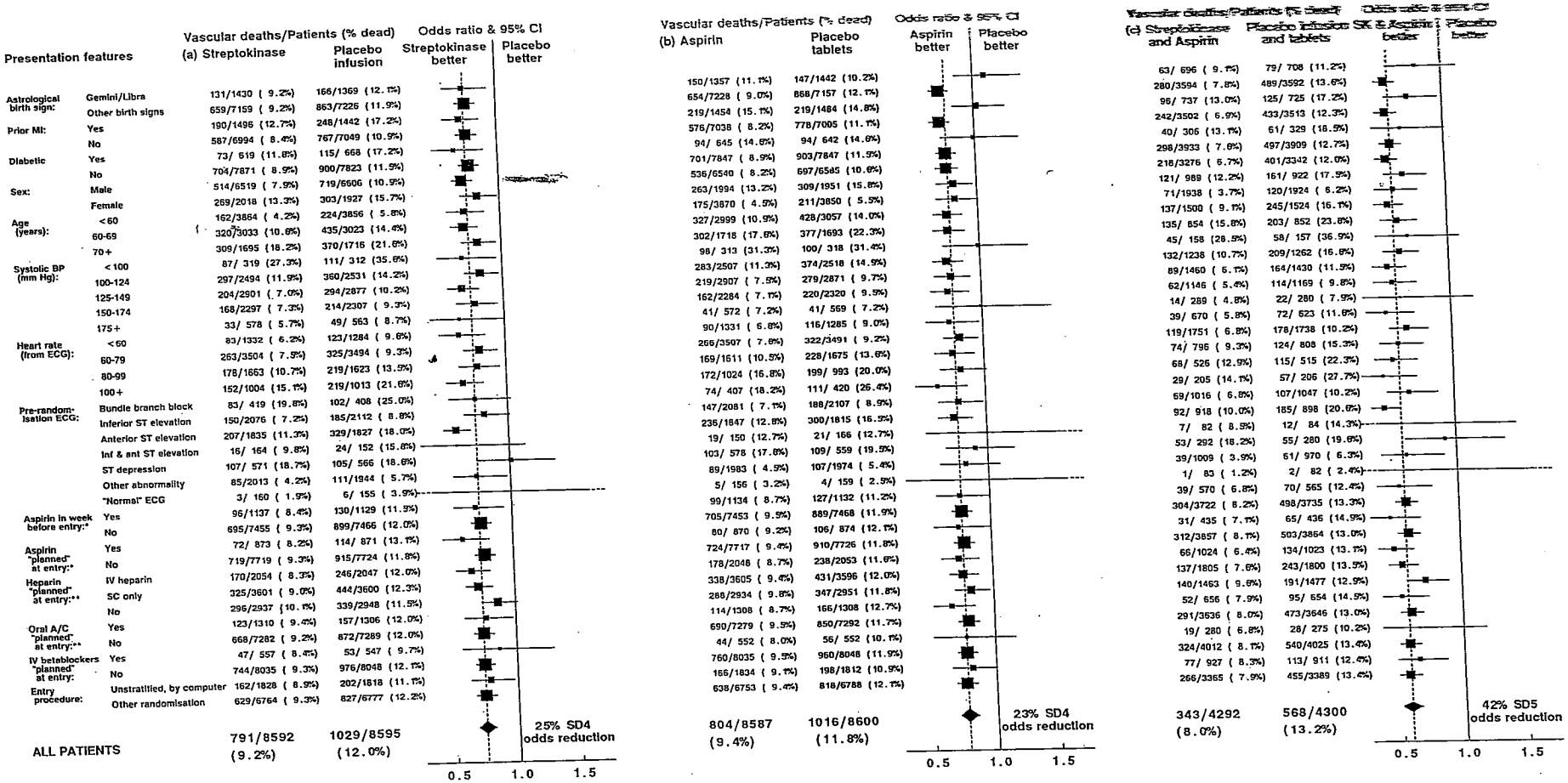

Fig 5—Subgroup analyses of the odds of vascular death in days 0–35.

Square sizes[5] 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 χ-squared test statistics 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 $p > 0.05$.)

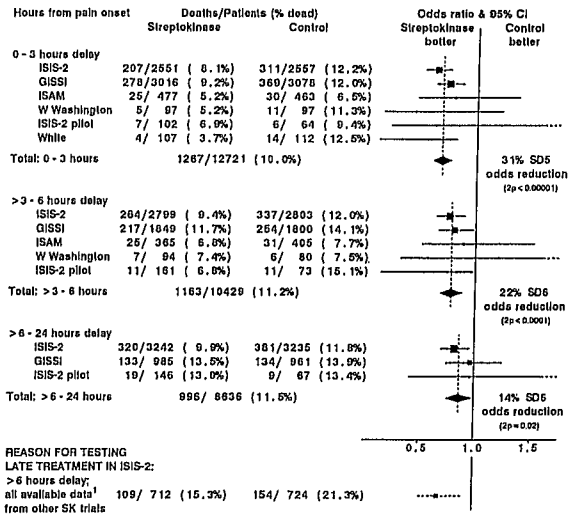

Fig 6—Reductions in the odds of early death, subdivided by time from pain onset: overview of the six randomised trials of 1·5 MU intravenous streptokinase (and of late treatment in other trials[1]).

The infusion duration was 60 min in 5 trials[3,12,23,32] and 30 min in White et al.[33] Square sizes and 95% confidence intervals are as in fig 3. The difference between the 31% reduction 0–3 hours after pain onset and the 14% reduction 6–24 hours after pain onset is 17% SD 7, 2p < 0·02.

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 I).—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,[3] 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 concordant 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

TABLE III—PERCENT REDUCTIONS IN VASCULAR EVENTS OBSERVED IN TRIALS OF MEDIUM AND LONG-TERM ANTIPLATELET THERAPY FOR SUSPECTED OR DEFINITE MYOCARDIAL INFARCTION

Vascular event	% reduction (SD) observed with antiplatelet therapy	
	(a) Acute MI (ISIS-2 main + pilot†)	*(b)* Long-term following MI (10 trials[5])
Non-fatal stroke*	46 (17)	42 (11)
Non-fatal reinfarction*	49 (9)	31 (5)
Vascular death	23 (4)	15 (5)
Any vascular event	28 (4)	25 (5)

*With survival to wk 5 in ISIS-2 and to the end of the scheduled treatment period in the 10 long-term trials.
†In the ISIS-2 pilot trial[12] there were 27/313 (8·6%) vascular deaths during the first 5 wk among patients allocated 4 wk of aspirin compared with 36/306 (11·8%) among those allocated placebo tablets. Among those discharged alive, reinfarctions in hospital were 7 *vs* 10 and strokes were 1 *vs* 2. The only other randomised trial in acute MI[6] involved 300 mg aspirin once only, with no further trial treatment after day 0, and yielded only a very slightly favourable result (total deaths by day 28: 159/1249 *vs* 172/1281).

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 overview[1] of previous trials (fig 6). Among such patients in ISIS-2 streptokinase produced a reduction in vascular mortality that was significant at week 5 ($2p = 0{\cdot}02$) and that has persisted well after week 5, with a median of 15 months of follow-up thus far ($2p = 0{\cdot}004$ for logrank[17] test of effect of streptokinase on overall mortality among 6477 patients entered 7–24 hours after pain). To obtain the most reliable test of this hypothesis, the results of ISIS-2 need to be considered along with those from other recent unconfounded randomised trials of rapid high-dose (1·5 MU within 1 hour) iv streptokinase regimens. Only two such trials[3,12] have included patients presenting more than 6 hours from pain onset, and these, along with ISIS-2 and ISAM,[23] are the four largest trials of a rapid high-dose regimen. There were no significant differences between their findings, and an overview of these results (fig 6) provides significant confirmation of benefit among patients treated after 6 hours. For patients treated within 0–3 hours and 3–6 hours of the onset of pain, the data now available from ISIS-2, GISSI, and the other trials should leave little doubt that fibrinolytic therapy reduces mortality—indeed, even the *lower* 95% confidence limits for the estimated mortality reductions are well away from zero. In contrast, although the observed mortality reduction is statistically significant ($2p = 0{\cdot}02$) among patients treated more than 6 hours after pain onset, it is still consistent with there being only a small benefit. In view of the pattern of *gradual* diminution of benefit with delay, however, and in view of the benefit from streptokinase after 6 hours in the previous trials (fig 6), it is likely that fibrinolytic therapy does produce some worthwhile benefit even when used 7–24 hours after pain onset. But, no analyses of ISIS-2 alone are likely to establish reliably which such patients can expect the greatest proportional benefit. (For example, the reduction in 5-week vascular mortality by streptokinase in patients treated 7–24 hours after pain onset was 22% SD10 [$2p < 0{\cdot}05$] among those with ST elevation recorded on their pre-randomisation ECG, which is similar to the 18% SD 7 [$2p = 0{\cdot}02$] mortality reduction among all patients entered late.)

When deciding whether to use fibrinolytic therapy in patients with suspected acute MI, particularly those presenting late, it is necessary to consider not only the possible benefits but also the possible risks. At least for streptokinase, however, the risks are small: side-effects such 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 [$\equiv 1/206$ *vs* 5], 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.

Antiplatelet 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[7]—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[9] than lower doses, but do not seem to be any more effective.[5] 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). Overall, therefore, among 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 trials[13] 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[5] of which also engendered two studies of aspirin for primary prevention,[25] and the other[1] of which also engendered the GISSI[3] 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 EMERA[26] 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 tPA[27,28] and APSAC[29] 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 would be even less statistically informative). Hence, it is not known which, if any, of the fibrinolytic agents is most effective in averting cardiac death and which, if any, carries the greatest risk of cerebral haemorrhage or other serious side-effects. 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 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 anterior infarct). Patients with systolic blood pressure 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 7) 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 large 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 suggestion[3] that the benefit among those treated within the first hour is much greater than among those treated a little later (fig 3a); but, a small decrease in the median delay to treatment (eg, from 5 hours to 4 hours[31]) does produce a small improvement in the mortality reduction (eg, from 20% to 23%; fig 6). Worthwhile improvements may therefore be achieved by simple measures, such as encouragement of prompt hospital admission and of treatment in the emergency room before transfer

coronary care. It might, however, be best to delay fibrinolytic treatment until hospital admission unless the patient's condition can be monitored during and after infusion, for streptokinase produces some side-effects (eg, sudden profound hypotension) that, although generally easy to manage in hospital, do require prompt medical attention.

Aspirin does not require particularly careful monitoring, and it might well be appropriate to start it as soon as possible (in the home, ambulance, or emergency room) provided there are no clear contraindications. Short-term antiplatelet therapy is likely to be applicable to almost all patients with suspected MI, since the side-effects of low-dose aspirin seem negligible and the drug costs are small. Aspirin could be used widely not only in developed countries but also in countries with limited medical resources. If one month of low-dose aspirin were to be given to just one million new patients a year—which is only a fraction of the worldwide total with acute MI—then a few tens of thousands of deaths, reinfarctions, and strokes could be avoided or substantially delayed (and these benefits could be doubled if low-dose aspirin were continued for at least a few more years[5]).

Although further research may eventually identify some fibrinolytic or antithrombotic regimens more effective than those tested in ISIS-2, streptokinase and aspirin are practicable, and are of demonstrated value and safety. If both are used widely then they should avoid several tens of thousands of deaths each year.

The most important acknowledgment is to the 17 187 patients who agreed to participate, and to the thousands of doctors and nurses in 417 participating hospitals who collaborated with the national coordinators in each country. The coronary care unit nurses in Oxford, Berlin, Bruxelles, Gent, Valencia, and Bellinzona, the computer department in Lyon, and the CTSU staff in Oxford provided the 24-hour randomisation service. The steering and data monitoring committees supervised the study and the ISIS trial office staff and the national coordinators collected and checked the data. The coordinator was supported by the British Heart Foundation. Sterling Drugs donated aspirin and its placebo, but otherwise the entire study was financed by Behringwerke, a subsidiary of Hoechst, the manufacturers of 'Streptase'. The study was, however, designed, conducted, analysed, and interpreted independently of the companies. The following centres and investigators collaborated (*steering committee member, and †data monitoring committee):

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Austria (117 patients).—Univ Klinik, Innsbruck: Dienstl F.*, Lechleitner P.; *KH Bludenz:* Schobel B.; *KH Bregenz:* Erhart K.; *KH Eisenstadt:* Silberbauer K.; *KH Kufstein:* Stuehlinger W.; *KH Muerzzuschlag:* Forenbacher H.; *KH Schwaz:* Ciresa M.; *KH St Johann (Tirol):* Baumgartl P.; *KH Zams:* Pall H.; *KH Zell am See:* Erd W.

Belgium (693 patients).—Universitair Ziekenhuis, Gent: De Backer G.*, Buylaert W., Michem N., Clement D., Rubbens L.; *Erasme, Bruxelles:* Komitzer M.*, Degre S., Barthels M., van der Valk C.; *St Vincentius, Antwerpen:* Goethals M.; *AZ St Jan, Brugge:* Vincke J.; *IMC d'Ixelles, Bruxelles:* Schoenfeld Ph., Poppe M.; *Joseph Bracops, Bruxelles:* Depaepe A., Rosier M.; *AZ VUB, Bruxelles.;* De Wilde Ph.; *Civil de Charleroi:* Picart N., Roosbeck E.; *IMC A Gailly, Charleroi:* Pinon F., Visee A.; *St Vincentius, Deinze:* De Clerck D.; *Stedelijk Ziekenhuis, Dendermonde:* Zenner R.; *St Vincentius, Gent:* Van Durme J.; *Volkskliniek, Gent:* Jordaens L.; *St Jozefkliniek, Gentbrugge:* Kluyskens Y.; *Notre Dame de Grace, Gosselies:* Sottiaux T., Charlot Chr.; *AZ Hoge Beuken:* Bruyneel K.; *Civil de Jumet:* Balthazar E., Dehavay M.; *OLV Ziekenhuis, Mechelen:* Beys J.; *IMC, Tournai:* Dereume G., Vasseur N.; *CGTR Le Rayon de Soleil, Vesale:* Henuzet C., Charlot N.; *St Elisabethkliniek, Zottegem:* Bladt D.

Canada (675 patients).—Hamilton General: Cairns J.*, Turpie A.*, Fraser K., Webb J.; *Bellville General:* Grant F., Vanslyke D., Taylor S., Pedley S.; *Joseph Brant, Burlington:* Carling L., Beare L.; *Cambridge Memorial:* Cooper J., Wilkinson D.; *Public General, Chatham:* Harnarine C., Pfaff S.; *St Joseph's, Chatham:* Willston M..; *Queensway General, Etobicoke:* Sevitt B., Daniels L., Wassmer S.; *Chedoke, Hamilton:* Finkelstein L., Cooper M.; *Henderson General, Hamilton:* Sealey B., Olde J.; *McMaster, Hamilton:* Falfen E., Minard J.; *St Joseph's, Hamilton:* Sullivan M., Tanser P., Kennedy D., Seager S.; *St Joseph's, London:* Goddard M., Janssen J.; *University Hospital, London:* Jablonsky G., Bradley R.; *Victoria, London:* Finnie K., Adkins B.; *Oakville-Trafalgar, Oakville:* Zawadowski A., Graham J.; *Oshawa General:* Bhargava R., Taylor S., Harper G.; *Peterborough Civic:* Hughes W., Jamieson S.; *St Joseph's, Peterborough:* Nawaz S., Lanovic A., Reesor J., Young J.; *Victoria, Renfrew:* Appleyard C., Riddell R.; *Plummer Memorial, Sault Ste Marie:* Stanton E., Rivet L.; *Norfolk General, Simcoe:* Chiu S., McCrea C.; *Sudbury Memorial:* Juma Z., Ballance S., Turcotte J.; *St Mary's, Timmins:* Cunningham H., Wilson L.; *Woodstock General:* Wilkey W., Parciak S.

Denmark (339 patients).—Rigshospitalet, Copenhagen: Pedersen F.*, Sandoe E.*, Kyst Madsen J.*; *Braedstrup:* Amtoft A.; *KAS Gentofte, Copenhagen:* Saunamaeki K., Svendsen J.; *Skt Lukas Stiftelsen, Copenhagen:* Tidstroem B.; *Fakse:* Hansen J.; *Farso:* Lindskov J.; *Frederica:* Hornum I.; *Give:* Deding A.; *Kalundborg:* Lindbjerg I.; *Kjellerup:* Scheibel M.; *Maribo:* Hilden M.; *Ringsted:* Marcussen H.; *Silkeborg Central:* Jensen T., *Soenderborg:* Ollendorf P.

Finland (433 patients).—Maria, Helsinki: Kala R.*; *University Central, Helsinki:* Heikkilä J.*; *Imatra District:* Itkonen A., Havakka E.; *Jokilaakso District:* Nyyssönen S., Lahtinen K.; *Kemijärvi District:* Säkö S., Tauriainen P.; *Keski-Pohjanmaa Central:* Halkosaari M., Salonen P.; *Kotka Central:* Salminen K., Silvennoinen M.; *Lappi Central:* Eloranta M., Autio R.; *Lohja District:* Koivunen L., Kaarlola A.; *Lounais-Häme District:* Koskelainen J., Ryhtä I.; *Mahnska District:* Wingren P-E., Sodo C.; *Mänttä District:* Vallittu H., Äikäs E.; *Mikkeli Central:* Tarssanen L., Virkki L.; *Porvoo District:* Härkönen M., Rask K.; *Raisio District:* Karmakoski J., Lattu M.; *Selkameri District:* Tuunanen V., Jaatinen R.; *Vaasa Central:* Lindroos M., Kivisalo M. *Ähtäri District:* Määttänen J., Mursula R.

France (827 patients).—Hôpital Cardiologique, Lyon: Boissel J-P.*, Leizorovicz A.*, Gillet J.; *Hôpital Sud, Amiens:* Quiret J., Hermida J-S.; *Centre Hospitalier, Annecy:* Dupont J.; *Hôpital Saint- André, Bordeaux:* Blanchot P., Lemetayer P.; *Centre Hospitalier Général, Dunkerque:* Demarq J.; *Hôpital André Mignot, Le Chesnay.;* Normand J., Schwob J.; *Hôtel Dieu, Le Creusot:* Ravisy J.; *Hôpital Emile Roux, Le Puy:* Viallet M.; *Centre Hospitalier Intercommunal, Longjumeau:* Roche P.; *Centre Hospitalier, Macon:* Cavallaro J., Auberger R.; *Centre Médical d'Evecquemont, Meulan:* Abastado M.; *Centre Hospitalier, Roanne:* Glière R.; *Centre Hospitalier, Romans:* Michelon G.; *Centre Hospitalier, Strasbourg:* Finckler L., Muller J.; *Centre Hospitalier, Tourcoing:* Beuscart C., Leroy O.; *Centre Hospitalier, Valence:* Grand A.; *Centre Médical, Vaux sur Seine:* Canny M.; *Centre Hospitalier Lucien Hussel, Vienne:* Veyre B.

Germany (1884 patients).—Klinikum Steglitz, Berlin: Schröder R.*, Schäfer H., Arntz R., Schröder R.; *Herz-Kreislauf-Klinik, Bad Bevensen:* Noetges A., Wolf R.; *Med Klinik, Bad Homburg:* Raisig S., Bodem G.; *St Gertrauden-KH, Berlin:* Ramdohr B., Grupp H.; *KH am Urban, Berlin:* Dissmann W., Topp H.; *Augusta-Krankenanstalten, Bochum:* Kniemann H., Böhle E.; *Knappschafts-KH, Bottrop:* Harbarth P., Schilling T.; *St Joseph, Bremerhaven:* Martin K.; *Städtische Kliniken, Darmstadt:* Frederking H.; *Knappschafts-KH, Dortmund:* Wagner P., von der Ecken B.; *St Johannes, Duisburg:* Beckmann M.; *St Vincenz-KH, Essen:* Toker Y.; *Franziskus-KH, Essen:* Dörwald R.; *Bürgerhospital, Frankfurt:* Gottstein U., Sedlmeyer I.; *St Josef, Gelsenkirchen:* Callsen H.; *Klinik am Eichert, Göppingen:* Giesler H.; *Allgemeines KH, Hagen:* Rox J.; *St Sixtus, Haltern:* Beythien R., Padel T.; *Allgemeines KH Bergedorf, Hamburg:* Seevers H.; *Evangelisches KH, Hamm:* Mösseler U.; *KH St Marienberg, Helmstedt:* Strauch A., Walther C.; *Med Klinik II, Köln-Merheim:* Griebenow R.; *Med Klinik I Krankenanstalten, Konstanz:* Aschoff G.; *Stadt KH Korbach:* Engelsing B., Nasher D.; *KH Landsberg:* Perl R., Gatz S.; *Luisen-KH, Lindenfels:* Huep W.; *St Vincenz-u.Elisabeth, Mainz:* Schwartz B., Weber M.; *Behring, Marburg:* Bernhardt W, Carls C, Muller J, Weidmann E.; *Kreis-KH Mechernich:* Neuhaus J., Mohr P.; *Klinikum Minden:* Ammer W.; *Kreis-KH Mosbach:* Heller A.; *Evangelisches KH, Mülheim/.Ruhr:* Kötter V.; *Med Klinik II u. III, Grosshadern, München:* Engelhardt D., Riess H.; *KH des 3 Ordens, München:* Weidinger P., Lindner D.; *Städtisches KH, Nettetal:* Appenrodt H.; *KH Neu-Ulm:* Spiker A.; *St Josef, Oberhausen:* Schulze-Wethmar H., Kremer G.; *St JosefSterkrade, Oberhausen:* Müting H., Nienhaus T.; *Prosper, Recklinghausen:* Becker E., Sodomann C.; *Knappschafts-KH, Recklinghausen:* Meyer W.; *Med Klinik I, Remscheid:* Löllgen H.; *Med Klinik II, Remscheid:* Zack W., Lang A.; *Diakonie-KH, Rotenburg:* Böttjer H.; *Kliniken der Stadt, Saarbrücken:* Zwirner K.; *Stadt-KH, Salzgitter-Bad:* Meister G.; *Kreis-KH, Schleswig:* Schoormans W.; *Med Klinik B Kantonsspital, St Gallen:* Huber B.; *KH vom Roten Kreuz, Stuttgart:* Kapune W., Rupp E.; *Knappschaftsklinik Sulzbach:* Konrad A.; *St Johannes-KH, Troisdorf-Sieglar:* Stratmann P.; *Kreis-KH Uelzen:* Borm P., Stamatelatos M.; *Klinikum der Landeshauptstadt Wiesbaden:* Piper C, von Egidy H.; *Reinhard-Nieter-KH, Wilhelmshaven:* Frerichs H.

Ireland (831 patients).—Beaumont Hospital, Dublin: Horgan J.*, O'Callaghan D., Ohman M., Boyle E., Crowe B.; *Castlebar General:* Lucey C., Roche M.; *Cavan General, Co Cavan:* Farrelly A., Fay A.; *County Hospital, Bantry, Co Cork:* McCoy D., Kingston J.; *Mallow General, Co Cork:* O'Sullivan P., O'Brien E.; *Regional, Wilton, Co Cork:* Erwin J., Fennell W., Palmer C.; *Letterkenny General, Co. Donegal:* Bannon L., Doyle H.; *St Michael's, Dun Laoghaire, Dublin:* Barniville H., Mason H.; *Naas General, Co Kildare:* Crowe M., Power J., Boland T.; *St Luke's, Kilkenny:* Mahon J., Leahy J.; *Barringtons, Limerick:* Holmes R., Geary A.; *Limerick Regional, Co Limerick:* Peirce T., Hayes J.; *Our Lady of Lourdes, Drogheda, Co Louth:* Muldoon B., O'Neill R., Costello T.; *Mullingar General:* Quinlan C., Weir A., Hyland M.; *Tullamore General, Co Offaly:* Taufe J., Quinn A.; *Sligo General, Co Sligo:* Collins D., Molihan A.; *St Joseph's, Clonmel, Co Tipperary:* O'Regan P., Sr Columba.; *Ardkeen, Waterford:* Fitzgerald G., Kennedy A.

Italy (GISSI liaison).—Mario Negri, Milano: Tognoni G.*, Franzosi M-G.*

New Zealand (281 patients).—Princess Margaret, Christchurch: Fitzpatrick M., White M.; *Waikato, Hamilton:* Freidlander D.; *Hutt Hospital:* Logan R., Dewar J.; *Palmerston North:* Campbell-Macdonald J., Hope N.

Norway (1067 patients).—Baerum: Kjekshus J.*; *Sentral-sjukehuset, Forde:* Reikvam A.*; *Sentral Sykehuset for Ostfold, Frederikstad:* Kahrs J.*; *Haukeland, Bergen:* Ronnevik P.; *Farsund:* Bjering E.; *Fylkessjukehuset i Floro:* Sindre R.; *Hammerfest:* Johansen J.; *Ringerike, Honefoss:* Tenstad O.; *Fylkessjukhuset Kristiansund:* Rongved G.; *Kongsvinger:* Anker E.; *Lillehammer Fylkessykehus:* Dahle M.; *Stensby, Minnesund:* Koss A.; *Vefsn, Mosjoen:* Haugnes T.; *Moss:* Moum B.; *Nordfjord:* Klykken B.; *Fylkessjukehuset Odda:*

Abbasi I.; *Sandefjord Sykehus:* Nordle K.; *Fylkessjukehuset Stord:* Asmervik J.; *Medstat a/s Strommen:* Almaas B.; *Vestfold Sentralsykehus, Tonsberg:* Otterstad J.; *Regionsykehuset Trondheim:* Blikom B.; *Tynset Sjukehus:* Paulsen D.; *Fylkessjukuset i Volda:* Bae E.

Spain (71 patients).—Dr Peset Aleixandre, València: Valentin V.*, Fernandez M.; *Villajoyosa, Alicante:* Fuster M.; *Francisco de Borja, Gandia:* Miralles L.; *Lluis Alcanys, Jativa:* Rodriguez M.; *Mare Nostrum, Palma de Mallorca:* Segui J.; *Puerto deSagunto:* Tormo C.; *Arnau de Vilanova, València:* Fajarnes F.; *Hospital Clinico, València:* Morell S.; *Hospital General, València:* Echanove I.

Sweden (1197 patients).—Östra, Göteborg: Wilhelmsen L.*†, Thorin M.; *Bollnäs:* Mascher G., Bodin L-G.; *Enköping:* Karlsson L.; *Härnosänd:* Pernér H., Larsson E.; *Hässleholm:* Petersson B.; *Hudiksvall:* Lundkvist L.; *Karlskoga:* Nyberg G., Persson E-B.; *Köping:* Malmros B., Nicol P.; *Kristinehamn:* Watz R.; *Ljungby:* Svensson K-A., Roberts A.; *Ludvika:* Frisell J-E.; *Mora:* Aronson D., Hedlund H.; *Nyköping:* Dahlberg A., Elsberg I.; *Örnsköldsvik:* Lövheim O., Körning G.; *Sandviken:* Ellström J., Holm A-M.; *Simrishamn:* Hallgren J, Gisselsson A.; *Södertälje:* Lindberg K., Hedh A.; *Sabbatsberg, Stockholm:* Hofman-Bang C., Senbom G.; *SCB Stockholm:* Hörte L-G.; *Sundsvall:* Möller B., Wallner G.; *Trelleborg:* Backmann R.; *Visby:* Hoffstedt E., Väss S.; *Ystad:* Lenner H., Armman K.

Switzerland (157 patients).—San Giovanni, Bellinzona: Malacrida R.*, Genoni M.*.; *Civico, Lugano:* Moccetti T.*.; *Kreuzspital Chur:* Ziegler H.; *Bezirksspital Grosshoechstetten:* Burger H.; *Bezirksspital Herzogenbuchsee:* Bosshard E.; *Morges:* Knobel P.; *Moutier:* Junod J.; *Regionalspital Rheinfelden:* Iselin H.; *Spital Schiers:* Wuelser U.; *Kantonsspital Stans:* Fischer H.; *Bezirksspital Waedenswil:* Moehr P.; *Zuercher Hoehenklinik Wald:* Brändli O.; *Neumuensterspital Zollikerberg:* Siegrist P.; *Buergeerspital Zug:* Keiser G.

United Kingdom (6213 patients).—Radcliffe Infirmary & John Radcliffe Hospital, University of Oxford: Collins R.* (co-ordinator), Sleight P.* (chairman), Peto R.*, Parish S.* (statisticians), Dove P.*, Cederholm-Williams S.*, Doll R.† (chairman), Armitage P.†, Conway M., Alexopoulos D., Halls H., Jackson D., Connelly K., King M., Lloyd P., Appleby P., Spence S., Skelt R., Scrimgeour A., Lim L., Richards S., Targett K., Fyson B., Simpson D., Marshall J., Phelps S., Caulfield J., Lane T., Mead G., Crtl P., Hafner B., Thompson E., Borcham J., Youngman L.; *British Heart Foundation:* Julian D.†; *Royal Sussex:* Chamberlain D.†; *Northern General, Edinburgh:* Warlow C.*; *Ashford, Middlesex:* Wilkinson P., Mathieson P.; *William Harvey, Ashford:* Wilson I., Cowley A.; *Barnet General:* Gray K., Phillips J.; *Basingstoke District:* Fowler J., Dre Paul B.; *Birmingham General:* Pentecost B., Lamb P.; *Bishop Auckland General:* Bateson M., Brunskill R.; *Pilgrim, Boston:* Nyman C., Shaw E.; *Bristol Royal Infirmary:* Channer K., Ranger A.; *Bury General:* Benaim M., Cronkshaw B.; *West Suffolk, Bury St Edmunds:* Siklos P, Edwards C.; *Law, Carluke:* Baxter R., Cromwell M.; *St Stephen's, Chelsea:* Hargreaves M., O'Keefe F.; *Broomfield, Chelmsford:* Murray M., Morris A.; *Colchester District General:* Handley A., Maskell G., Shaw J.; *Coleraine:* Finnegan O., Thompson O.; *Crawley:* Parkinson K., Boolaky M.; *Cumberland Infirmary:* Robson R., Kewley D.; *Dorset County, Dorchester:* Ashfield R., Colwell S.; *Downe, Co Down:* MacAleenan F.; *Daisy Hill, Co Down:* Devlin J., McConville M.; *Dumfries & Galloway Royal Infirmary:* Armstrong A., McDonald M.; *Milesmark, Dunfermline:* Malone D., Northridge D., Coyle C.; *Ealing:* Owen R., Wheildon M.; *St Mary's, Eastbourne:* McLeod A., Bordoli G.; *GRO, Edinburgh:* Hill G.; *Royal Air Force, Ely:* Amroliwalla F., Cousins S.; *Southern General, Glasgow:* Hume R., McGowan J.; *Victoria Infirmary, Glasgow:* McGuiness J.; *James Paget, Great Yarmouth:* Grabau W., Stevens A.; *Royal Surrey County, Guildford:* Moher M., Vickery M.; *Harrogate District:* Larkin H., Stewart M.; *Hereford County:* Pitcher D., Bird C.; *Hertford County:* Keir P., Thomas S.; *Hexham General:* Brackenridge R., Pencott I.; *Hinchingbrooke District General:* Henderson R., Wingfield T.; *Nobles, Isle of Man:* Bourdillon R., Kenna C.; *Kent & Canterbury:* Taylor D., Kamson G.; *Crosshouse, Kilmarnock:* Groden B., Jamieson A.; *Kingston:* Medd W., Oakes-Garnett R.; *Llandough:* Routledge P., Morris J.; *Llandudno General:* Galpin O., Duval A.; *Macclesfield District General:* Davies E., Lomas M.; *Margate:* Lillicrap D., Hucey D.; *Monklands District General:* Rodge J., Hume F.; *Newmarket:* Kerrigan G., Foster C.; *County Hospital, Oban:* Henderson A., Cameron A.; *Ornskirk & District General:* McIver M., Wilson D.; *Farnborough, Orpington:* Wharton C., Ramsay Y.; *Orpington:* Williams J., Stevens A.; *Royal Alexandra, Paisley:* McAlpine S., Gibson C.; *Whiston, Prescott:* Macmillan R., Daniels J.; *Royal Preston Infirmary:* Watt D., Clulow J.; *Royal Berkshire, Reading:* North K., Fletcher A.; *Birch Hill, Rochdale:* Davidson C., Wood E.; *Scarborough:* Clark R., Scott R.; *Royal South Hants, Southampton:* Wood D., Jones V.; *Southport General:* Hanley W., Brookfield S.; *OPCS, Southport:* Foster E., Halliwell J., Sides S., Edge E.; *Staffordshire General:* Francis J., Paulose A.; *Staincliffe General:* Kemp T., Pinfield L.; *Stracathro:* Callaghan T., Henderson H., Mitchell A.; *Sunderland General:* Mittra B., McKinnon E.; *Good Hope, Sutton Coldfield:* Eddy J., Bartholomew M.; *Tameside General:* Hussini M., Greenhough C.; *Taunton & Somerset:* Sanderson J., Gledhill B.; *Torbay Hospital, Torquay:* Dewhurst N., Wilkinson R.; *Vale of Leven:* Carmichael H., Hunter E.; *Manor, Walsall:* Cunnington A., Cottam P.; *Queen Elizabeth II, Welwyn Garden City:* Keir P., Engel M.; *Weymouth & District:* Ashfield R., Colwell S.; *War Memorial, Wrexham:* Sissons C., Jones M.; *New Cross, Wolverhampton:* Pidgeon J., Williams G.; *Worcester Royal Infirmary:* Tibbuît D., Caldwell J.; *Worthing:* McBrien D., Signy M., Lawson D.; *Wycombe General:* Hendry W., Hadfield P.; *Wythenshawe, Manchester:* Brooks N., Bennett D., Coppinger T.; *Yeovil Infirmary:* Palferman T.; *York District:* Boyle R., Marshall P.

United States (407 patients).—Brigham and Women's Hospital, Boston, MA: Hennekens C.*, Alexander P., Eberlein K., Goldhaber S., Hebert P., Vincent D.; *NHLBI Clinical Trials Branch, Bethesda, MD:* Yusuf S.*.; *University of Chicago, IL:* Meier P.†; *Akron General Medical Center, OH:* Heiselman D., Reinfeld C.; *VA Medical Center, Allen Park, MI:* Sabharwal S., Ashwell B.; *VA Medical Centre, Atlanta, GA:* D'Amato P., Clark C.; *Aurora Community, MO:* Gudapati R., Kinder V; *Greater Baltimore Medical Center, MD:* Biddison J., Long M.; *Caylor-Nickel, Bluffton, IN:* Collins J., Lindsey P.; *Good Samaritan, Cincinatti, OH:* Razavi A., Small E.; *Fairview General, Cleveland OH:* Watts R., Wilinski D.; *Corning, NY:* Mieczkowski J., Whitehead D.; *VA Medical Center, Dayton, OH:* Suryaprasad A., Erker M.; *RE Thomason General, El Paso, TX:* DiNardo-Ekery D., Bohne V.; *Evanston, IL:* McDonough T., Hubbard J.; *Farmington Community, MO:* Grix G., St Gemme S.; *Glens Falls, NY:* Morrissey J., Cottone D.; *Community General Osteopathic, Harrisburg, PA:* Jeffries R., March J.; *Hinds General Hospital, Jackson, MS:* Harper W., Genesse M.; *Stanton County, Johnson, KS.:* Troup W., James J.; *Lakewood, OH:* Reynolds R., Nesta J.; *Lawrence Memorial, KS:* Pees G., Stockdale R.; *Beebe Hospital of Sussex, Lewes, DE:* Bolourchi H., Dick C., Jackson R.; *Lindsborg Community, KS:* Loder B., Fredrickson D., Lucas S.; *Long Island College, NY:* Scarpa W., Ferraioli L.; *Alton Ochsner Medical Foundation, Los Angeles, CA:* Genton E., Landry J.; *Lakewood, Morgan City, CA:* Blereau R., Cortez C.; *Henry Clay Frick Community, Mount Pleasant, PA:* Lynn R., Brown S., Bell A.; *Ball Memorial, Muncie, IN:* Whitaker J., Elam M.; *Leonard Morse, Natrick, MA:* Pomfret D., Giacalone M.; *Jersey Shore Medical Center, Neptune, NJ:* Boak J., Thom R.; *St Raphael, New Haven, CT:* Dock D., Mason J., Acampora M.; *Bronx Municipal, New York, NY:* Keefe D., Connolly T., Survillo A., Williams S.; *The Staten Island, New York, NY:* Costantino T., Sturzynski A.; *Sterling, New York, NY:* Lockhart E.; *Christ Hospital, Oak Lawn, IL:* Cuadros H., Wash J.; *University Hospital, Puerto Rico:* Veray F., Torres M.; *William Beaumont, Royal Oak, MI:* Timmis G., Tollis C., Worden E.; *Peninsula General, Salisbury, MD:* Agarwal B., Heda H., Morcum D.; *Firelands Community, Sandusky, OH:* Young D., Stradtman J.; *St Francis Regional Medical Center, Wichita, KS:* Evans R., Sweet D., Stroot J.; *VA Medical Center, Witchita, KS:* Pelletier L., Depler G.; *Zurbrugg Memorial, Willingboro, NJ:* Ginsberg F., Halgas C.; *Mt Ascutney, Windsor, VT:* Conger B., Hamilton K.; *Choate-Symmes Health Service, Woburn, MA:* Tucker K., Kane M.; *Worcester Memorial, MA:* Greenberg J., Mills R., Granger J.

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