THE LANCET

Vol 339 Saturday 28 March 1992 No 8796

ORIGINAL ARTICLES

ISIS-3: a randomised comparison of streptokinase *vs* tissue plasminogen activator *vs* anistreplase and of aspirin plus heparin *vs* aspirin alone among 41 299 cases of suspected acute myocardial infarction

ISIS-3
(THIRD INTERNATIONAL STUDY OF INFARCT SURVIVAL)
COLLABORATIVE GROUP

41 299 patients entering 914 hospitals up to 24 h (median 4 h) after the onset of suspected acute myocardial infarction were randomised between streptokinase (SK: 1·5 MU infused over about 1 h), tissue plasminogen activator (tPA, duteplase: 0·60 MU/kg infused over about 4 h), or anisoylated plasminogen-streptokinase activator complex (APSAC, anistreplase: 30 U over about 3 min). All patients were to receive aspirin (162 mg/day enteric-coated), with the first tablet chewed for rapid and full antiplatelet effect. Half of all patients were randomly allocated subcutaneous calcium heparin (12 500 IU starting at 4 h and given twice daily for 7 days or until prior discharge) in addition to aspirin, and the other half were to receive aspirin alone.

Aspirin plus heparin versus aspirin alone—The addition of heparin to aspirin was associated with an excess of transfused or other major non-cerebral bleeds (1·0% aspirin plus heparin *vs* 0·8% aspirin alone; $2p < 0·01$) and of definite or probable cerebral haemorrhage (0·56% *vs* 0·40%; $2p < 0·05$), but with no significant differences in total stroke (1·28% *vs* 1·18%). Reinfarctions were slightly less common among those allocated aspirin plus heparin (3·16% *vs* 3·47%; $2p = 0·09$). There was no significant difference in the pre-specified endpoint of 35-day mortality (2132 [10·3%] aspirin plus heparin *vs* 2189 [10·6%] aspirin alone). During the scheduled heparin treatment period there were slightly fewer deaths in the aspirin plus heparin group (days 0–7 in hospital: 1534 [7·4%] *vs* 1633 [7·9%]; $2p = 0·06$), with a slight convergence by day 35 (598 further deaths [3·1% of survivors] *vs* 556 [2·9%]). The pattern was similar to that observed in the GISSI-2 trial, so that in both trials combined there was a significant reduction in mortality during the scheduled treatment period (2071 [6·8%] *vs* 2239 [7·3%]; $2p < 0·01$). This indicates avoidance of 5 deaths (SD 2) per 1000 patients allocated this high-dose subcutaneous heparin regimen in addition to aspirin, but some of any early benefit may be lost after heparin ceases, with no significant mortality advantage in days 0–35 (both trials: 3100 [10·0%] *vs* 3172 [10·2%]) or during follow-up to 6 months.

SK versus APSAC—APSAC was associated with significantly more reports of allergy causing persistent symptoms and of non-cerebral bleeds, but not of transfused bleeds or of reinfarctions. There was a slight excess of strokes with APSAC (1·04% SK *vs* 1·26% APSAC; $2p = 0·08$), much of it appearing soon after treatment started (strokes during days 0–1: 0·50% SK *vs* 0·73% APSAC; $2p < 0·02$) and being attributed to cerebral haemorrhage (0·24% SK *vs* 0·55% APSAC; $2p < 0·0001$). No significant difference was observed in reinfarction (3·47% SK *vs* 3·55% APSAC). There was no significant mortality difference during days 0–35, either among all randomised patients (1455 [10·6%] SK *vs* 1448 [10·5%] APSAC) or among the pre-specified subset presenting within 0–6 h of pain onset and with ST elevation on the electrocardiogram in whom fibrinolytic treatment may have most to offer (861 [10·0%] SK *vs* 855 [9·9%] APSAC). No significant difference in 6-month survival was apparent overall or in the subset.

SK versus tPA—tPA was associated with significantly fewer reports of allergy causing persistent symptoms and of hypotension requiring drug treatment, and with significantly more reports of non-cerebral bleeds, but not of transfused bleeds. There was a significant excess of strokes with tPA (1·04% SK *vs* 1·39% tPA; $2p < 0·01$), much of it appearing soon after treatment started (strokes during days 0–1: 0·50% SK *vs* 0·92% tPA;

Collaborators and participating centres are listed at the end of the report. Correspondence: ISIS, Clinical Trial Service Unit and Department of Cardiovascular Medicine, Radcliffe Infirmary, Oxford OX2 6HE, UK

2p < 0·0001) and being attributed to cerebral haemorrhage (0·24% SK *vs* 0·66% tPA; 2p < 0·00001). Fewer reinfarctions were observed with tPA (3·47% SK *vs* 2·93% tPA; 2p < 0·02). There was no significant mortality difference during days 0–35, either among all randomised patients (1455 [10·6%] SK *vs* 1418 [10·3%] tPA) or among the 0–6 h ST elevation subset (861 [10·0%] SK *vs* 822 [9·6%] tPA), and no difference in 6-month survival was apparent. These findings reinforce those from the similar GISSI-2 trial with, in both trials combined, zero difference in 35-day mortality (2413/24 176 [10·0%] SK *vs* 2411/24 118 [10·0%] tPA) and no significant difference in 6-month survival. There were 5 per 1000 fewer reinfarctions with tPA (783 [3·26%] SK *vs* 671 [2·80%] tPA; 2p < 0·005), and 4 per 1000 more strokes with tPA (239 [1·00%] SK *vs* 324 [1·35%] tPA; 2p < 0·001), with half of this excess being of fatal stroke and half of non-fatal stroke.

Lancet 1992; **339**: 753–70.

Introduction

During acute myocardial infarction (MI), rapid dissolution of coronary artery thrombus can preserve myocardium and reduce mortality,[1] but fibrinolytic regimens that lyse coronary artery clots more aggressively may also lyse protective thrombus more aggressively, causing an increase in haemorrhagic strokes or other bleeds.[2] Similarly, more aggressive antithrombotic regimens, perhaps involving early intravenous heparin, may prevent coronary artery occlusion after fibrinolytic therapy but may also cause an increase in cerebral or other haemorrhage. It cannot be assumed,[3] therefore, that the *overall* clinical efficacy of fibrinolytic or antithrombotic regimens depends solely on the rapidity of coronary recanalisation and on its persistence. The aim of ISIS-3 was to assess directly this balance between the benefits and risks of different antithrombotic regimens and of different fibrinolytic regimens.

Balance of benefits and risks: aspirin plus heparin versus aspirin alone

ISIS-2 showed that 162 mg/day of aspirin for 1 month greatly reduced reinfarction (particularly among patients given fibrinolytic therapy), stroke, and death.[4] A single dose of at least 160 mg of aspirin has a profound antiplatelet effect within 1 h,[5,6] but lower daily doses (eg, 75–80 mg) may take a few days to exert their full antiplatelet effects.[7,8] It may be prudent, therefore, in acute MI to start immediately with at least 160 mg (as in ISIS-2, GISSI-2[9] and its international extension,[10] and some other studies[11]). Taken together, several small trials of heparin in acute MI suggest some protective effects,[12] although the evidence for heparin is weaker than for aspirin. Addition of heparin to an effective aspirin regimen might offer slighly better protection than aspirin alone, but perhaps at the risk of somewhat more bleeding. The previous heparin trials do not provide direct evidence as to whether any benefits of heparin would be additional to those of aspirin, for aspirin was not routinely used in most. Likewise, though ISIS-2 proved that aspirin plus heparin was better than heparin alone,[4] it did not assess whether the combination was better than aspirin alone. To assess this directly, therefore, GISSI-2[9,10] and the present ISIS-3 trial have randomised patients either to aspirin plus heparin or to an effective dose of aspirin alone.

For several days after MI, patients are at increased risk of rethrombosis and reinfarction,[4] so any heparin regimen may need to continue for at least the first week. This may be more practicable with a fixed-dose subcutaneous regimen (as in the present study) than with an intravenous regimen, particularly if frequent dose adjustments are required to protect against excessive prolongation of the activated partial thromboplastin time (aPTT) following fibrinolytic therapy. (For example, in a fibrinolytic trial[13] that involved an immediate 5000 IU intravenous heparin bolus followed by 1000 IU/h infusion adjusted periodically,[14] two-thirds of patients had aPTTs above 85 seconds at 6 h and one quarter still did so at 24 h, when the median value was 60 s). After a delay of some hours, a twice-daily 12 500 IU subcutaneous heparin regimen generally produces moderate effects on coagulation (increasing aPTT from a mean control value of about 35 s to a mean of about 50 s[15]), similar to the average effects of the same total dose infused intravenously.[16,17] This subcutaneous regimen was considered, therefore, to have a fairly low potential risk of haemorrhage, especially during the first few hours when fibrinolytic therapy is active. At least in the absence of aspirin, however, it had been shown to have substantial antithrombotic effects in acute MI.[15,18] Both ISIS-3 and GISSI-2 have assessed the effects of adding this heparin regimen to aspirin among patients receiving fibrinolytic therapy, and therefore the best evidence comes from consideration not of each separately but of their combined results.

Balance of benefits and risks: SK versus tPA versus APSAC

Standard regimens of streptokinase (SK), tissue plasminogen activator (tPA), or anisoylated plasminogen-streptokinase activator complex (APSAC, anistreplase), can all lyse coronary thrombus, help preserve ventricular function, and reduce mortality in acute MI.[4,19–22] They differ, however, in the rapidity with which they lyse thrombus: after 90 min, coronary artery patency rates are higher with tPA (irrespective of whether the standard alteplase-tPA[23–27] or the standard duteplase-tPA[28–31] regimen is used: table I) and, probably, with APSAC than with SK.[32] So, the newer agents might be even better than SK at preventing cardiac death, but might increase the risk

TABLE I—ALL AVAILABLE TRIALS OF THE EFFECTS ON 90 MIN CORONARY ARTERY PATENCY (TIMI GRADE 2 OR 3) OF (*a*) THE CURRENTLY STANDARD ALTEPLASE-tPA REGIMEN, AND (*b*) THE ISIS-3 DUTEPLASE-tPA REGIMEN

(*a*) Standard alteplase-tPA regimen			(*b*) ISIS-3 duteplase-tPA regimen†		
	Patency at 90 min			Patency at 90 min	
Study	No	%	Study	No	%
TIMI-B[23]	59/83	*71%*	ESPRIT[28]	177/251	*71%*
TAMI-I[24]	119/167	*68%*	Grines et al[29]	155/230	*67%*
GAUS[25]	84/121	*69%*	Kalbfleisch et al[30]	330/478	*69%*
TIMI-IIA[26]	98/131	*75%**			
ECSG-5[27]	39/51	*76%**			
Overall (confidence interval: 67–77%)	399/553	*72%*	Overall (confidence interval: 65–73%)	662/959	*69%*

*Based on angiograms performed between 15 and 200 min (mean 2 h) in TIMI-IIA and between 60 and 120 min in ECSG-5.
†In the study of Koster et al[31] dosage was not by weight, but the 20 patients given the highest dose per kg received a median of 0 43 MU/kg within 90 min (as in ISIS-3) and 12 (60%) achieved patency.

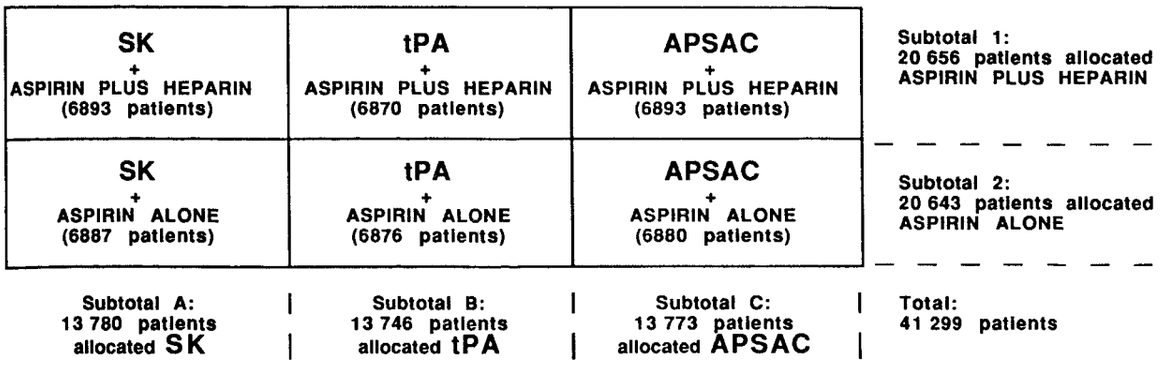

Fig 1—Factorial design of ISIS-3.

41 299 patients: 36 381 in whom the responsible clinician considered there to be a "clear indication" for fibrinolytic therapy, plus half of the 9475 in whom the indication was considered "uncertain".

of cerebral haemorrhage. (Indeed, an alteplase-tPA dose 50% higher than currently recommended was associated with about 10 extra cerebral haemorrhages per 1000 patients.[2]) Moreover, in directly randomised comparisons between different fibrinolytic regimens, these early differences in coronary artery patency lasted only a few hours,[32,33] and there were no significant differences between the effects of these different regimens in ventricular function.[34-37] Indirect comparison of the mortality results for patients presenting within 6 h in the main trials of SK (ISIS-2,[4] GISSI-1,[19] and ISAM[20]), of tPA (ASSET[21]), and of APSAC (AIMS[22]) suggested that APSAC might be somewhat more effective, but none of these mortality reductions was significantly better or worse than the overall average of about one-quarter. Hence, any real difference in mortality (or serious morbidity) is unlikely to be substantial, and it can therefore be assessed reliably only by direct randomisation of large numbers of patients. These are provided both by the open GISSI-2 trial[9,10] of over 20 000 patients randomised between SK and tPA, and by the present placebo-controlled ISIS-3 trial of over 40 000 randomised between SK, tPA, and APSAC. For SK *versus* tPA, therefore, the best evidence again comes from the combined results of ISIS-3 and GISSI-2.

TABLE II—BASELINE CHARACTERISTICS RECORDED BEFORE RANDOMISATION (AS A PERCENTAGE OF THOSE RANDOMISED)

Characteristic	Overall percent
Female	27·1
Diabetic	11·3
Previous MI	21·7
Previous stroke	3·6
Cigarette smoker	41·3
Previous gastrointestinal bleed or ulcer	8·6
Age (yr)	
<60	39·1
60–69	34·8
≥70	26·1
Hours from pain onset	
0–6	78·2
7–12	14·4
13–24	7·4
Hours since pain ended	
0–6	98·1
7–12	1·4
13–24	0·5
Systolic BP (mm Hg)	
<100	6·0
100–174	86·2
175+	7·8
Heart rate	
<60	11·8
60–99	73·5
100+	14·7
Pre-randomisation ECG	
Bundle branch block	4·1
Anterior ST elevation	34·9
Inferior ST elevation	33·5
Other ST elevation	8·5
ST depression	7·2
Other abnormality	8·4
Normal ECG	3·4
0-6 hours from pain onset, ST elevation	62·6
"Uncertain" indication for fibrinolytic therapy	11·9

Patients and methods

To encourage recruitment, the trial procedures were simple. Patient entry involved no forms (only a short telephone call to a 24 h randomisation service). Trial treatments were conveniently packaged, the use of ancillary treatments was not restricted, and all that was required after discharge was completion of a simple single-sided form relating to in-hospital events. Follow-up after discharge was only of mortality, and was conducted through government records wherever possible. Perhaps as a result, 914 hospitals in 20 countries randomised a total of 45 856 patients between September, 1989, and January, 1991.

Patients for whom their physicians thought there was a "clear" indication for fibrinolytic therapy were randomised equally between SK, tPA, and APSAC, whereas those for whom the indication was considered "uncertain" (perhaps because the patient presented more than 6 h after pain onset or because there was no definite ST segment elevation on the initial electrocardiogram) were randomised equally between fibrinolytic therapy (SK, tPA, or APSAC) and open control (ie, no placebo). The decision as to whether there was a "clear" or an "uncertain" indication for fibrinolytic therapy in a particular patient was left entirely to the responsible physician, and the criteria could differ substantially from one doctor to another even within the same hospital. The present report is of the results among all 41 299 patients, whether in the "clear" or "uncertain" indication category, who were to receive fibrinolytic therapy (and those "uncertain indication" patients who were not allocated fibrinolytic therapy will be reported elsewhere).

Treatment

All 41 299 patients were randomised in a 3 × 2 factorial study design[38,39] between three different fibrinolytic regimens and two different antithrombotic regimens (fig 1). Patients were randomly allocated immediate treatment with one of three intravenous fibrinolytic regimens: one-third allocated SK (1·5 MU of 'Streptase' infused over about 1 h), one-third tPA (0·04 million clot lysis units of duteplase per kg body weight as an initial 1 min bolus, 0·36 MU/kg as a "lytic" dose during the remainder of the first hour, and then 0·067 MU/kg per h as a "maintenance" infusion for the next 3 h), and one-third APSAC (30 U of 'Eminase' injected over about 3 min). All patients were allocated two ampoules (one active and one placebo), both of which were to be given: the first always looked like APSAC and the second either like SK or like tPA. To keep APSAC and tPA at about 5°C, for long-term stability, trial treatment packs were distributed in cold boxes, and each coronary care unit was provided with a small refrigerator to store the packs.

All patients were to receive oral aspirin (162 mg in enteric-coated tablets given daily for one month, starting immediately with the first tablet crushed or chewed for a rapid antiplatelet effect). Half of all

TABLE III—COMPLIANCE WITH ALLOCATED TREATMENT, AND OTHER MEDICAL MANAGEMENT IN HOSPITAL (AS A PERCENTAGE OF THOSE SURVIVING TO DAY 35 FOR WHOM A DISCHARGE FORM WAS RECEIVED)

	Antithrombotic comparisons		Fibrinolytic comparisons		
—	Aspirin + heparin	Aspirin	SK	tPA	APSAC
Antiplatelet therapy					
In hospital	98·2	98·3	98·2	98·4	98·2
At discharge	81·6	83·0	82·2	82·3	82·4
Trial heparin					
Started	88·5	—	45·8*	45·9*	45·6*
Completed	77·7	—	40·0	40·6	39·8
Trial or non-trial heparin					
Intravenous	10·1	14·0	12·0	12·2	11·9
IV or high-dose sc	92·4	17·9	55·1	55·5	55·2
Any heparin	93·5	25·4	59·6	59·6	59·4
Oral anticoagulant					
In hospital	4·6	5·4	4·8	5·5	4·7
At discharge	4·4	4·8	4·5	4·9	4·3
Trial fibrinolytic					
Started	97·1	97·1	96·8	97·0	97·4
Completed	94·8	94·9	93·0	94·3	97·4

*High-dose subcutaneous (sc) heparin was allocated to 50% in each fibrinolytic group.

patients were allocated randomly to receive aspirin plus calcium heparin (a fixed-dose regimen of 12 500 IU 'Calciparine', starting about 4 h after randomisation and given subcutaneously twice daily for 7 days or until prior discharge), and half to receive aspirin alone (with heparin avoided unless the responsible physician considered some form of anticoagulation to be *clearly* indicated). All use of oral anticoagulants and all use of heparin beyond one week was to be avoided unless considered clearly indicated.

The trial treatments were to be interrupted only if this was thought clearly indicated by the responsible physician. Physicians were free to use any additional therapy they considered to be indicated. Compliance with trial treatment in hospital and the use of non-trial therapy was recorded on the single-sided form completed after discharge (see below).

Eligibility

Patients were eligible if they were thought to be within 24 h of the onset of the symptoms of suspected or definite acute MI (with or without ECG changes), and to have no definite contraindications to SK, tPA, or APSAC. Contraindications to fibrinolytic therapy were specified not by the protocol but by the responsible physician, and so it was merely suggested that these might include *either* conditions associated with a high risk of adverse effects, in particular bleeding (such as severe trauma within the previous few weeks, or stroke, gastrointestinal haemorrhage, or ulcer within the previous few months, or known allergy to SK), *or* conditions associated with only a small likelihood of worthwhile benefit (such as negligibly low risk of cardiac death, or high risk of death from some other life-threatening disease). Hypertension or previous SK use were not necessarily contraindications unless the responsible physician judged them to be so. Patients were still eligible for ISIS-3 even if aspirin or heparin was thought to be clearly contraindicated or if it was thought that aspirin alone was definitely not enough (ie, that some anticoagulant was clearly indicated). In such cases, patients were still to be randomised and the allocated antithrombotic regimen was then modified as thought appropriate for that particular patient.

Randomisation

Entry to the study was by telephone to central 24 h services. Baseline details were to be recorded (table II), either directly onto computer or first on computer-generated randomisation lists, before a specific trial treatment pack was to be allocated. (The correct procedure was carried out everywhere except in East Germany, where it was not possible to be sure that the 347 patients recorded on the lists were properly randomised without foreknowledge of the next treatment: these few patients [0·8%] were therefore excluded, but the results among them were entirely typical, so their exclusion has made no material difference to any of the analyses presented.) The computer used a "minimisation" algorithm,[40] which limited chance differences between the treatment groups in these baseline features. Whether or not the trial treatment was actually given, patients remained in their originally allocated treatment group for an "intention-to-treat" analysis, and the few inadvertent second entries were disregarded. Each treatment pack contained a reply-paid pre-addressed card which confirmed that the correct treatment pack had been taken and also provided identifiers for mortality follow-up even if a discharge form (see below) was not completed.

Discharge

At discharge, a simple single-sided form was to be returned to the trial office. This provided further identifiers to assist central mortality follow-up after discharge, and brief details of the treatments actually given in hospital, of any apparent side-effects of treatment, and of major events in hospital. For any stroke, the collaborating clinician was to record when it occurred (allowing, in particular, subdivision of strokes on days 0–1 or later, as in ISIS-2[4]), to estimate whether the eventual disability would be "significant" or "not significant",[4] and to indicate whether the stroke was a "probable cerebral bleed" or an "infarct/unknown type". For all reports of stroke, further details (including any relevant investigations, such as computerised tomographic [CT] scans and necropsy reports) were then requested from investigators. Confirmation or refutation of the stroke and its aetiology was based

TABLE IV—REPORTED SIDE-EFFECTS OF TRIAL TREATMENT IN HOSPITAL (UP TO DAY 35 OR PRIOR DISCHARGE)

	Antithrombotic comparisons				Fibrinolytic comparisons						
—	A+H	A alone	Difference %A+H−%A alone		SK	tPA	APSAC	Difference %SK−%tPA		Difference %SK−%APSAC	
No with discharge forms.	20 400	20 375	%	SD	13 607	13 569	13 599	%	SD	%	SD
Allergy											
Any	673	619	0·26	0·17	490	109	693	2·80	0·18**	−1·49	0·25**
Causing persistent symptoms	60	61	−0·01	0·05	38	12	71	0·19	0·05‡	−0·24	0·08†
Profound blood pressure fall											
Any	2129	2135	−0·04	0·30	1604	961	1699	4·71	0·35**	−0·71	0·40
Requiring drug treatment	1244	1219	0·12	0·24	914	591	958	2·36	0·28**	−0·33	0·31
Non-cerebral bleed											
Any	1276	788	2·39	0·22**	614	709	741	−0·71	0·26†	−0·94	0·26‡
Day 0–1	839	617	1·08	0·18**	414	528	514	−0·85	0·22‡	−0·74	0·22‡
Day 2–7	393	137	1·25	0·11**	177	152	201	0·18	0·13	−0·18	0·14
Day 8–35	44	34	0·05	0·04	23	29	26	−0·04	0·05	−0·02	0·05
Transfused (or other "major")	209	156	0·26	0·09†	118	109	138	0·06	0·11	−0·15	0·12
Day 0–1	114	101	0·06	0·07	65	66	84	−0·01	0·08	−0·14	0·09
Day 2–7	77	36	0·20	0·05‡	39	33	41	0·04	0·06	−0·01	0·07
Day 8–35	18	19	−0·01	0·03	14	10	13	0·03	0·04	0·01	0·04

*, †, ‡, §, ** correspond to $2p < 0·05$, $< 0·01$, $< 0·001$, $< 0\ 0001$ $< 0\ 00001$

TABLE V—EFFECTS OF ALLOCATED TREATMENT ON CLINICAL EVENTS IN HOSPITAL (UP TO DAY 35 OR PRIOR DISCHARGE)

	Antithrombotic comparisons				Fibrinolytic comparisons						
	A+H	A alone	Difference %A+H−%A alone		SK	tPA	APSAC	Difference %SK−%tPA		Difference %SK−%APSAC	
No with discharge forms:	20 400	20 375	%	SD	13 607	13 569	13 599	%	SD	%	SD
Cardiogenic shock	1413	1442	−0·15	0·25	969	918	968	0·36	0·31	0·00	0·31
Heart failure	3411	3529	−0·60	0·37	2361	2279	2300	0·56	0·46	0·44	0·46
Cardiac rupture	268	269	−0·01	0·11	190	172	175	0·13	0·14	0·11	0·14
Pulmonary embolism	70	88	−0·09	0·06	58	44	56	0·10	0·07	0·01	0·08
Ventricular fibrillation	1105	1142	−0·19	0·23	770	751	726	0·12	0·28	0·32	0·28
Cardiac arrest (VF or other)	1946	2009	−0·32	0·29	1336	1297	1322	0·26	0·36	0·10	0·36
Reinfarction											
Any	645	707	−0·31	0·18	472	397	483	0·54	0·21*	−0·08	0·22
Day 0–1	187	219	−0·16	0 10	145	131	130	0·10	0·12	0·11	0·12
Day 0–7	488	573	−0·42	0·16†	382	306	373	0·55	0·19†	0·06	0·20
Day 8–35	157	134	0·11	0·08	90	91	110	−0·01	0·10	−0·15	0·10
Any, not dying day 0–35	378	414	−0·18	0·14	266	225	301	0·30	0·16	−0·26	0·17
Stroke+											
Any	261	240	0·10	0·11	141	188	172	−0·35	0·13†	−0·23	0·13
(*a*) Timing											
Day 0–1	149	143	0·03	0·08	68	125	99	−0·42	0·10§	−0·23	0·09*
Day 0–7	220	200	0·10	0·10	109	164	147	−0·41	0·12‡	−0·28	0·12*
Day 8–35	41	40	0·00	0·04	32	24	25	0·06	0·06	0·05	0·06
(*b*) Aetiology											
Definite haemorrhage	93	62	0·15	0·06*	25	76	54	−0·38	0·07**	−0·21	0·07†
Def or prob haemorrhage	114	82	0·16	0·07*	32	89	75	−0·42	0·08**	−0·32	0·08§
Definite infarct	82	84	−0·01	0·06	66	55	45	0·08	0·08	0·15	0·08*
Def or prob infarct/unknown	147	158	−0·05	0·09	109	99	97	0·07	0·11	0·09	0·11
(*c*) Severity											
Died in hospital	128	118	0·05	0·08	66	93	87	−0·20	0·09*	−0·15	0·09
Disabled at discharge	81	87	−0·03	0·06	48	60	60	−0·09	0·08	−0·09	0·08
No significant disability	52	35	0·08	0·05	27	35	25	−0·06	0·06	0·01	0·05
(*d*) Not dying in days 0–35											
Any	133	122	0·05	0·08	75	95	85	−0·15	0·10	−0·07	0·09
Timing: day 0–1	58	57	0·00	0·05	32	48	35	−0·12	0·07	−0·02	0·06
Timing: day 0–7	111	98	0·06	0·07	58	80	71	−0·16	0·09	−0·10	0·08
Aetiology: def/prob haem	41	26	0·07	0·04	10	36	21	−0·19	0·05‡	−0·08	0·04*

*, †, ‡, §, ** correspond to 2p < 0·05, < 0·01, < 0·001, < 0 0001, < 0 00001

+ A few reported strokes were reclassified as transient ischaemic attacks (7 A + H *vs* 14 A alone, NS; 5 SK *vs* 7 tPA *vs* 9 APSAC, NS) or as other neurological events (8 A + H *vs* 4 A alone, NS; 3 SK *vs* 4 tPA *vs* 5 APSAC, NS)

on blind central review of these records by one consultant neurologist using standard WHO definitions of stroke.[41] There was, in general, close agreement between the collaborating clinicians and the central reviewer, but a few reported strokes were reclassified as transient ischaemic attacks (ie, symptoms disappearing completely within 24 h) or other neurological events (such as subdural haematomas and spinal cord lesions). Strokes were then further subdivided as follows:

Definite haemorrhagic stroke—Haemorrhage (primary intracerebral, subarachnoid, or secondary to cerebral infarction) confirmed by CT scan within 14 days of stroke onset or by necropsy or lumbar puncture;

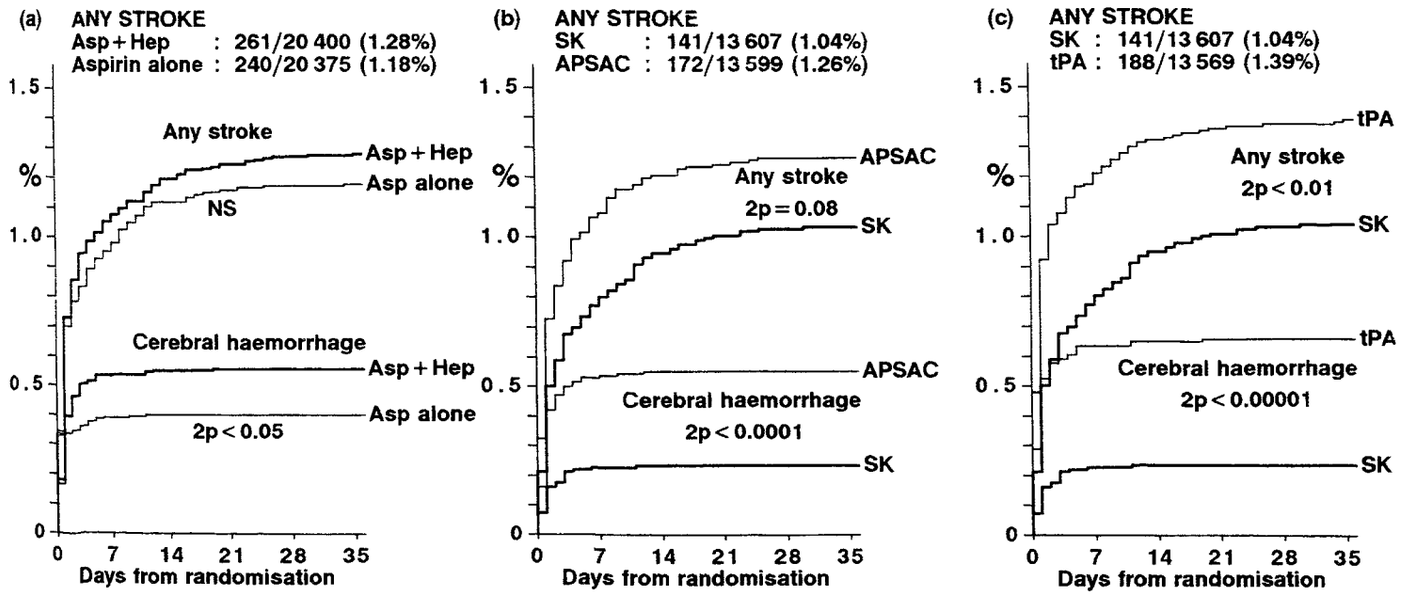

Fig 2—Cumulative percentage with any stroke (upper lines) and with (definite or probable) cerebral haemorrhage in hospital up to day 35 or prior discharge.

(*a*) All patients allocated aspirin plus heparin (thicker line) *vs* all allocated aspirin alone; (*b*) all patients allocated SK (thicker line) *vs* all allocated APSAC; (*c*) all patients allocated SK *vs* all allocated tPA.

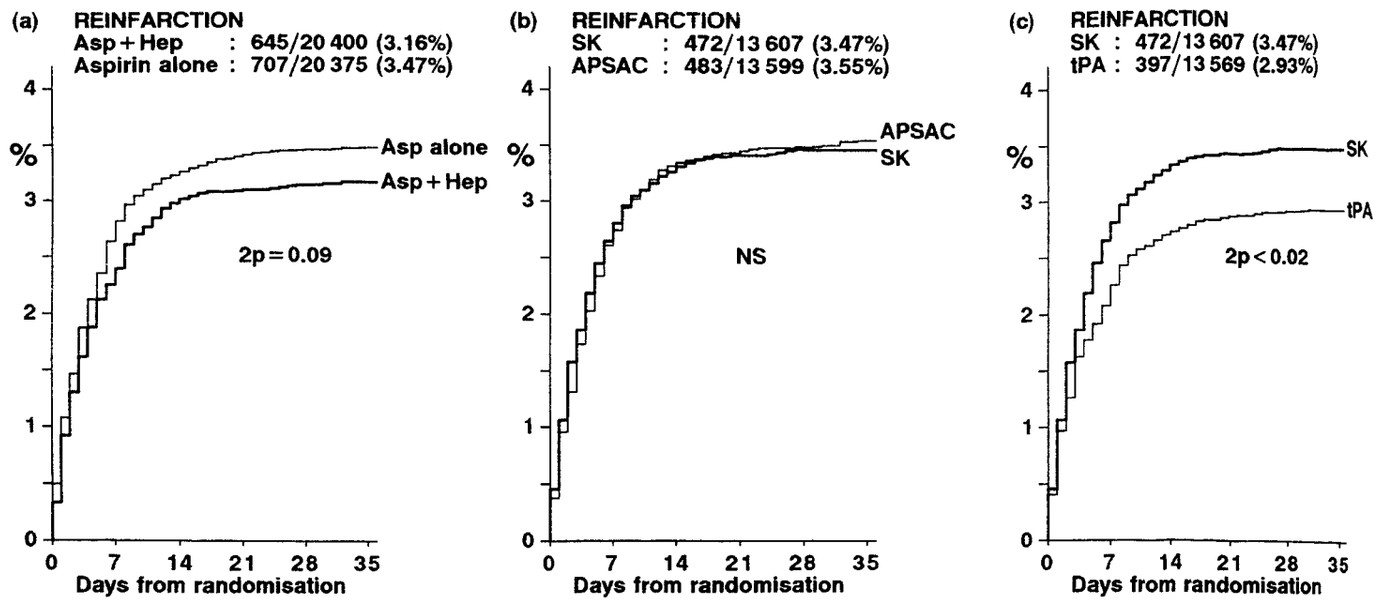

Fig 3—Cumulative percentage with reinfarction in hospital up to day 35 or prior discharge.

Legend as for fig 2.

Probable haemorrhagic stroke—Haemorrhage reported by collaborating clinician without such CT scan, necropsy, or lumbar puncture results, but with clinical signs or symptoms strongly suggestive of cerebral haemorrhage (ie, death within 24 h of onset, sudden severe headache, rapidly declining level of consciousness, coma);

Definite cerebral infarct—CT scan performed within 14 days of onset of a definite stroke that was either normal or had evidence of infarction present;

Probable cerebral infarct—All other unrefuted strokes, including any of unknown aetiology.

Follow-up

Discharge forms (which report only in-hospital events) were by February, 1992, available for 99% of all patients. The numbers missing were 256 aspirin plus heparin *vs* 268 aspirin alone and 173 SK *vs* 177 tPA *vs* 174 APSAC. Discharge alive was at a median of 9 days, and the completeness of mortality follow-up is 99% to discharge, 92% to 5 weeks, and (by life table methods) 68% to 6 months, again with no systematic differences between the treatment groups. 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 41 299 randomised patients are included in the present analysis. Available cause-of-death information was reviewed blind of treatment allocation by the trial coordinator, and causes subdivided into "definitely non-vascular" causes and "vascular" (ie, definitely or possibly vascular) causes.[4]

Statistical methods

The main analyses are by allocated treatment (ie, they are "intention-to-treat" analyses[39]). The protocol specified three main comparisons: (i) SK *vs* tPA *vs* APSAC among all randomised patients, (ii) SK *vs* tPA *vs* APSAC among patients randomised 0–6 h after pain onset with ST elevation when randomised, and (iii) aspirin plus heparin *vs* aspirin alone among all randomised patients. Although these comparisons were all to be of 5-week *vascular* mortality, only 0·8% of the deaths within the first 5 weeks were classified as non-vascular—and, of these, some may well have been due, at least in part, to vascular events. Moreover, the number of non-vascular deaths was similar in each treatment group. Hence, chief emphasis in the present report is on total mortality. The effects of the trial treatments on various non-fatal events in hospital and on longer-term mortality were also to be reported. For major endpoints (such as mortality and stroke) the semi-open comparison of SK *vs* tPA is not a problem, while for minor side-effects (such as allergies, hypotension, and non-transfused bleeds), the full placebo-control for the comparisons of SK *vs* APSAC and of tPA *vs* APSAC allows assessment of any biases in the comparison of SK *vs* tPA (of which there was no evidence at all). Comparisons of survival to 6 months involve time-to-death analyses by logrank methods; but, for events in hospital and deaths during the first 5 weeks, comparisons involve simple analyses of total numbers affected.[39] The three-way comparison of SK *vs* tPA *vs* APSAC is analysed as two pairwise comparisons of SK with each of the newer treatments. Two-sided p-values (2p) are cited throughout (with $2p > 0{\cdot}05$ generally described as "not significant", NS), and absolute differences are given with one standard deviation (SD).

During recruitment, the steering committee, sponsors, collaborators, and administrative staff were to remain ignorant of the interim results, which were reviewed periodically by an independent data monitoring committee. No clear differences emerged during this monitoring, and so randomisation continued until Jan 31, 1991, by which time almost all the drugs provided for the trial had been used.

Results

The present report is of 41 299 "clear" or "uncertain" indication patients randomised at a median of 4 h after the onset of suspected acute MI in a factorial design (fig 1). The large size of the study (and the use of "minimisation") ensured good balance between the treatment groups for the main pre-randomisation prognostic features that were measured (table II), and should do likewise for those that were not.

Among patients allocated aspirin plus heparin, 98% received antiplatelet therapy and 92% received intravenous or high-dose subcutaneous heparin. Among patients allocated aspirin alone, 98% received antiplatelet therapy but 18% were also given some intravenous or high-dose subcutaneous heparin. Thus, there is only a 74% difference between these two treatment groups in the proportions who actually received some such heparin. Active fibrinolytic trial treatment was given in 97% of patients allocated SK or tPA and in just over 97% of those allocated APSAC (table III). In each of the three fibrinolytic groups, 98% received antiplatelet therapy and 55% received intravenous or high-dose subcutaneous heparin (table III).

TABLE VI—EFFECTS OF ALLOCATED TREATMENT ON DEATHS IN DAYS 0–35 AMONG (i) ALL PATIENTS AND (ii) PATIENTS PRESENTING WITHIN 0–6 H WITH ST ELEVATION

—	Fibrinolytic comparisons			Difference %SK − %tPA		Difference %SK − %APSAC	
	SK	tPA	APSAC				
(i) All patients	13 780	13 746	13 773	%	SD	%	SD
Any	1455 (10·6%)	1418 (10·3%)	1448 (10·5%)	0·24	0·37	0·05	0·37
(*a*) Timing							
Day 0–1	699 (5·1%)	649 (4·7%)	700 (5·1%)	0·35	0·26	−0·01	0·26
Day 2–7	357 (2·6%)	415 (3·0%)	378 (2·7%)	−0·43	0·20*	−0·15	0·19
Day 8–35	399 (2·9%)	354 (2·6%)	370 (2·7%)	0·32	0·20	0·21	0·20
(*b*) Antithrombotic allocation							
Aspirin plus sc heparin	726 (10·5%)	684 (10·0%)	722 (10·5%)	0·58	0·52	0·06	0·52
Aspirin alone	729 (10·6%)	734 (10·7%)	726 (10·6%)	−0·09	0·53	0·03	0·52
(ii) 0–6 h, ST elevation	8643	8571	8622	%	SD	%	SD
Any	861 (10·0%)	822 (9·6%)	855 (9·9%)	0·37	0·45	0·05	0·46
(*a*) Timing							
Day 0–1	421 (4·9%)	389 (4·5%)	408 (4·7%)	0·33	0·32	0·14	0·33
Day 2–7	201 (2·3%)	236 (2·8%)	218 (2·5%)	−0·43	0·24	−0·20	0·23
Day 8–35	239 (2·8%)	197 (2·3%)	229 (2·7%)	0·47	0·24	0·11	0·25
(*b*) Antithrombotic allocation							
Aspirin plus sc heparin	425 (9·8%)	389 (9·1%)	427 (9·9%)	0·69	0·63	−0·13	0·64
Aspirin alone	436 (10·2%)	433 (10·1%)	428 (9·9%)	0·05	0·65	0·22	0·65

*2p < 0·05.

Aspirin plus heparin (20 656 patients) *vs* aspirin alone (20 643 patients)

Effects on reported side-effects and other clinical events in hospital

Non-cerebral bleeds (generally minor, such as oozing from puncture sites, microscopic haematuria, or blood-streaked vomit or sputum) were recorded more commonly among aspirin plus heparin allocated patients (6·3% aspirin plus heparin *vs* 3·9% aspirin alone; 2p < 0·00001: table IV). Half of this excess was in days 0–1 (4·1% *vs* 3·0%; 2p < 0·00001), showing that this moderate heparin regimen already had definite effects on coagulation even in this early period, and half was in days 2–7 (1·9% *vs* 0·7%; 2p < 0·00001). There was also a small excess of transfused or other major non-cerebral bleeds (1·0% *vs* 0·8%; 0·26% SD 0·09 excess; 2p < 0·01). The excess risk of any type of non-cerebral bleed increased with age (< 70 yr: 5·0% aspirin plus heparin *vs* 3·4% aspirin alone; ≥70 yr: 9·8% *vs* 5·3%: 2p < 0·00001 for the difference between these excess risks).

No significant difference in the overall risk of stroke was observed (261 [1·28%] aspirin plus heparin *vs* 240 [1·18%] aspirin alone: table V and fig 2). A small but significant excess of strokes attributed to definite or probable cerebral haemorrhage among patients allocated aspirin plus heparin (114 [0·56%] *vs* 82 [0·40%]; 0·16% SD 0·07 excess; 2p < 0·05) was counterbalanced by a non-significant shortfall of strokes attributed to infarct or unknown cause (147 [0·72%] *vs* 158 [0·78%]). The risk of stroke increased with age, but even among patients aged 70 yr or over the addition of subcutaneous heparin to aspirin was not associated with any significant excess of stroke (2·32% aspirin plus heparin *vs* 2·23% aspirin alone) or of cerebral haemorrhage (0·90% *vs* 0·79%). Reinfarctions were recorded in hospital slightly less commonly among those allocated aspirin plus heparin (3·16% *vs* 3·47%: 0·31% SD 0·18 difference; 2p = 0·09: table V and fig 3). This reduction arose during the scheduled heparin treatment period (reinfarctions during days 0–7: 2·39% aspirin plus heparin *vs* 2·81% aspirin alone; 0·42% SD 0·16 difference; 2p < 0·01), with a very slight and non-significant excess of reinfarction thereafter (0·77% *vs* 0·66%). There were no significant differences between these treatment groups in the reported incidence of other clinical events (table V).

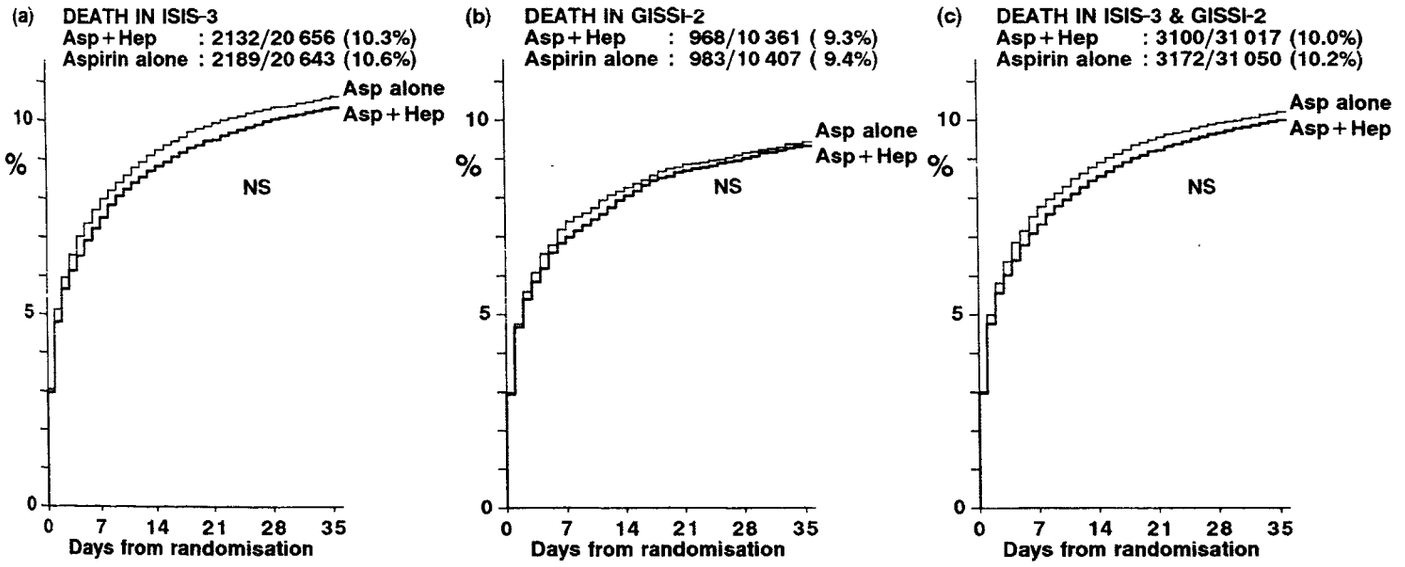

Fig 4—Cumulative percentage dead in days 0–35 in ISIS-3 and in GISSI-2: aspirin plus heparin *versus* aspirin alone.

All patients allocated aspirin plus heparin (thicker line) *vs* all allocated aspirin alone in (*a*) ISIS-3; (*b*) GISSI-2; (*c*) ISIS-3 and GISSI-2 combined

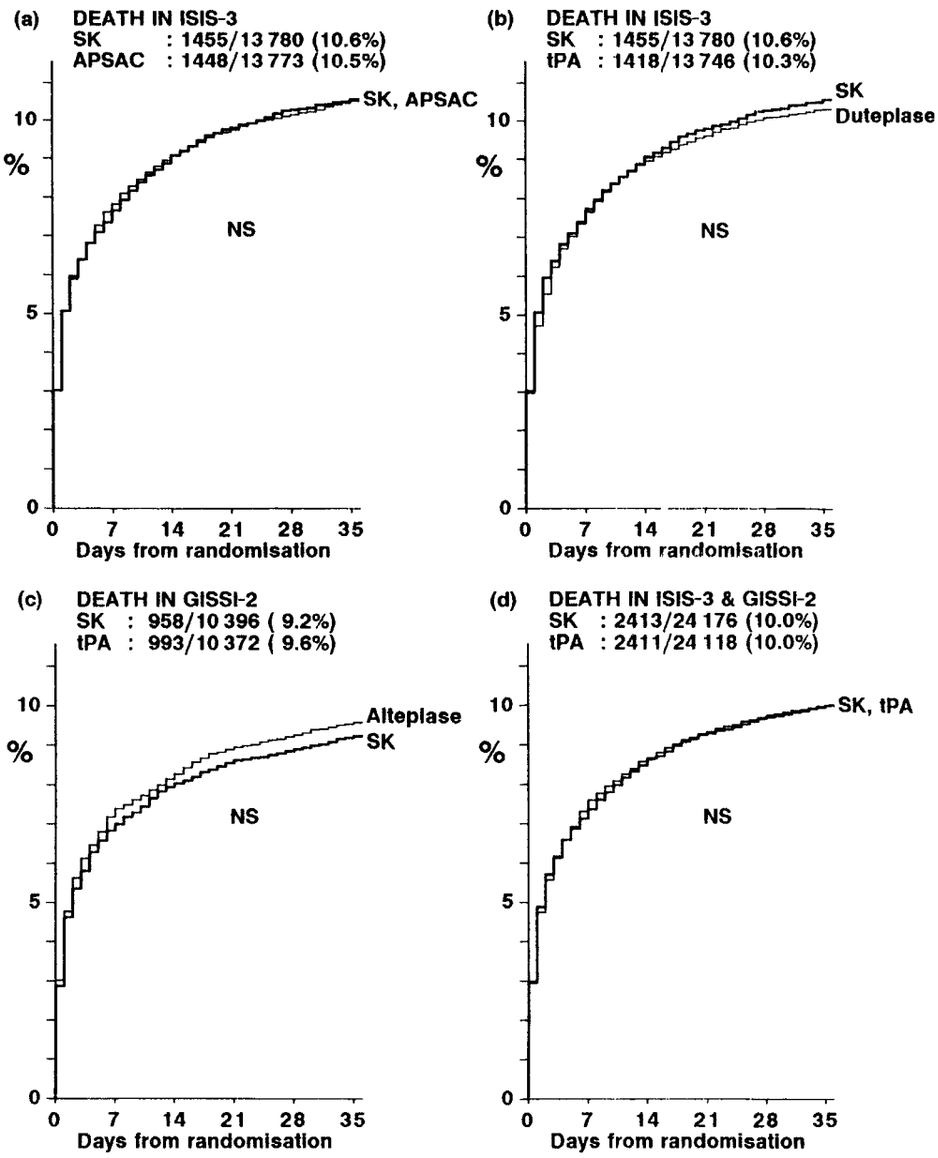

Fig 5—Cumulative percentage dead in days 0–35 in ISIS-3 and in GISSI-2: fibrinolytic comparisons.

(*a*) All patients allocated SK (thicker line) *vs* all allocated APSAC in ISIS-3 only; (*b, c, d*) all patients allocated SK *vs* all allocated tPA in (*b*) ISIS-3; (*c*) GISSI-2; (*d*) ISIS-3 and GISSI-2 combined.

Effects on mortality in the first 5 weeks and later

Non-vascular deaths in days 0–35 were evenly distributed (18 aspirin plus heparin *vs* 18 aspirin alone), and subsequent analyses are of total mortality. During the scheduled heparin treatment period there were slightly fewer deaths in the aspirin plus heparin group (ie, days 0–7 in hospital: 1534 [7·4%] *vs* 1633 [7·9%]; 2p = 0·06) with a slight convergence during further follow-up to day 35 (598 further deaths [3·1% of survivors] *vs* 556 [2·9%]). This analysis of mortality during the scheduled treatment period was, however, not pre-specified, and there was no significant difference in terms of the pre-specified endpoint of 35-day mortality (2132 [10·3%] aspirin plus heparin *vs* 2189 [10·6%] aspirin alone: table VI and fig 4). Nor was there any significant difference in 6-month survival (fig 6: 0·1% SD 0·4 difference).

Streptokinase (13 780 patients) *vs* APSAC (13 773 patients)

Effects on reported side-effects and other clinical events in hospital

Allergic reactions were reported more commonly in the APSAC group than in the streptokinase group (3·6% SK *vs* 5·1% APSAC; 2p < 0·00001: table IV). Most of these allergic reactions were minor, but about one-tenth were described as causing persistent symptoms (0·3% *vs* 0·5%; 2p < 0·002). Hypotension was also reported slightly more commonly in the APSAC group (11·8% SK *vs* 12·5% APSAC; 2p = 0·08), with about half these episodes requiring drug treatment (6·7% *vs* 7·0%), but these differences were not conventionally significant. Non-cerebral bleeds were reported significantly more commonly among patients allocated APSAC (4·5% SK *vs* 5·4% APSAC: 2p < 0·001), particularly during days 0–1 (3·0% *vs* 3·8%; 2p < 0·001). Only about one-fifth of these bleeds required transfusion, and there were no significant differences in transfused bleeds between SK and APSAC, either overall (0·9% *vs* 1·0%) or if attention was restricted to days 0–1 (0·5% *vs* 0·6%).

Compared with streptokinase, there was a slight excess with APSAC of total stroke (141 [1·04%] SK *vs* 172 [1·26%] APSAC; 0·23% SD 0·13 excess; 2p = 0·08: table V and fig 2), which was largely of disabling or fatal stroke (114 [0·84%] *vs* 147 [1·08%]; 2p < 0·05). Much of this stroke excess with APSAC appeared early after the start of treatment (strokes during days 0–1: 68 [0·50%] SK *vs* 99 [0·73%] APSAC; 2p < 0·02), and was attributed to definite

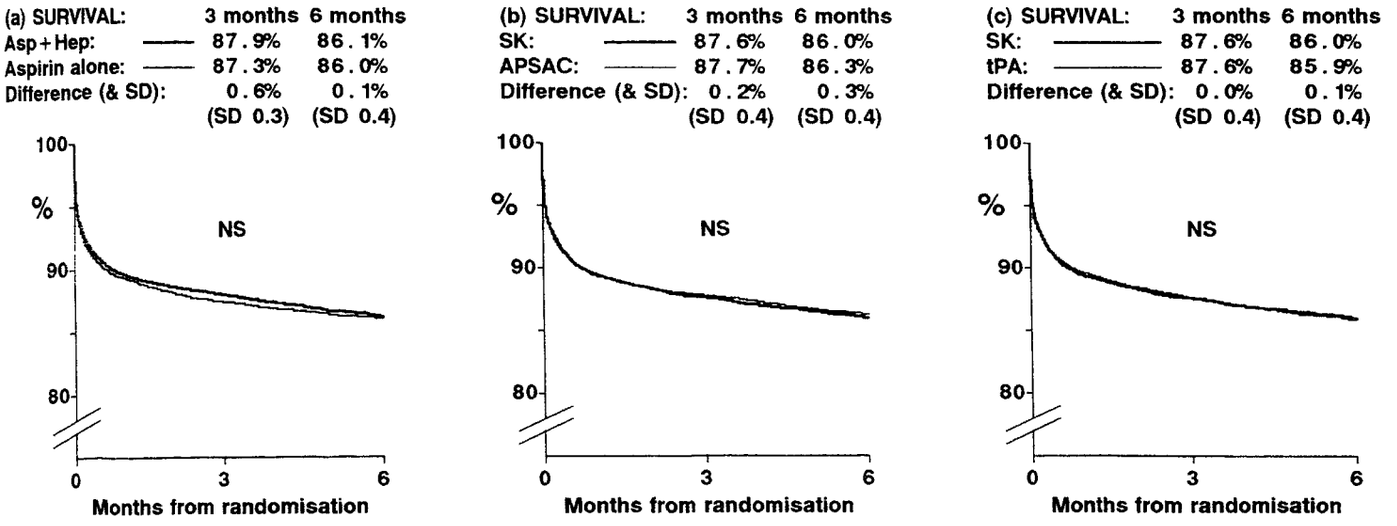

Fig 6—Life table estimates of 3-month and 6-month survival in ISIS-3.

By life table methods, follow-up to 3 months is 84% complete, and to 6 months is 68% complete. For the subset of patients presenting within 0–6 h of pain onset with ST elevation, the survival differences at 6 months were: (a) 0·2% SD 0·4; (b) 0·3% SD 0·5; and (c) 0·2% SD 0·5

or probable cerebral haemorrhage (32 [0·24%] *vs* 75 [0·55%]; 2p < 0·0001). The excess of cerebral haemorrhage with APSAC was observed both among patients allocated aspirin plus heparin (17 [0·25%] SK plus heparin *vs* 48 [0·71%] APSAC plus heparin; 2p < 0·0001) and among those allocated aspirin alone (15 [0·22%] *vs* 27 [0·40%]; 2p < 0·06). No significant differences were observed between SK and APSAC in reinfarction (472 [3·47%] *vs* 483 [3·55%]: table V and fig 3) or in the reported incidence of other clinical events (table V).

Effects on mortality in the first 5 weeks and later

Non-vascular deaths in days 0–35 were evenly distributed (13 SK *vs* 13 APSAC), and subsequent analyses are of total mortality. There was no significant difference in mortality at any time throughout the first 5 weeks among all randomised patients (1455 [10·6%] SK *vs* 1448 [10·5%] APSAC: table VI and fig 5) or among that subset of patients presenting within 0–6 h of pain onset with ST elevation on their electrocardiograms (861 [10·0%] *vs* 855 [9·9%]). No significant difference in 6-month survival was apparent overall (fig 6: 0·3% SD 0·4 difference) or in the subset.

Streptokinase (13 780 patients) *vs* tPA (13 746 patients)

Effects on reported side-effects and other clinical events in hospital

Allergic reactions were reported much more commonly with streptokinase than with tPA (3·6% SK *vs* 0·8% tPA; 2p < 0·00001: table IV). Most of these allergic reactions were minor, but again about one-tenth were described as causing persistent symptoms (0·3% *vs* 0·1%; 2p < 0·001). Hypotension was also more common with SK than with tPA (11·8% *vs* 7·1%; 2p < 0·00001), and about half of these episodes required drug treatment (6·7% *vs* 4·4%; 2p < 0·00001). Comparison of the patients randomised in the "uncertain indication" part of ISIS-3 between fibrinolytic therapy (SK *vs* tPA *vs* APSAC) and open control indicates that tPA is, however, still associated with some increase in the risk of hypotension (67 [4·4%] of 1512 tPA-allocated patients *vs* 69 [1·5%] of 4494 controls; 2p < 0·00001), albeit a somewhat smaller increase than with SK or APSAC. Non-cerebral bleeds were reported significantly more commonly among patients allocated tPA (4·5% SK *vs* 5·2% tPA; 2p < 0·01), particularly during days 0–1 (3·0% *vs* 3·9%; 2p < 0·0002), but there was no significant difference in the incidence of bleeds that required transfusion (0·9% *vs* 0·8%).

Compared with streptokinase, there was a significant excess with tPA of total stroke (141 [1·04%] SK *vs* 188 [1·39%] tPA; 0·35% SD 0·13 excess; 2p < 0·01: table V and fig 2), which was largely of disabling or fatal stroke (114 [0·84%] *vs* 153 [1·13%]; 2p < 0·02). Much of this stroke excess with tPA appeared early after the start of treatment (strokes during days 0–1: 68 [0·50%] *vs* 125 [0·92%]; 2p < 0·0001), and was attributed to definite or probable cerebral haemorrhage (32 [0·24%] *vs* 89 [0·66%]; 2p < 0·00001). The excess of cerebral haemorrhage with tPA was significant both among patients allocated aspirin plus heparin (17 [0·25%] SK plus heparin *vs* 49 [0·72%] tPA plus heparin; 2p < 0·001) and among those allocated aspirin alone (15 [0·22%] *vs* 40 [0·59%]; 2p < 0·002). Likewise, it was significant both among those under 70 yr of age (23 [0·23%] SK *vs* 48 [0·48%] tPA; 2p < 0·005) and among those aged 70 or more (9 [0·25%] *vs* 41 [1·16%]; 2p < 0·00001).

Reinfarctions were recorded in hospital significantly less commonly among patients allocated tPA (472 [3·47%] SK *vs* 397 [2·93%] tPA; 2p < 0·02: table V and fig 3), whether in the presence of aspirin plus heparin (3·39% SK *vs* 2·74% tPA) or in the presence of aspirin alone (3·54% *vs* 3·11%). No significant differences were observed between SK and tPA in the reported incidence of other clinical events (table V).

Effects on mortality in the first 5 weeks and later

Non-vascular deaths in days 0–35 were evenly distributed (13 SK *vs* 10 tPA), and subsequent analyses are of total mortality. There was no significant difference in mortality at any time throughout the first 5 weeks among all randomised patients (1455 [10·6%] SK *vs* 1418 [10·3%] tPA: table VI and fig 5) or among that subset of patients presenting within 0–6 h of pain onset with ST elevation on their electrocardiograms (861 [10·0%] *vs* 822 [9·6%]). No significant difference in 6-month survival was apparent overall (fig 6: 0·1% SD 0·4 difference) or in the subset.

Discussion

Previous trials of antiplatelet[4] and of fibrinolytic therapy[4,19-22] have shown that, for many types of patient with suspected acute MI, the survival benefits of active treatment outweigh any risks (in particular, of bleeding or of stroke). Such treatments have therefore become routine in many parts of the world, saving tens of thousands of lives each year. In the hope of greater benefits there has been much research into more potent antithrombotic regimens and, particularly, into more potent fibrinolytic regimens. But, since treatments that attack coronary artery thrombi more effectively may also cause greater risks of bleeding (the greatest danger being of intracerebral haemorrhage), large randomised trials are needed that can reliably assess the *balance* of benefits and risks of the various treatments. So far, ISIS-3 and GISSI-2[9,10] are the only large trials that provide such evidence for the addition of a widely practicable heparin regimen to an immediately effective antiplatelet regimen, and for the comparison of newer fibrinolytic agents (APSAC or tPA) with the most widely tested fibrinolytic (SK), and their results are considered together in this discussion.

Antithrombotic therapy: adding heparin to aspirin

Early in the 1980s, it was shown that a single dose of aspirin needs to be about 2 mg/kg (ie, 160 mg in an 80 kg patient) to produce near-total inhibition of thromboxane metabolites, and that lower daily doses (eg, 40–80 mg) take a few days before they have their full antiplatelet effect (as indicated by more than 95% inhibition of serum thromboxane B_2).[5,6] Recent observations, both in normal volunteers and in patients with unstable angina, confirm that an initial 75 mg dose may still leave substantial thromboxane activity.[7,8] This suggests[42] that, to ensure a near-maximum antiplatelet effect of aspirin on the first day, treatment in acute MI should begin with 160 mg (which was shown to have a substantial protective effect in ISIS-2, and so was adopted for all patients in ISIS-3) or perhaps even more (as in GISSI-2).

Indirect clinical confirmation of this comes from studies of the effects of anticoagulation on coronary artery patency after fibrinolysis. In one such study,[43] coronary artery patency 7–24 h after tPA was higher in patients who had received intravenous heparin than in those who had received just one 80 mg aspirin tablet (82% patent of 100 allocated heparin alone *vs* 52% of 93 allocated 80 mg aspirin alone): this difference is statistically significant but, because the study was small, the size of the difference is uncertain. A similar sized difference in patency was seen at 48–72 h in another small study[44] that compared the same heparin regimen *vs* no antiplatelet therapy (71% patent of 42 allocated heparin *vs* 43% of 42 allocated no antiplatelet). In contrast, the larger ECSG-6 trial[11] compared a higher initial dose of aspirin (250–300 mg, because 75–125 mg had previously been associated with a high rate of reocclusion[27]) plus the same heparin regimen *vs* 250–300 mg aspirin. This study found only a small difference in coronary artery patency at 48–120 h (83% patent of 265 allocated aspirin plus intravenous heparin *vs* 75% of 253 allocated aspirin alone). Whether the contrast between the results of the larger ECSG-6 study and those of the smaller study of 80 mg aspirin[43] is due chiefly to differences in aspirin dose (as is suggested by the similarity of the results of the latter study[43] to those of the small study of heparin *vs* no aspirin[44]), to the timing of angiography, or to chance fluctuations in the smaller study results, it is only the ECSG-6 results (of an *adequate* aspirin dose plus early intravenous heparin *vs* the same aspirin dose) that are directly relevant to the interpretation of the GISSI-2 and ISIS-3 trials. ECSG-6 suggests that the difference in patency between adequate aspirin and adequate aspirin plus intravenous heparin may be real, but small.

What is optimal for coronary artery patency may not, however, be optimal for clinical care since more intensive antithrombotic therapy may be associated with greater risk of haemorrhage. To limit the risks of bleeding, the subcutaneous heparin regimen studied in ISIS-3 and GISSI-2 was not intensive and its start was delayed (until 4 h in ISIS-3, which was immediately after any tPA was to have ended, and until 12 h in GISSI-2, which was 9 h after any tPA was to have ended). Even with these precautions, there were small but statistically significant increases of transfused bleeds in ISIS-3 (1·0% aspirin plus subcutaneous heparin *vs* 0·8% aspirin alone; $2p < 0·01$) and in GISSI-2 (1·0% *vs* 0·5%; $2p < 0·001$: table VII). In ISIS-3, there was also a small marginally significant excess of strokes attributed to cerebral haemorrhage in the heparin group ($2p < 0·05$), although this was counterbalanced by a slight shortfall in other strokes.

In GISSI-2[9,10] there was a marginally significant trend in favour of the addition of heparin when deaths during the scheduled treatment period (ie, from 12 h after randomisation until discharge: 537 [5·4%] aspirin plus heparin *vs* 606 [6·0%] aspirin alone; $2p < 0·05$: table VII) were considered.[45] A similar pattern was observed in ISIS-3, so that overall in ISIS-3 and GISSI-2 combined there was a significant reduction in mortality during the scheduled treatment period (2071 [6·8%] *vs* 2239 [7·3%]; $2p < 0·01$). Some patients allocated heparin did not actually receive it, while some of those allocated no heparin actually received some (with the net difference in the use of high-dose heparin in ISIS-3 being about three-quarters). Hence, the apparent benefit during the scheduled heparin treatment period of about 5 (SD 2) deaths avoided per 1000 patients *allocated* heparin suggests a benefit of about 7 per 1000 from *actual* use of this subcutaneous heparin regimen. Analyses just during the scheduled heparin treatment period were not pre-specified in either study protocol, and during the period when heparin was not scheduled to be given there were slightly more deaths among those who had been allocated heparin. So, in ISIS-3 and GISSI-2 combined (table VII and fig 4), there was no significant difference in 35-day mortality (2 SD 2 fewer deaths per 1000 allocated heparin) or in 6-month survival. In contrast, ISIS-2 showed that *allocation* of 162 mg/day aspirin reduced 35-day mortality by 24 SD 5 ($2p < 0·00001$) per 1000 patients, and indicated that the benefits of aspirin were about the same size irrespective of whether intravenous heparin, subcutaneous heparin, or no heparin was scheduled to be used.[4] In terms of mortality, therefore, antiplatelet therapy is of proven benefit irrespective of heparin use, whereas as long as adequate antiplatelet therapy is used there is as yet no definite direct proof that extra survival can be obtained from adding heparin.

In view of the significant (5 SD 2 per 1000; $2p < 0·01$) mortality difference during the scheduled subcutaneous heparin treatment period, it may well be that some heparin regimen would produce at least a small improvement in 35-day survival, and perhaps even in long-term survival. More intensive heparin regimens might produce somewhat greater benefits, but might also increase the risk of

TABLE VII—ISIS-3 AND GISSI-2 COMBINED: COMPARISON OF ASPIRIN PLUS HEPARIN *VS* ASPIRIN ALONE AND OF SK *VS* tPA

Clinical events up to day 35 or prior discharge, and any deaths	Antithrombotic comparisons				Fibrinolytic comparisons			
	Aspirin + heparin	Aspirin alone	Difference %A+H − %A alone		SK	tPA	Difference %SK − %tPA	
	See footnote		%	SD	See footnote		%	SD
Transfused bleed								
ISIS-3	209 (1·0%)	156 (0·8%)	0 26	0·09†	118 (0·9%)	109 (0·8%)	0·06	0·11
GISSI-2	103 (1 0%)	57 (0·5%)	0·45	0·12‡	96 (0·9%)	64 (0·6%)	0·31	0·12*
Both trials	312 (1·0%)	213 (0 7%)	0·32	0·07§	214 (0·9%)	173 (0·7%)	0·17	0·08*
Reinfarction								
ISIS-3	645 (3·2%)	707 (3·5%)	−0·31	0·18	472 (3·5%)	397 (2·9%)	0·54	0·21*
GISSI-2	282 (2·7%)	303 (2·9%)	−0 19	0·23	311 (3·0%)	274 (2·6%)	0·35	0·23
Both trials	927 (3 0%)	1010 (3·3%)	−0·27	0 14	783 (3 3%)	671 (2·8%)	0·46	0·16†
Reinfarction, alive at day 35								
ISIS-3	378 (1·9%)	414 (2·0%)	−0·18	0·14	266 (2·0%)	225 (1·7%)	0·30	0·16
GISSI-2	218 (2·1%)	239 (2·3%)	−0·19	0·20	242 (2·3%)	215 (2·1%)	0·25	0·20
Both trials	596 (1·9%)	653 (2·1%)	−0·18	0·11	508 (2 1%)	440 (1·8%)	0·28	0·13*
Stroke								
ISIS-3	261 (1·3%)	240 (1·2%)	0·10	0 11	141 (1 0%)	188 (1·4%)	−0·35	0·13†
GISSI-2	115 (1·1%)	119 (1·1%)	−0·03	0·15	98 (0·9%)	136 (1·3%)	−0·37	0·15*
Both trials	376 (1·2%)	359 (1·2%)	0·06	0·09	239 (1·0%)	324 (1·4%)	−0·36	0·10‡
Stroke, alive at day 35								
ISIS-3	133 (0·7%)	122 (0·6%)	0·05	0 08	75 (0·6%)	95 (0·7%)	−0·15	0·10
GISSI-2	68 (0·7%)	62 (0·6%)	0·06	0·11	56 (0·5%)	74 (0·7%)	−0·17	0·11
Both trials	201 (0·7%)	184 (0·6%)	0·06	0·06	131 (0·5%)	169 (0 7%)	−0·16	0·07*
Cerebral haemorrhage								
ISIS-3	114 (0 6%)	82 (0·4%)	0·16	0·07*	32 (0·2%)	89 (0·7%)	−0·42	0·08**
GISSI-2	36 (0·3%)	38 (0·4%)	−0·02	0·08	30 (0·3%)	44 (0·4%)	−0·14	0·08
Both trials	150 (0·5%)	120 (0·4%)	0 10	0·05	62 (0·3%)	133 (0·6%)	−0·30	0·06**
Cerebral haem, alive at day 35								
ISIS-3	41 (0·2%)	26 (0·1%)	0·07	0·04	10 (0·1/%)	36 (0·3%)	−0·19	0·05‡
GISSI-2	23 (0·2%)	10 (0·1%)	0·13	0·06*	13 (0·1%)	20 (0·2%)	−0·07	0·06
Both trials	64 (0·2%)	36 (0·1%)	0·09	0·03†	23 (0·1%)	56 (0·2%)	−0 14	0·04‡
Death in scheduled heparin period (see footnote)								
ISIS-3 (days 0–7, in hosp)	1534 (7·4%)	1633 (7 9%)	−0·48	0·26	1045 (7·6%)	1056 (7·7%)	−0·10	0·32
GISSI-2 (>12 h, in hosp)	537 (5·4%)	606 (6·0%)	−0·65	0·33*	558 (5·5%)	585 (5 8%)	−0·29	0·33
Both trials	2071 (6·8%)	2239 (7·3%)	−0·53	0·21†	1603 (6·7%)	1641 (6·9%)	−0·18	0 23
Death in days 0–35								
ISIS-3	2132 (10·3%)	2189 (10·6%)	−0 28	0·30	1455 (10·6%)	1418 (10 3%)	0·24	0·37
GISSI-2	968 (9·3%)	983 (9·4%)	−0·10	0·40	958 (9·2%)	993 (9·6%)	−0·36	0·40
Both trials	3100 (10·0%)	3172 (10·2%)	−0·22	0·24	2413 (10·0%)	2411 (10·0%)	−0·02	0·27
Death by 6 mo (life table analyses)								
ISIS-3	13·90% SD 0·25	14·01% SD 0·25	−0·10	0·36	14·03% SD 0·31	14·14% SD 0·31	−0·12	0·44
GISSI-2	12·01% SD 0·32	12·19% SD 0·32	−0·18	0·45	11·80% SD 0·32	12·39% SD 0·32	−0·59	0·45
Both trials	13·18% SD 0·20	13·32% SD 0·20	−0·14	0·28	12·95% SD 0·22	13·30% SD 0·22	−0·36	0·32

*, †, ‡, §, ** correspond to 2p < 0 05, < 0 01, < 0 001, < 0·0001, < 0 00001

Denominators in ISIS-3 are as in fig 1 for deaths and table IV for other events, and in GISSI-2 are as in figs 4 and 5 (except for the endpoint of deaths during the scheduled heparin period in GISSI-2 10 014 aspirin plus heparin *vs* 10 081 aspirin alone and 10 067 SK *vs* 10 028 tPA)

Analyses just during the scheduled heparin period were not pre-specified in the study protocols: these periods comprise days 0–7 but before discharge in ISIS-3, and >12 h but before discharge (or day 35 if earlier) in GISSI-2.

haemorrhage, particularly when started at the same time as fibrinolytic therapy when the haemorrhagic risk is already increased. ISIS-3 provides some information about this, albeit from non-randomised comparisons, with transfused bleeds among 2·2% of the patients who at some time (early or late) in hospital were given non-trial intravenous heparin *versus* 0·8% among those who were given only subcutaneous heparin (table VIII). This non-randomised comparison may slightly underestimate the haemorrhagic risk (for an early bleed when the fibrinolytic treatment is given may prevent intravenous heparin from being started, biasing the non-randomised intravenous *vs* subcutaneous comparison). Some of the other non-randomised heparin comparisons in table VIII, however, are not just slightly but grossly biased. For example, since early death prevents heparin from being started subsequently, mortality among patients who, non-randomly, received "no heparin" is artificially high. Conversely, reinfarction may lead to subsequent intravenous heparin use, so reinfarction among people who, non-randomly, received "intravenous heparin" is also likely to be artificially high. The excess of total stroke (but not, apparently, of cerebral haemorrhage) among patients receiving intravenous heparin might also reflect such biases since it cannot be accounted for by any baseline patient characteristics (as is also the case for the other associations in table VIII). These biases emphasise the need for directly randomised evidence on different heparin regimens, as in the GUSTO study now in progress.[13]

Fibrinolytic therapy: SK versus APSAC

Both SK and APSAC produce systemic depletion of fibrinogen, with a substantial anticoagulant effect that persists for several hours. In addition, APSAC has a particular affinity for fibrin, not just in coronary artery thrombi but also in protective haemostatic plugs elsewhere. Perhaps because of this, APSAC was associated with significantly more non-cerebral bleeds than SK, and with an excess risk of stroke (equivalent to 2 per 1000 patients given APSAC) which was observed early after the start of treatment and was chiefly attributed to a highly significant ($2p < 0·0001$) excess of cerebral bleeding. The hypotensive and allergic reactions that occur with SK and APSAC are

TABLE VIII—NON-RANDOMISED COMPARISONS BETWEEN ISIS-3 PATIENTS WHO RECEIVED INTRAVENOUS, SUBCUTANEOUS, OR NO HEPARIN AT ANY TIME IN HOSPITAL

Outcome, subdivided by actual heparin use (see footnote)	Fibrinolytic comparisons			All patients
	SK	tPA	APSAC	
No with discharge form				
Intravenous heparin	1605	1635	1612	4852
Subcutaneous only	6350	6283	6304	18 937
No heparin	5652	5651	5683	16 986
Intravenous heparin				
Transfused bleed	2·1%	2·0%	2 7%	2·2%
Reinfarction	8·8%	8 0%	9·2%	8·7%
Stroke	1·7%	2·3%	2·2%	2·1%
Cerebral haemorrhage	0·2%	0·7%	0·9%	0·6%
Death, day 0–35	9·2%	9·4%	10·0%	9·5%
Subcutaneous only				
Transfused bleed	0·7%	0·7%	0·9%	0·8%
Reinfarction	2·9%	2·4%	2·8%	2·7%
Stroke	0·9%	1·2%	1·1%	1·1%
Cerebral haemorrhage	0 3%	0·6%	0·5%	0·5%
Death, day 0–35	8·8%	8·1%	8·3%	8·4%
No heparin				
Transfused bleed	0·7%	0·6%	0·7%	0·7%
Reinfarction	2·6%	2·1%	2 7%	2·5%
Stroke	1·0%	1 3%	1·2%	1·2%
Cerebral haemorrhage	0·2%	0 7%	0·5%	0·5%
Death, day 0–35	12·9%	13·0%	13·1%	13·0%

91·0% of the sc heparin was high dose Patients given iv heparin may also have been given sc heparin

The non-randomised comparisons between patients who received iv, sc, or no heparin are potentially biased, and some are grossly biased For example, since early death prevents heparin being started subsequently, mortality among patients who received "no heparin" is artificially high (13 0%, as against 8·6%, among those who did survive long enough to receive some heparin), especially on days 0–1 (7 9% *vs* 2·8%) Conversely, reinfarction (and possibly occlusive stroke) may lead to iv heparin use, so reinfarction among people who received iv heparin at some time during their hospital stay is also artificially high

TABLE IX—ISIS-3 AND GISSI-2 COMBINED: EFFECTS OF ALLOCATED TREATMENT ON DEATHS IN DAYS 0–35 AMONG (i) ALL PATIENTS AND (ii) PATIENTS PRESENTING WITHIN 0–6 H WITH ST ELEVATION

—	Fibrinolytic comparisons		Difference %SK − %tPA	
	SK	tPA		
(i) All patients	24 176	24 118	%	SD
Any	2413 (10 0%)	2411 (10·0%)	−0·02	0·27
(*a*) Timing				
Day 0–1	1180 (4·9%)	1144 (4·7%)	0·14	0·19
Day 2–7	602 (2·5%)	687 (2·8%)	−0·36	0·15*
Day 8–35	621 (2·6%)	580 (2·4%)	0 16	0·14
(*b*) Antithrombotic allocation				
Aspirin + sc heparin	1178 (9·7%)	1200 (10·0%)	−0·22	0·38
Aspirin alone	1235 (10·2%)	1211 (10·0%)	0·19	0·39
(ii) 0–6 hours, ST elevation	19 039	18 943	%	SD
Any	1819 (9·6%)	1815 (9·6%)	−0·03	0·30
(*a*) Timing				
Day 0–1	902 (4·7%)	884 (4·7%)	0·07	0·22
Day 2–7	446 (2·3%)	508 (2·7%)	−0·34	0·16*
Day 8–35	461 (2·4%)	423 (2·2%)	0·19	0·15
(*b*) Antithrombotic allocation				
Aspirin + sc heparin	877 (9·2%)	905 (9·6%)	−0·38	0·42
Aspirin alone	942 (9·9%)	910 (9 6%)	0·33	0·43

*2p < 0 05.

generally mild, and with SK in ISIS-2 were not associated with any increased risk of death. When such reactions are produced by SK they often arise during the 1 h infusion, and generally resolve quickly without any treatment other than slowing the infusion rate or not giving the whole dose. But when they occur with APSAC (which is given as a bolus over just a few minutes) these options are not available. This may explain why, in the ISIS-3 placebo-controlled comparison of SK and APSAC, more patients given APSAC had allergic reactions.

The small AIMS trial[22] of APSAC among patients presenting within 6 h of the onset of symptoms with ST elevation had indicated a particularly favourable mortality reduction. But, *indirect* comparisons of the AIMS result with those of the major trials of SK did not indicate any statistically significant heterogeneity of the sizes of the benefits, and the *direct* randomised comparison of SK with APSAC among the very much larger numbers studied in ISIS-3 shows no difference whatsoever in 35-day or in 6-month mortality (either overall or when attention is restricted to the type of patients studied in AIMS). The 35-day mortality rates with SK and with APSAC were similar to each other in the presence of aspirin plus heparin (10·5% SK *vs* 10·5% APSAC) and in the presence of aspirin alone (10·6% *vs* 10·6%: table VI). This was still true if attention was restricted to that subset of patients presenting within 0–6 h with ST elevation (aspirin plus heparin: 9·8% SK *vs* 9·9% APSAC; aspirin alone: 10·2% *vs* 9·9%). Overall, the absolute difference in 35-day mortality between SK and APSAC was zero (SD 4) per 1000 patients treated, with 95% confidence intervals ranging from 8 fewer to 7 more deaths per 1000 with APSAC.

Fibrinolytic therapy: SK versus tPA

Unlike SK and APSAC, tPA is a human protein and contains no bacterial protein, and in ISIS-3 it caused fewer allergic reactions and somewhat less hypotension than SK or APSAC. Whereas SK and APSAC activate plasminogen efficiently throughout the intravascular compartment, tPA activates plasminogen efficiently only when bound to fibrin, for which tPA has a high affinity. Thus, tPA results in less depletion of circulating fibrinogen but more rapid coronary artery patency than SK or APSAC, although with all three agents the patency rates continue to increase beyond 90 min and appear similar within just a few hours.[32,33] tPA is produced either in the active "double-chain" form or in the less active "single-chain" form (but this difference is unlikely to be of much importance, since cleavage of the single-chain molecule occurs spontaneously immediately after single-chain tPA enters the circulation). The tPA studied in ISIS-3 is an almost pure double-chain product (Wellcome Foundation "duteplase"), and is therefore not identical to the predominantly single-chain product (Genentech "alteplase") that was studied in GISSI-2.[30,46] The main reason for hoping that tPA might be better than SK was that, with the currently standard regimens, tPA can open coronary arteries somewhat faster, with the recommended alteplase-tPA regimen[23-27] and the ISIS-3 duteplase-tPA regimen[28-31] giving similarly high 90 min patency rates of about 70% (table I).

For the comparison of SK with tPA, data are available not just from ISIS-3 but also from GISSI-2, and these two trials are therefore considered together. Perhaps through its more potent early action, tPA was associated with more strokes than SK in ISIS-3, confirming a similar finding in GISSI-2 (table VII). In the two trials combined, there was a highly significant excess of strokes (239 [1·00%] SK *vs* 324 [1·35%] tPA; $2p < 0·001$), equivalent to 4 extra strokes per 1000 patients treated with tPA, with most of this excess occurring within the first day or so of giving tPA and being attributed to an even more highly significant ($2p < 0·00001$)

excess of cerebral haemorrhage. In contrast, there were fewer reinfarctions with tPA than with SK in both trials, equivalent overall to a difference of 5 per 1000 ($2p < 0.005$) —and, although reinfarction is difficult to define reliably, there is no good reason to attribute this difference to bias.

In GISSI-2, there were slightly though non-significantly more deaths among patients allocated tPA (958 [9·2%] deaths among 10 396 patients allocated SK *vs* 993 [9·6%] deaths among 10 372 allocated tPA), whereas in ISIS-3 there were slightly though non-significantly fewer with tPA (fig 5 and table VII). In the two trials combined, there was no apparent difference at all in 5-week mortality (2413 [10·0%] SK deaths *vs* 2411 [10·0%] tPA deaths), and 6-month follow-up indicated a very slight, but non-significant, advantage to SK (table VII). In the two trials combined, the 35-day mortality rates with SK and with tPA were similar to each other in the presence of aspirin plus heparin (9·7% SK *vs* 10·0% tPA) and in the presence of aspirin alone (10·2% *vs* 10·0%: table IX). This was also the case among that subset of patients presenting within 0–6 h with ST elevation (aspirin plus heparin: 9·2% SK *vs* 9·6% tPA; aspirin alone: 9·9% *vs* 9·6%). The absolute 35-day mortality difference observed between SK and tPA in these trials combined was zero (SD 3) per 1000 patients treated, with 95% confidence intervals ranging from 5 fewer to 6 more deaths per 1000 with tPA.

Some of the early strokes caused death, and therefore the excess of fatal strokes with tPA is already included in the equality of the mortality results. However, tPA produced not only a significant ($2p < 0.01$) excess of 2 per 1000 fatal strokes but also a significant ($2p < 0.02$) excess of 2 per 1000 non-fatal strokes. In both instances this was attributed to an excess of cerebral haemorrhage, which was highly significant ($2p < 0.001$) both for fatal and for non-fatal cerebral haemorrhage. Subtraction of the highly significant excess of stroke deaths with tPA from the non-significant difference in total mortality does not provide any evidence whatsoever that tPA is better than SK at preventing other deaths. For there was no significant difference between SK and tPA in these other deaths at 35 days or at 6 months.

Fibrinolytic and antithrombotic "interactions"

It has been hypothesised that if there had been earlier and more intensive heparinisation in GISSI-2 and ISIS-3 then this might have produced a mortality result substantially in favour of tPA, because tPA produces better 90 min patency than SK and antithrombotic therapy helps keep these vessels open, perhaps avoiding death from reinfarction.[46,47] Some of the arguments used in support of this suggestion are invalid. For example, uncorrected indirect comparisons have been made[3,48-50] between the mortality rates with tPA and subcutaneous heparin in the large studies (GISSI-2 and ISIS-3) and the very much lower rates with tPA and intravenous heparin in some small studies where the average age, and hence the average risk, was much lower. (In this context, it is noteworthy that mortality in what was by far the largest randomised trial of tPA plus intravenous heparin, ASSET,[21] was similar to that in the large trials of SK[4,19,20] and of APSAC[22]). Patients included in different studies may differ with respect to some important prognostic factors—not just age but also severity of infarct, ventricular function, medical history &c—that are of much greater relevance to overall outcome than any differences between the fibrinolytic regimens used. Hence, such non-randomised comparisons of the mortality rates (or stroke rates) in different trials are subject to potential biases that are far larger than the treatment differences that they have, inappropriately, been used to assess. These biases may either obscure the sort of treatment differences that might realistically be expected or masquerade as a large treatment difference when none actually exists. Restriction of attention to the properly randomised comparisons of different regimens is, therefore, required in order to avoid such large "patient-selection" biases.[39]

TABLE X—SHORT-TERM MORTALITY RESULTS (DEATHS/PATIENTS) FROM DIRECTLY RANDOMISED COMPARISONS OF DIFFERENT FIBRINOLYTIC REGIMENS

(i) SK *vs* APSAC trials	SK	APSAC
Lopez-Sendon et al[55,56]	1/25	1/22
Vogt[57]	3/86	6/89
Hogg et al[58]	6/63	4/65
Invasive[59]	3/58	2/58
TEAM-2[60]	13/182	11/188
Subtotal: small trials	26/414	24/422
ISIS-3 & small trials	1481/14 194	1472/14 195
Overall comparison	10·4% *vs* 10·4%; NS	
(ii) SK *vs* tPA trials	SK	tPA
ECSG-1[53]	3/65	3/64
TIMI-I[54]	10/159	11/157
White et al[35]	10/135	5/135
PAIMS[36]	7/85	4/86
Subtotal: small trials	30/444	23/442
ISIS-3, GISSI-2, & small trials	2443/24 620	2434/24 560
Overall comparison	9·9% *vs* 9·9%; NS	
(iii) tPA *vs* APSAC trials	tPA	APSAC
Bassand[37]	7/93	5/90
TAPS[51]	5/210	17/211*
TEAM-3[52]	14/163	10/162
Subtotal: small trials	26/466	32/463
ISIS-3 & small trials	1444/14 212	1480/14 236
Overall comparison	10·2% *vs* 10·4%; NS	

*Of the subtotals, totals, and 12 small trials, only 1 small trial[51] is conventionally significant; its results are not confirmed by the other trials of the same question and the overall scatter of the 12 small trial results about zero is no greater than could be expected by chance alone if all the fibrinolytic regimens in them were equivalent ($\chi^2_{12} = 12{\cdot}5$; NS)

Even among the randomised comparisons, however, bias could be introduced by selective data-dependent emphasis on the result of one or other small trial (or of a subgroup within a trial), particularly if this is done because the result is extreme in some way. For example, much has been made[49,50] of the large mortality difference (2·4% tPA *vs* 8·1% APSAC) observed in the open tPA and APSAC Patency Study (TAPS).[51] But, as its name implies, that small study was designed to compare the effects of these agents on patency rates rather than on mortality, and its mortality results are not supported by the results of the other small randomised trials of tPA *vs* APSAC[37,52] (which, if anything, go against tPA: table X). Similarly, consideration of all rather than just one or another of the small trials of SK *vs* tPA[35,36,53,54] in the presence of heparin, or of SK *vs* APSAC,[55-60] does not provide any clear evidence of a difference in mortality between these regimens. The small trials, even in aggregate, cannot reliably assess the sort of differences in mortality (perhaps a few deaths per thousand[46]) that might exist between these different regimens. Only with the large-scale randomised comparisons in GISSI-2 and ISIS-3 can both these problems of selective biases and of random errors be avoided (see the three "overall comparisons" in table X).

In GISSI-2 and ISIS-3, all patients were to receive a substantial daily dose of aspirin that is known to halve reinfarction after fibrinolysis, so the number of reinfarctions was not large. Furthermore, there were significantly (and

unexpectedly) *fewer* reinfarctions with tPA than with SK or APSAC. These findings make it unlikely that better control of reinfarction will improve the effects of tPA much more than those of SK or APSAC. Finally, in ISIS-3 and GISSI-2 combined, 35-day mortality among patients allocated aspirin alone was slightly lower with tPA than with SK, whereas the opposite pattern was observed among patients allocated aspirin plus heparin (table IX: the patients who fared best of all were those allocated SK plus aspirin plus subcutaneous heparin, although these differences were not clearly significant). These observations suggest that more intensive heparinisation is unlikely to produce a large effect on the relative merits of SK and tPA (which is what is also weakly suggested by the comparisons in table VIII). Moreover, heparin itself can cause bleeding, so more intensive heparinisation might cause more cerebral haemorrhage, particularly during the early hours when tPA and APSAC are already causing a few cerebral haemorrhages. Hence, any extra stroke risks with more heparin might be slightly worse for tPA and APSAC than for SK.

Implications for research and clinical practice

Differences in patient selection or in details of the chosen regimens could, of course, produce at least small differences in the relative merits of different drugs. Studies such as ISIS-3 and GISSI-2 should not, therefore, be taken as definitive evidence that tPA or APSAC can never be better than SK (or vice versa) in any circumstances. Instead, they should be taken as definitive evidence that any mortality differences between different antithrombotic regimens or between different fibrinolytic regimens are unlikely to be large: that is, any mortality differences may well involve a few deaths per thousand, one way or another, but probably not a few deaths per hundred. The corollary of this is that differences of a few per thousand patients in fatal or disabling side-effects (such as the excess of stroke seen with tPA and APSAC) need to be taken more seriously than has sometimes been the case in discussions of the relative merits of different antithrombotic and different fibrinolytic regimens.[61] ISIS-3 and GISSI-2 suggest that, although there may be some slight advantage of adding subcutaneous heparin to aspirin, there are no substantial differences in mortality between these regimens.

It is important not to let uncertainty as to *which* antithrombotic or fibrinolytic regimen to use routinely engender uncertainty as to *whether* to use antithrombotic and fibrinolytic therapies routinely. ISIS-2 showed that worthwhile survival advantages can be obtained by routine use of antiplatelet therapy in almost all patients with suspected acute MI, and by the use of fibrinolytic therapy in a wide range of such patients, including the elderly.[4]

The most important acknowledgment is to the tens of thousands of patients who took part in ISIS-3, and to the thousands of doctors and nurses who collaborated with the national coordinators in each country. The coronary care unit staff in Athens, Bellinzona, Berlin, Bruxelles, Gent, Valencia, and Warsaw, the computer department in Lyon, the Radcliffe Infirmary switchboard and the Clinical Trial Service Unit (CTSU) in Oxford provided 24 h randomisation services. The coordinator was supported by the British Heart Foundation. The UK Department of Health tobacco products research trust supported epidemiological studies in ISIS-2 and in ISIS-3. GISSI-2 and the International Study Group kindly provided unpublished data and many additional analyses. Sterling Drugs donated aspirin, Sanofi donated calcium heparin, and Behringwerke (a subsidiary of Hoechst) donated streptokinase, but otherwise the study was funded by the Wellcome Foundation, who manufactured the tPA, and SmithKline Beecham, who manufactured the APSAC. The study was, however, designed, conducted, analysed, and interpreted independently of all the companies. The following centres and investigators collborated (* steering committee, † data monitoring committee, ‡ no patients could be entered from these countries becuse of delays in processing regulatory approval):

Australia‡: *Royal Melbourne:* Hunt D*, Varigos J*

Austria (1120 patients): *Univ Klinik, Innsbruck:* Dienstl F*, Lechleitner P*, Mauel Ch, Dienstl A; *KH Bad Ischl:* Gmeiner R, Kronabethleitner G; *KH Baden* Thumb N, Lavicka C, *KH Bludenz* Schobel B, Sprenger M; *KH Schulschw, Braunau* Täuber K, Rheina-Wolbeck G; *KH Bregenz:* Hugel H, Bereuter B, Bischoff HP; *KH Bruck/Mur* Schellnegger W, Korthals Ch, Gruber M, *KH Deutschlandsberg:* Spath P, Stupnicki Th, Gaberc B; *KH Dornbirn:* Abbrederis K, Studer E; *KH Eisenstadt:* Silberbauer K, Juhasz M; *Univ Klin, Graz:* Klein W, Grisold M, Eber B; *KH Grieskirchen:* Remsa G; *KH Hall i T:* Schmalzl F, Jud M, Said M, *KH Hartberg:* Stepan KM, Pichler H; *KH Horn* Bratusch-Marrain P; *LKH Klagenfurt II:* Sterz H, Wernisch M; *KH Knittelfeld* Rainer W, Lorenzoni H; *KH Hohenems.* Sutterlütti G, Kopf A, Metzler J; *KH Krems:* Kronik G; *KH Kufstein:* Stuhlinger W, Maier J, Schauer N; *KH Leoben:* Borkenstein J, Fuhrmann W, Pölzl G; *KH Lienz.* Fritzer W, Sint G; *AKH Linz* Leisch F, Felbermayer M, Kerschner K; *KH Barm Bruder, Linz* Clodi PH, Steinmaurer HG; *KH Barm Schw, Linz:* Kuhn P, Baumgartner H, Kratzer H; *KH Elisab, Linz:* Nesser J, *KH Melk:* Prohaska R, Brunner W; *KH Ried i Innkr:* Renner F, Demmelbauer K; *KH Rottenmann.* Schneider T, Winter D; *KH St Johann i T:* Baumgartl P, Reiger I; *LKH I Med, Salzburg:* Sandhofer F, Kaserer P, Atzenhofer K; *LKH II Med, Salzburg:* Sailer S, Ursin Ch, Weitgasser R; *KH Schwarzach* Lenzhofer R, Schuster R, Gersdorf D, *KH Schwaz:* Ciresa M, Bode C; *KH Steyr:* Kleinberger G, Brunhuber W; *KH Vocklabruck:* Fereberger W, Gruber A, *KH Kreuzschw, Wels:* Pachinger O, Hinterreiter H; *Allg Polikln, Wien:* Tiso B, Anderle K; *KH Barm Schw, Wien:* Preitschopf H, Pfaffenberger D, Weiss P; *KH Floridsdorf, Wien.* Peschl L, Zeilinger M; *Hanusch KH, Wien:* Aldor E, Gaul G, Deutsch E; *Kais Elis Sp, Wien:* Kubicek F, Auinger A, Martys Th; *KH KF Josef I, Wien.* Tragl KH, Maleschitz P, Gremmel F; *KH KF Josef III, Wien:* Honetz N, Landesmann B, Prohaska H, *KH Rudolfstiftung, Wien:* Slany J, Karnik R, Valentin A; *KH St Vinzenz, Zams:* Pall H, Schonherr HR; *KH Zell a See:* Erd W, Heiss G, Lasser W.

Belgium (747 patients): *Universitair Ziekenhuis, Gent:* De Backer G*, Buylaert W, Missault L, Clement DL; *Erasme, Bruxelles* Kornitzer M*, Abramowicz M, Degre S; *Universitair Ziekenhuis, Antwerpen:* Bossaert L, Demey H; *Beloeil* Dieudonne P, Coupez M, *Komingin Fabiola, Blankenberge:* Dendooven DJP; *du Bois de L'Abbaye:* Calay G, Denoel T; *St Jozefkliniek, Bornem:* Herssens MP; *AZ VUB, Bruxelles:* Dewilde Ph, Huyghens L; *Brugman Bruxelles:* Telerman M, De Vriendt J; *ICM d'Ixelles, Bruxelles:* Faniel R, Popee M; *Joseph Bracops, Bruxelles:* Depaepe A; *St Pierre Bruxelles:* Bernard R, Segar R; *Braine-l'Alleud:* Guerisse P, Adant D; *AZ St Jan, Brugge:* Vandekerckhove Y, van der Stichele E, Vincke J, Muyldermans L; *Civil de Charleroi:* Picard N, Renaux A, *IMC A Gailly, Charleroi:* Pinon F, Plennevaux V; *Civil de Chatelet:* Derbaudrenghien J-P; *de la Madeleine:* Rivière A, De Rijeke A; *H Hartkliniek, Eeklo:* de Sonville AM; *Volksklinek Gent.* Haerens RAP, Jordaens L; *St Jozefkliniek, Gentbrugge:* Kluyskens Y, Francois B; *Notre Dame de Grace, Gosselies:* Sottiaux T, Charlot C; *AZ Hoge Beuken, Hoboken* Bruyneel K, *Hutois.* El Allaf D, Jacoby M-C; *Civil de Jumet:* Balthazar E, Jadoul M-J; *St Barbaraziekenhuis, Lanaken:* Prihadi S; *OLVZ, Mechelen:* Beys J; *Ste Camille Namur* Fautsch G, Lambert P; *Stadskliniek St Niklaas:* Thiels H, van de Weghe C; *Twoli IMMS.* Laurent M, Corvezzo A-M; *Civil de Tournai:* Desplanque L, Voet J-P; *IMC Tournai* Dereume C, Samayn M; *Notre Dame de Tournai:* Hamoir V, Cardon M, *CGTR Le Rayon de Soleil, Vesale:* Henuzet C, Charlot N; *Emmanuelziekenhuis, Wetteren* Robbens EJ, Baetens PR; *AZ St Elisabeth, Zottegem:* Dierickx S, Bladt D.

Canada (2918 patients): *Hamilton General* Cairns J*, Turpie A*, Fraser K, Petitti R; *Belleville General:* Curry Grant F, Vanslyke D; *Brantford General:* Bate L, Kott D; *Joseph Brant Memorial, Burlington:* Carling L, Beare L; *Calgary General:* Roth D, Beresford P; *Holy Cross, Calgary* Lesoway R, Cowan J; *Cambridge Memorial:* Vizel S, Wilkinson D; *Charles Le Moyne:* Timothee J-R, LaMontaine P; *Public General, Chatham:* Harnarine CC, Wilston M, Pfaff S; *Hotel Dieu, Cornwall:* Baitz T, Pollock R, Epps E; *Credit Valley:* Druck M, Laughlin A; *Cowichan District, Duncan.* Hilton D, MacKenzie G; *Royal Alexandra, Edmonton:* Hui W, Kvill L; *University of Alberta, Edmonton:* Burton JR, Harris L; *Queensway General, Etobicoke:* Sevitt B, Wassmer S; *St Joseph's, Guelph:* Raco D, Aisan G, Snow K; *Halifax Infirmary:* Crofts P, Haestis A; *Chedoke McMaster, Hamilton* Finkelstein L, Dunford J; *Henderson General, Hamilton:* Sealey B, Olde J; *McMaster University Med Centre, Hamilton:* Fallen E, Cooper M; *St Joseph's, Hamilton:* Sullivan M, Kennedy D; *Royal Inland, Kamloops:* Reid R, Prins J; *Kingston General:* Matangi M, Robb-Blenderman L; *Hotel Dieu, Kingston:* Abdollah H, McCue P; *St Mary's, Kitchener:* Fowlis R, McGoey V, Pallas P; *St Joseph's, London:* Goddard M, Janssen J; *University, London:* Jablonsky G, MacKinnon D; *Victoria, London:* Finnie K, Adkins B, *Mississauga General:* Rebane T, Sanauka A; *Montréal General:* Burgess BJ, Hanycz C; *Hotel Dieu de Montréal:* Latour Y, Bajenais L; *Sacre-Coeur de Montréal:* Nasmith JB, Gaudette G; *Royal Victoria, Montréal:* Fitchett D, Toyota V; *York County, Newmarket.* Hess A, Jacques M; *Greater Niagara:* Chan YK, Zaniol D; *North Bay Civic* Bowker B, Penno LN, Vainio J; *Oshawa General:* Bhargava R, Ellis M; *Ottawa Civic:* Williams WL, Kearns S-A; *Grey-Bruce RHC, Owen Sound:* Keeling CJ, Glass S; *Peel Memorial:* Borts D, Petrovan S; *Penticton Regional:* Ashton T, Barr D, *Peterborough Civic* Hughes WG, Sayer S; *St Joseph's, Peterborough:* MacKenzie B, Young J; *St Sacrement, Québec* Cote MA, McCabe L; *St John Regional:* Marr D, Haycox C; *Scarborough General:* Roth S, Smith J; *Norfolk General, Simcoe:* Chiu S, McCrea C; *Stratford General:* Fuller D, Smith P; *Sudbury Memorial:* Juma Z, Chorny L, Waldick K; *Surrey Memorial:* Kornder J, Mackie M; *McKellar General, Thunder Bay:* Leitrants P, DuBois-Wing G; *Port Arthur, Thunder Bay:* Lai C, Aquino-Russell C; *St Joseph's General, Thunder Bay:* Masood KM, Gurney T; *Vancouver General.* Fung A, Valmonte P, *Lion's Gate, Vancouver:* Imrie J, Dart M; *Richmond General, Vancouver:* Jue J, Moore J; *St Paul's, Vancouver:* Thompson CR, Primeau A; *University, Vancouver:* Nath C, Vorderbrugge S, Jakubowski A, Fraser J; *Verdun General:* Brophy J, Labelle D; *Victoria General:* Morch J, Peet G, Mildenberger R, McGrath M; *Centenary, West Hill* Ricci AJ, Bozek B; *North Branson, Willowdale:* Strauss M, Colonna M; *St Boniface, Winnipeg:* Smith H, Schillberg M; *Woodstock General:* Carter P, Parciak S.

Denmark‡: *Fakse:* Fritz-Hansen P*, Skagen K*.

Finland (712 patients): *Maria, Helsinki:* Kala R*, Pajari R, Wahlstedt I; *University Central, Helsinki:* Heikkila J*; *Ähtari District:* Määttänen J, Mursula R; *Heinola.* Vallittu H; *Malmi, Helsinki:* Kohvakka A, Rannikko C; *Iisalmi District:* Laitinen R, Riipinen N; *Imatra District:* Kovanen H, Syrjakari A; *Jokilaakso District:* Nyyssönen S, Myllys E; *Kanta-Hame Central:* Saksa M, Suuronen S; *Kemijarvi District:* Viinikka J; *Keski-Pohjanmaa Central:* Halkosaari M, Salonen P-L; *Länsi-Uusimaa District:* Lindström C; *Lappi Central:* Eloranta M, Autio R-M; *Lohja District:* Suhonen O, Lyytikäinen R; Lounais-Hame District: Koskelainen J, Ryhtä S; *Malmska District:* Linna M, Bjorklund M; *Mikkeli Central:* Tarssanen L; *Porvoo District:* Härkonen M, Rask C; *Raisio District:* Karmakoski J, Lattu M; *Rauma District:* Saarelainen E, Valmunen H; *Riihimaki District:* Tiukka T, Komulainen S; *Selkamen District:* Tuunanen V, Sjogård H-M; *Vaasa Central:* Kivela H.

France (1170 patients): *Hôpital Cardiologique, Lyon:* Boissel J-P*, Leizorovicz A*; *Notre Dame de la Miséricorde, Ajaccio:* Colonna D, Leandri JJ; *Allauch:* Escande M,

Diadema B; *Universitaire, Amiens:* Jarry G, Quiret JC; *Régional et Universitaire, Angers:* Geslin P; *Annecy:* Dupont JC; *Victor Dupouy, Argenteuil:* Fruchaud J; *Clinique Cardiologique Jean Paoli, Arles:* Gauthier J; *Aubenas:* Haddad J; *Robert Ballanger, Aulnay sous Bois:* Montely JM, Hanania G; *Louis Pasteur, Bagnols sur Ceze* Allard-Latour G, *Clinique de la Dhuys, Bagnolet:* Zerah G; *Germon et Gauthier, Bethune:* d'Hautefeuille B, Mycinski C; *Hôpital Saint André, Bordeaux:* Le Metayer P, Warin JF, *Régional et Universitaire, Brest:* Boschat J; *Briancon:* Sibille JP, Yaici K; *Douai* · Dujardin JJ, Joly P; *Dragugnan:* Latour F, Camilleri JF; *Dunkerque:* Werquin S, Ghaddar H, Dubeaux PA, Moulron S; *Intercommunal, Fréjus:* Mossaz R; *Freyming Merlebach:* Dambrine P, Gabriel A; *Gueret:* Bessede G; *Sanofi, Gentilly:* d'Azémar P; *Départemental Les Oudaires, La Roche sur Yon:* Gully C; *La Seyne sur Mer:* Grellet C, Beltran J; *de Versailles, Le Chesnay,* Normand JP, Schwob J; *Le Puy:* Viallet M; *Longjumeau.* Tran Thanh X; *Hôpital des Chanaux, Macon:* Cavallaro J, Auberger R; *Universitaire Marseille Nord, Marseille:* Rossi P, Dolla E; *Polyclinique Saint Henri, Nantes:* Cebron JP, Banus Y; *Niort:* Page A, Denis C, Le Bris H; *Hôpital du Haut Lévêque, Pessac:* Durrieu C, Besse P; *Universitaire La Milétrie, Poitiers* · Barraine R; *Polyclinique de Courlancy, Reims:* Carette B, Thiernesse R; *Romans sur Isere:* Michelon G, Karam C; *Hôpital Victor Provo, Roubaix:* Haftel Y, Demarcq JM, Dufossez F, *Saint Aubin les Elbeuf:* Toussaint C; *Général, Saint Die:* Bourdon JL, Bragard MF, Vine F, *Central, Strasbourg:* Brandt CM, Fincker JL; *Régional, Thionville:* Houplon M, Thisse JY; *Intercommunal, Toulon:* Sommer A, Raufast D; *Dron, Tourcoing:* Leroy O, Beaucaire G; *Valence:* Grand A, Huret JF, Fichter P; *Valenciennes:* Socolovsky C, Manouvrier J; *Lucien Hussel, Vienne:* Veyre B.

Germany (5118 patients): *Klinikum Steglitz, Berlin:* Schroder R*, Schroder R, Schäfer H; *Charité, Berlin:* Kothe K*; *Luisen-Hospital, Aachen:* Ontyd J, *St Nikolaus-Stiftshospital, Andernach:* Degen H, Hügl E; *Stadt Krankenanstalten, Aschaffenburg:* Juchems R, Frese W; *Herz-Kreislauf-Zentrum, Bad Bevensen:* Notges A, Wolf R, *Klinik d Hochtaunuskreises, Bad Homburg:* Raisig S, Bodem G; *Klinikum, Bamberg:* Diamantis M, Grohmann H; *Kries KH, Belzig:* Hessler M; *Marien KH, Bergisch Gladbach:* Hinzmann S, Frotz H; *KH am Urban, Berlin:* Topp H, Dissmann W; *Ev. Wald-KH, Berlin:* Justiz R, *Humboldt KH, Berlin:* Menges M, Thimme W; *KH Neukolln, Berlin:* Wagner J, Henzgen R; *KH Spandau, Berlin:* Burbach H; *St Gertrauden-KH, Berlin:* Ramdohr B, Grupp H-J; *Wenckebach-KH, Berlin:* Kuckuck H; *Stadt Krankenanstalten, Bielefeld:* Kuhn H, Gerenkamp T; *Augusta Krankenanstalt, Bochum:* Altmaier K, Nagelkramer D; *Malteser-KH, Bonn:* Kessler FJ, Mattias P; *Knappschafts-KH, Bottrop* : Harbarth P; *Stadt KH Brandenburg:* Haase J; *Stadt Klinikum, Braunschweig:* Haedicke Ch; *KH Links der Weser, Bremen.* Jansen A; *Rot-Kreuz-KH, Bremen:* Zschiedrich H, *St Joseph Hospital, Bremerhaven:* Martin K; *Land KH, Coburg:* Medau HJ, Avenhaus H; *Klinikum, Cottbus:* Kamke W; *Elisabethstift, Darmstadt:* Szappanos L; *Stadt Kliniken, Darmstadt:* Frederking H; *Kreis KH, Detmold:* Zulfacar A; *Stadt Kliniken, Dortmund:* Saul FW: *KH Lutgendortmund, Dortmund:* Runte F, Wellmann W, *KH Duren:* Simon H, von der Lohe E; *Ev KH, Dusseldorf:* Asshoff D; *Med Klinik Benrath, Dusseldorf:* Lengert G, Schoppe WE, *Kreis KH, Emmendingen* · Wetzel P; *Elisabeth-KH, Essen.* Sabin GV, Walter A; *Franziskus-KH, Essen:* Dörwald R; *Knappschafts-KH, Essen:* Papenberg J, Warning A; *Burgerhospital, Frankfurt/M:* Sedlmeyer I; *Frankfurt/O:* Zieger K; *Nordwest-KH, Frankfurt/M;* Heller A; *St Josef-KH, Freiburg:* Tomas W; *Burgerhospital, Friedberg:* Hentschel M, Meier J; *Kreis KH, Furstenwalde:* Groschke KV, *Elisabeth-KH, Gelsenkirchen.* Kniemann H; *Evangelisches KH, Gelsenkirchen:* Greitemeier A, *St Josef-KH, Gelsenkirchen:* Callsen H; *Klinikum 1, Gera.* Bernhardt G; *St Barbara-Hospital, Gladbeck:* Graupner M, Geisler LS; *Stadt KH, Gutersloh:* Wefers U; *Allgemeines KH, Hagen:* Rox J; *St Salvator KH, Halberstadt.* Haaf J; *St Sixtus Hospital, Haltern:* Beythien R-D; *Allg KH Harburg, Hamburg:* Weiss B; *Ev KH, Hamm:* Mosseler U, Hulskamp Ch; *Stadt KH, Hanau:* Reinemer H, Becker H-J; *KH Siloah, Hannover:* von Leitner E-R; *St Josefs-KH, Heidelberg.* Stein U, Hild R; *Stadt KH, Heilbronn:* Berentelg J, Cyran J; *KH St Marienberg, Helmstedt:* Schwartz BR; *Paracelsus-Klinik, Hemer:* Riebeling V, Raether Ch; *Kreis KH, Herford.* Folttmann Ch, Schmitz-Huebner U, *Marien-KH, Herne:* Lenga P, Odenthal H-J; *St Josefs KH, Hilden.* Christern H; *Stadt KH, Hildesheim:* Bodman K-F; *Stadt KH, Itzehoe:* Pape C; *Universitat, Jena:* Thiele R; *Malteser-KH St Elisabeth, Julich:* Matte A; *Stadt Klinikum, Karlsruhe:* Ruffmann K, Mehmel H; *Elisabeth-KH, Kassel:* Hackethal G; *Oberallgäu-Klinik, Kempten* Hiemeyer V, Kirchmann H; *Stadt KH, Kiel.* Gutschmidt H-J; *KH Holweide, Koln:* Saborowski F, Schneider M; *KH Merheim, Koln:* Griebenow R; *KH Porz, Koln* · Hossmann V; *St Antonius-KH, Koln.* Scholz D, Mies R, *Uniklinik, Koln:* Klocke RK, Hopp HW; *Kath KH Siebengebirge, Konigswinter.* Kummerhoff PW, *Kreis KH, Konigs-Wusterhausen:* Ruffert HJ; *Stadt KH, Korbach:* Engelsing B; *Stadt Krankenanstalt, Krefeld:* Knoch K, Grosser KD; *KH Maria Hilf, Krefeld:* Dichgans M, Peters U; *Kreis KH, Lahr:* Wiedemer B, Fleischmann D; *Stadt KH, Landsberg:* Perl R, Gatz S; *Kreis KH, Landshut:* Sigl G; *Universitat, Leipzig:* Hellmund FD; *Stadt KH, Leverkusen:* Jansen W, Geppert R, *Kreis KH, Lubben.* Dinter M; *Ludwigslust-Schwerin:* Korber HG; *Krankenanstalten, Ludwigsburg:* Liebau G; *Med Universitat, Lubeck:* Muller-Esch G; *Stadt KH, Luneburg:* Niederstadt H; *Bezirks KH, Magdeburg* Siedentopf K; *Med Akademe, Magdeburg:* Grund S; *Heinrich-Lanz-KH, Mannheim:* Nissen P; *Klinikum, Mannheim:* Buss J, Heene DL, *Behring, Marburg:* Delvos U, Jessel A, Muller J; *St Elisabeth-KH, Mayen:* Potthoff H-J; *Kreis KH, Mechernich:* Neuhaus J, Mohr P; *Klinikum, Minden:* Ammer GFJ, Bleiching P; *St Josef-KH, Moers:* Stalman R, Langner R; *Ev KH, Mulheim ad Ruhr:* Kotter V; *KH Bogenhausen, Munchen:* Nowak FG, Buchholz Ch; *Klinikum Grosshadern, Munchen:* Engelhardt D, Hiller E; *KH Harlaching, Munchen* · Lindlbauer R, Scheinpflug W; *KH Neuperlach, Munchen:* Henselmann L, Fischer JL; *Krankenanstalt Rotes Kreuz, Munchen:* von Arnim Th; *Stadt KH, Nettetal:* Appenrodt H; *KH Neuruppin:* Reichelt A; *Kreis KH, Neu-Ulm* · Wenk K; *St Josef-KH, Oberhausen:* Kremer GJ, Schulze-Wethmar H; *Kreis KH, Offenburg:* Stephinger U; *Stadt Kliniken, Osnabruck:* Schadowski M, Junge-Hulsing G; *KH d Landkreises, Peine* · Beck OA; *Klinikum Potsdam:* Angerstein HG; *Kreis KH, Prien:* Hannemann H-R; *Prosper-Hospital, Recklinghausen:* Becker E; *Kreis KH, Reutlingen:* Hust MH, Braun BB; *Herz-u Kreislaufzentrum, Rotenburg/F:* Bali M, Walther H; *Diakonie KH, Rotenburg/W* Bottjer H; *Kreis KH, Rudersdorf:* Dahn G; *Thuringen Klinik, Saalfeld:* Pocher K; *Stadt Kliniken Winterberg, Saarbrucken:* Zwirner K; *St Marien-KH, Siegen:* Schuster P, Neuhaus Chr; *KH Staaken:* Hampel D; *Stadt KH, Singen* · Kehl J, Kley HK; *Kreis KH, Springe:* Besser N; *KH, Starnberg:* Lydtin H, Trenkwalder P, *Kantonspital, St Gallen* · Huber B; *Ev Elisabeth-KH, Trier:* Wertgen Th, Kronig B. *KH d Barmh Bruder, Trier* Hauptmann K; *St Johannes KH, Troisdorf.* Handrup R; *Klinikum, Wiesbaden* Piper Ch, Von Egidy H; *Stadt KH, Wolfsburg:* Winter R, Aly FW; *Missionsarztl KH, Wurzburg:* Fink H, Köhler B; *Ferd Sauerbruch-Klinikum, Wuppertal:* Hohler H; *KH Bethesda, Wuppertal:* Bottcher D, Wiebringhaus E.

Greece (382 patients): *Hygeia, Athens:* Karatzas N*; *Alexandra, Athens:* Moulopoulos S, Nanas S; *Evangelismos, Athens.* Kollettis M, Krespi P, Tsitouris G, Zarkos E; *Laiko, Athens.* Bakoulas G, Hatzizacharias A, Makis T, Vogiatzi P; *NIMTS, Athens:* Heliades A, Karagiorga K; *Red Cross, Athens:* Athanasiadis D, Louvros N, Nicolaou V, Skoufas P; *Amalia Fleming:* Antonatos P, Constantinou L, Deliyannis A, Kefalas C, Ghikopoulos M; *Soteria, Athens:* Gazetopoulos N, Georgiades S, Kandes K; *IKA Pentelis, Melissia:* Papazoglou N, Triandes G; *Piraeus General, Nikaia:* Papasteriades E, Petropoulakis P; *St Andreas, Patras:* Hahalis G, Sirimbeis S; *Tzanio Piraeus:* Cokkinos D, Olympios Ch· *IKA Panagia, Thesalonika:* Kyrpizides Ch, Papazachariou G; *Panarkadikon, Tripolis:* Stavrides A, Terzis S; *Achilopoulion, Volos:* Tsaknakis Th, Ntinopoulos P, *Asclepeion, Voula:* Christakos S, Kyfnides C.

Ireland (1191 patients): *Beaumont, Dublin:* Horgan J*, O'Callaghan D*, Herlihy M; *Ardkeen:* Fitzgerald G, Kennedy A; *Bantry General:* McCoy D, Kingston J; *Cavan General:* Farrelly A, Fay MP; *Ennis General, Co Clare:* Curtin D; *Bon Secours, Cork:* Kenny J, *Cork Regional.* Fennell W, Palmer C; *South Infirmary, Cork:* Cahill N, Topham M; *St Joseph's Medical, Clonmel* · Regan P, Hewitt M; *St James, Dublin:* Walsh M; *St Vincent's, Dublin:* Maurer B, Burke Y; *University College, Galway* Daly K, Carr S; *St Luke's, Kilkenny:* Mahon J, Comerford A; *Letterkenny General* Bannan L, Doyle H; *Limerick Regional.* Peirce T, O'Sullivan M; *Mallow General:* Sullivan P, O'Brien E; *Mullingar General:* Quinlan C; *Nenagh General:* Lomass B, Powell R; *Our Lady of Lourdes, Drogheda:* Muldoon B, Costello T; *Portlaoise General:* Connaughton J, Kiernan T, Gallagher E; *Sligo General:* Murray D, Molohan M; *Tullamore General:* Taaffe J, Quinn M; *Wexford General* · McKiernan P: *Castlebar General:* Lucey C.

Italy (GISSI liaison): *Mario Negri, Milan:* Tognoni G*, Franzosi M-G*, Maggioni A*.

Luxembourg (20 patients): *Centre Hospitalier, Luxembourg* · Beissel J, Erpelding J.

Netherlands (1517 patients): *Centre for Human Drug Research, Leiden:* Cohen A*, Koster R*, van Vliet A, van der Jagt A; *Twenteborg ZH, Almelo.* Bouma HG; *Maasziekenhuis, Boxmeer:* Smits WC; *ZH de Baronie, Breda:* Middelhoff CJ; *Gelderse Vallei, Ede:* van Kalmthout PM; *Diakonessenhuis, Eindhoven:* Relik-van Wely L; *Medisch Spectrum Twente, Enschede:* Molhoek GP; *Oosterschelde ZH, Goes:* Liem AH; *Diaconessenhuis, Groningen:* Takens LH; *St Elisabeth's Gasthuis, Haarlem:* Kan G; *de Tjongerschans, Heerenveen:* Jochemsen GM; *Groot Ziekengasthuis, Hertogenbosch:* van der Pol JHJ; *Zeeweg ZH, Ijmuiden:* Kainama JJ; *St Jozefziekenhuis, Kerkrade:* Boehmer AG; *Diaconessenhuis, Leiden:* Witteveen S; *St Elisabeth ZH, Leiderdorp:* Van Rees C; *Medisch Spectrum Twente, Oldenzaal:* Kuiper H; *Ikazia ZH, Rotterdam:* Kerker JP; *St Franciscus Gasthuis, Rotterdam:* Veerhoek MJ, *Maria ZH, Tilburg:* Vet AJT; *St Elisabeth ZH, Tilburg:* Pasteuning WH; *ZH Oudenrijn, Utrecht:* Roozendaal H; *St Joseph ZH, Veghel:* Relik-van Wely L; *St Jans Gasthuis, Weert:* Penn HJ; *Streekziekenhuis, Winterswijk:* Stevens JVC, *St Zeister Alg ZH, Zeist:* van Bogerijen L; *Ysselland ZH, Rotterdam:* Nio SL.

New Zealand (1084 patients): *Green Lane, Auckland* · White H*, Scott M; *Auckland:* MacMahon S*; *Ashburton:* Audeau M; *North Shore, Auckland:* Frankish P; *Middlemore, Auckland.* Caruana M; *Blenheim:* Durham D; *Princess Margaret, Christchurch:* Wong K; *Grey Hospital, Greymouth:* Holt P; *Waikato, Hamilton:* Friedlander D; *Memorial, Hastings:* Luke R; *Hutt:* Mann S; *Masterton:* de Silva K; *Nelson.* Jackson W; *Rotorua:* Bruns B; *Tauranga.* Nairn L, *Timaru:* Frenneaux M; *Wellington:* Leslie P; *Whakatane:* Jorgensen P.

Norway‡: *Baerum:* Kjekshus J*, Reikvam A*.

Poland (524 patients): *Grochowski, Warsaw:* Ceremuzynski L*, Budaj A, Cedro K, Cybulski J, Statuch C; *Bielanski, Warsaw:* Zengteler J, Tomczak D; *Bródnowski, Warsaw:* Kuch J, Sczaniecka O; *Wolski, Warsaw:* Wojtulewicz L, Komorowska M; *Pogotowia Ratunkowego, Warsaw:* Dyduszynski A, Wasiutynska E; *MSW, Warsaw:* Zochowski RJ, Kochmanski M; *Klinika Kardiologii AM w Bydgoszczy:* Nartowicz E, Paczkowska B; *I Klinika Kardiologii AM w Krakowie:* Dubiel JP, Mroczek-Czernecka D; *Dietla, Krakow:* Maciejewicz J, Kurleto J; *Narutowicza, Krakow:* Smielak-Korombel W, Grzelewski JT.

South America (EMERAS liaison): Paolasso E*, Diaz R*.

Spain (605 patients): *Dr Peset Aleixandre, Valencia:* Valentin V*, Valls F, Miralles L; *Hospital Clinico Universitario de Valencia.* Llopis R; *Hospital Arnau de Vilanova:* Fajarnes F; *Hospital General de Valencia:* Echanove I; *Hospital Francisco de Borja:* Mazza S; *Hospital Lluis Alcanys:* Rodriguez M; *Hospital de Sagunto* · Tormo C; *Hospital General, Castellon:* Ferrandis A, Rodriguez D; *Hospital de Villajoyosa-Benidorm:* Fuster M; *Clinica Mare Nostrum:* Segui J; *Hospital Carlos Haya:* Vera A, Torrado E, *Hosp Univ Virgen de la Victoria:* Garcia Alcantara A, Carpintero JL; *Hospital Virgen de la Arrixaca:* Torres G, Rodriguez P; *Hospital General, Murcia:* Mira E; *Hospital Santa Maria de Rosell* · Jimeñez F, Allegue JM; *Hospital Antonio Coello Cuadrado:* Goñi F; *Hospital Txagorritxu:* Camacho I; *Hospital de Soria:* Lopez O; *Centre Hospitalari de Manresa:* Jodar L; *Hospital 12 de Octubre:* Malillos M.

Sweden (1902 patients): *Östra, Goteborg:* Wilhelmsen L*†, Thorin M; *Hudiksvall:* Lundkvist L*, Ångman K; *Avesta:* Perers G; *Bollnas:* Mascher G; *Borås:* Skogstrom K, Rosqvist C; *Enköping:* Karlsson L; *Harnösand:* Hemmingsson L-O; *Hassleholm:* Pettersson B; *Karlskoga:* Engström B; *Kiruna:* Erkstam G; *Kristinehamn:* Watz R; *Koping:* Malmros B, Nicol P; *Ludvika;* Frisell JE; *Lund:* Persson S; *Lycksele:* Bjurman A; *Mora:* Aronson D; *Norrtalje:* Svensson G; *Nykoping:* Dahlberg A; *Örnskoldsvik:* Lovheim O; *Sandviken:* Ellstrom J, Brodersson H; *Simrishamn:* Hallgren J; *Sabbatsberg, Stockholm:* Liljefors I, Wennerstrom L, *Sundsvall:* Moller B; *Saffle:* Gillgren L; *Soderhamn:* Terent A, Mohaupt D; *Sodertälje:* Nyberg A, Dahlin L; *Trelleborg:* Bachmann R; *NÄL, Trollhattan:* Redfors A; *Visby:* Hoffstedt E; *Ystad:* Arnman K.

Switzerland (824 patients): *Civico, Lugano:* Moccetti T*, Lechuga S; *San Giovanni, Bellinzona:* Malacrida R*, Genoni M*, *Spital Altstatten:* Hangartner PJ; *Regionalspital, Biel:* Jenni C; *Kreisspital, Bulach:* Vogelin HP; *Regionalspital, Burgdorf:* Gerber A; *Kreuzspital, Chur:* Wüscher V; *Ospedale Distrettuale, Faido:* Wunderlich P; *Spital, Flawil:* Schonenberger EM; *Kantonspittal, Freiburg:* Quartenoud B; *Kantonsspital, Glarus:* Wojtyna W, Rhyner K; *Spital, Grenchen:* Schlup P; *Bezirksspital, Grosshochstetten:* Burger H; *Bezirkskrankenhaus, Heiden:* Weisser H, Kehl O; *Regionalspital, Herisau.* Herzer H; *Bezirksspital, Herzogenbuchsee:* Bosshard E; *Bezirksspital March-Hof, Lachen:* Mader A; *Kreisspital, Mannedorf:* Knoblauch M, Frösch Th; *Oespedale Beata Vergine, Mendrisio:* Noseda G, Reiner M; *Kantonsspital, Munsterlingen:* Biedermann HP; *Spital, Murten:* Baumgartner G; *Hôpital des Cadolles, Neuchatel:* Enrico JF; *Kantonsspital, Olten:* Hammerli R, Romanens M; *Hôpital Regional, Porrentruy:* Bernhardt JP; *Regionalspital, Rheinfelden:* Iselin HU; *Kantonales Spital Rorschach:* Pfister M; *Kreisspital, Rue.* Frei A; *Hôpital de la Beroche, St Aubin:* Laperrouza C; *Kantonsspital, Sarnen:* Dorn P; *Kantonsspital, Schaffhausen:* Frey R; *Schweiz Pflegerinnenschule:* Morell B, Federmann M; *Spital, Schiers:* Wulser U; *Limmattelspital, Schlieren* · Caduff B; *Burgerspital, Solothurn:* Lupi GA; *Kantonsspital, Stans:* Wegmann D; *Spital, Thusis:* Veragut UP; *Ospedale Italiano, Viganello:* Beretta-Piccoli C; *Spital, Wadenswil:* Garzoli G; *Kantonales Spital, Walenstadt:* Schmidt D, Keel HJ; *Zurcher Hohenklinik, Wald:* Brandli O; *Kreisspital, Wetzikon:* Vontobel H; *Spital, Wil:* Muller T; *Neumunsterspital, Zollikerberg:* Siegrist P.

United Kingdom (England, Scotland, Wales, & Northern Ireland; 20 681 patients): *Radcliffe Infirmary & John Radcliffe, University of Oxford.* Collins R* (coordinator), Sleight P* (chairman of steering committee), Peto R*, Parish S* (statisticians), Doll R† (chairman of data monitoring committee), Armitage P†, Cederholm-Williams S*, Conway M*, Dove P*, Flather M*, Marshall J*, Youngman L*, Appleby P, Baigent C, Barton J, Boag V, Boreham J, Foster C, Foster S, Hafner B, Halls H, Jackson D, Jayne K, Keech A, King M, Knight S, Lloyd P, Lyon V, Marsden C, Mead G, Murphy K, Phelps S, Pipilis A, Radley A, Spence S, *British Heart Foundation:* Julian D*; *Royal Sussex:* Chamberlain D*; *Western General, Edinburgh:* Warlow C†, Sandercock P* (neurological reviewer); *National Heart, London.* Fox K†; *Aberdeen Royal Infirmary:* Kenmure ACF, Crombie M; *Woodend General, Aberdeen.* Jeffers A; *Nevill*

Hall, Abergavenny: Gilbertson C, Goodfield R; *Monklands District General, Airdrie:* Rodger JC, Currie K; *Vale of Leven District General, Alexandria:* McCruden DC, Hunter E; *Stirling, Alnwick:* Rose P; *Amersham General:* Regan RJ, Cooper D; *William Harvey, Ashford:* Wilson IV, Cowley A; *Ashington:* Young ET, Anderson W; *Ysbyty Gwynedd, Bangor:* Maxwell RT, Croft-Banton G; *Barnet General:* Gray KE, Phillips J; *North Devon District, Barnstaple:* George M, Phipps J; *Basildon:* Woodgate DJ, Holmes S; *Basingstoke District:* Fowler JM, dre Paul B; *Wellcome, Beckenham:* Malcolm A, Moody G; *Bedford General:* Buchanan AA, Flisher D; *Belfast City:* O'Keeffe DB, Chessler M; *Arrowe Park, Birkenhead:* Meecham J, Clinton S; *Dudley Road, Birmingham:* Watson RDS, Ellis K; *General, Bishop Auckland:* Bateson MC, Smith L; *Blackburn Royal Infirmary & Queen's Park, Blackburn:* Myers A, Myers T; *Bolton General:* Bhalla KK, Kaneen A; *Bolton Royal Infirmary:* Hearn K, Greenhalgh L; *Pilgrim, Boston:* Nyman CR, Shaw E; *Bradford Royal Infirmary:* Morrison G, Long L, *Princess of Wales, Bridgend:* Chappell AG, Smith A; *Bristol Royal Infirmary:* Pitts Crick J, Ranger A; *Frenchay, Bristol:* Burns-Cox CJ, Derrick J; *Bromley:* Harris P, Saunders D; *General, Burnley:* Watson CC, Halliwell S; *West Suffolk, Bury St Edmunds:* Siklos P, Edwards C; *Addenbrooke's, Cambridge:* Weissberg P, Waters C, *Law, Carluke:* Baxter RH, Walker U; *St Helier, Carshalton:* Pumphrey C, Jacob R; *Broomfield District General, Chelmsford:* Murray M, Joy M: *Cheltenham General:* Roscoe P, Smith M; *St Richard's Chichester:* Reid CJ, McArthur Y; *Corbett:* Flint J, Hey A; *Crawley:* Gossage A, Boolaky M; *Leighton, Crewe:* Hall JI, Hodgson K; *Cumberland Infirmary:* Robson RH, Brown S; *Joyce Green, Dartford & West Hill, Dartford:* Brennand-Roper D, Greenan B; *Derby City.* Bateman JRM, Chady V; *Dewsbury District:* Kemp TM, Morris L; *Dorset County, Dorchester:* Ashfield R; *Dorking:* Foster K, Down J; *Buckland, Dover:* Hyde J; *Noble's, Douglas, IOM:* Bourdillon RE, Warham APR; *Russells Hall, Dudley:* Flint J, Joshi M; *Ninewells, Dundee:* McNeill GP, McKie S; *Milesmark, Dunfermline:* Malone DNS, Coyle C; *General Register Office, Edinburgh:* Calder H; *St Margaret's, Epping:* Milne J; *SmithKline Beecham, Epson & Crawley:* Cregeen R, Hasler S, Heath P, McDonald M· *Epsom District:* Robb GH, Ferrar M; *Falkirk & District Royal:* McSorley PD, Campbell J; *Farnborough:* Wharton CFP, Ramsey Y; *Frimley Park:* Boyd M, Tabb W; *Furness General:* Sykes CA, Whitehead M; *Queen Elizabeth, Gateshead:* Jones CTA, Gourley Y; *Glasgow Royal Infirmary:* Cobbe SM, Callaghan A-M; *Southern General, Glasgow:* Fyfe T, McGowan J; *Victoria Infirmary, Glasgow:* McGuinness JB, Smith M; *Gloucester Royal Infirmary:* Jones MBS, Clemmey-Law J; *Royal Naval, Gosport:* Marsh AR, Logan JG; *James Paget, Great Yarmouth:* Grabau WJ, Biddle S; *Inverclyde Royal, Greenock:* Mackay A, Little K; *Royal Surrey County, Guildford:* Foley T; *Halton General:* Mallya RK, Lewis R; *Princess Alexandra, Harlow:* Milne JR; *Harrogate District:* Larkin H, Stewart M; *Hartlepool General:* Tildesley G, Elder P; *Hemel Hempstead:* Bayliss J Aldegather J; *County, Hereford:* Pitcher D, McGuire C; *Hertford County:* Keir P, Larter-Whitcher GP; *Hexham General:* Wright AJ, Pencott I; *Hillingdon:* Sutton GC, Thurston M; *Huddersfield Royal Infirmary:* Hunt ET, Kerrigan P; *Hinchingbrooke, Huntingdon:* Henderson RG; *King George's, Ilford:* Edelman J, Greig J; *Raigmore, Inverness.* Kerr F, Calder G; *General, Jersey:* Ginks WR, Vickers A; *Kettering General:* Baines G, Woodcock J; *Kidderminster General:* Summers GD, Fadlon A; *Victoria, Kirkcaldy:* Lawrie DM, Scott G; *Royal Lancaster Infirmary:* Brown AK, Williams A; *Leicester Royal Infirmary:* Barnett D, Ibbotson D; *Llandough:* Routledge PA, Morris J; *Ysbyty Llandudno:* Galpin OP, Nolan M; *Llanelli General.* Ebden P, Williams J; *Central Middlesex, London:* Dancy M; *Charing Cross, London:* Guz A, Povey E; *Ealing, London:* Owen R, Wheildon M; *Homerton, London:* Tunstall Pedoe DS, Joseet M; *King's College, London:* Jewitt D, D'Souza A; *Newham General, London:* Timmis A, Ranjadayalan K; *North Middlesex, London:* Banim S, Darbyshire L; *St Bartholomew's, London:* Nathan AW, Elstob J; *Whittington, London:* Patterson D, Rose A, *Luton & Dunstable:* Stodell M, Newman J; *Macclesfield District General:* Davies ETL, Lomas M; *Trafford General, Manchester:* Stephens WP, Sykes R; *Withington, Manchester:* Brownlee W; *Wythenshawe, Manchester:* Brooks N, Coppinger T; *Sanofi, Wythenshawe, Manchester.* Bews S, Fallowfield J; *Mansfield & District General:* Rowley J; *Thanet District General, Margate.* Lillicrap DA, Underwood M; *Middlesbrough General:* McCormack P, Currie Y; *Neath General:* Kahan R, Thomas M; *Newcastle General:* Evemy KL, Gray J; *Royal Victoria Infirmary, Newcastle:* Adams PC, Easton J; *Newmarket General:* Kerrigan GNW, Doy S; *Norfolk & Norwich:* Brooksby IAB, Creasy P; *Friarage, Northallerton:* Holgate P, Rooney E; *George Eliot, Nuneaton:* Hollinrake K, Perry G; *County, Oban:* Henderson AK, MacKenzie F; *Ormskirk & District General:* MacIver M, Goulbourne S; *Orpington:* Wharton CFP, Ramsay Y; *Orsett:* Woodgate DJ, Reeve S; *West Cornwall, Penzance:* Gibbons D, Sims D; *Perth Royal Infirmary:* Wood R, Crozier E; *Pontefract General Infirmary:* White C, Gibson CG, *Poole General:* McLeod AA, Clarke S; *Queen Alexandra & St Mary's, Portsmouth:* Watkins J, Roberts K, Fitzgerald E; *Whiston, Prescot:* MacMillan RR, Daniels J; *Royal Preston:* Watt DAL, Golder M; *Battle, Reading.* Bell J, Huggins S; *Royal Berkshire, Reading:* Simpson H, Filler M; *Alexandra, Redditch:* Lowry PJ, Owen L, *East Surrey, Redhill:* Lyons JP, King N; *Glan Clwyd, Rhyl:* Green GJ, Lynch E; *Birch Hill, Rochdale;* Coupe MO, Clegg JE; *Rotherham District General:* Haste AR, Goodwin S; *Hospital of St Cross, Rugby:* Basu AK, Hinds S; *Hope, Salford:* Barnes P, Haybyrne J; *Salisbury General Infirmary;* Gent AE, Ghosh A; *Scarborough:* Clark RS, Caunt J; *Scunthorpe General:* Batson GA, Hulme D; *Northern General, Sheffield:* Campbell S, Cashell M; *Royal Hallamshire, Sheffield:* Channer K, Hodgson I; *Shotley Bridge General:* Simpson G, Moon J; *Royal Shrewsbury:* Simmons ME, Marvelly E; *Queen Mary's, Sidcup:* Basu A, Hozier H; *Solihull:* Burge S, Cotton E; *General, Southampton:* Waller DG; *Royal South Hants, Southampton:* Leatherdale BA, Jones V; *Southend General:* Mellor J, Burgess K, Nelson S; *District General, Southport:* Hanley WB, Black R; *OPCS, Southport:* Harris DP, Tan E; *Ingham Infirmary, South Shields:* Bryson LG, Courteney S; *St Albans City:* Bayliss J, Aldegather J; *Stirling Royal Infirmary:* Smith JFB, Maclean K; *Stepping Hill, Stockport:* Martin MA, Waldron K; *City General, Stoke:* Davis JAS, Lawton R; *Stonehouse:* Matthews DM, Murphy C; *Stracathro:* Callaghan TS, Mitchell A; *Sunderland District General:* Chazan B, McKinnon E; *King's Mill, Sutton-in Ashfield:* Lloyd-Mostyn R, Carroll FJ; *Morriston, Swansea:* Evans KE, Lewis B; *Singleton, Swansea:* Rees H, Powell J; *Taunton & Somerset:* Sanderson J, Manning R; *Princess Royal, Telford:* Heber ME, Turner A; *Torbay;* Dewhurst NG, Davis J; *Royal Cornwall (Treliske), Truro:* Mourant AJ, Garside C; *Pinderfields General, Wakefield:* Walker WC, Holloway S; *Warrington District General:* Bentley SJ, Inglesby E; *Queen Elizabeth II, Welwyn GC:* Keir P, Engel M; *Sandwell District General, West Bromwich:* Cadigan PJ, Mohan M; *Weymouth & District:* Ashfield R; *Wharfedale General:* Berkin KE, Oliver P; *Wigan Royal Infirmary:* Naqvi N, Belshaw M; *Royal Hampshire County, Winchester:* Brooke AP, Powell-Jackson J; *Clatterbridge, Wirral:* Silas JH, Halewood S; *New Cross, Wolverhampton:* Pidgeon JW, Poole G; *Worcester Royal Infirmary, Ronkswood:* Tibbutt DA, Platt S; *Bassetlaw District General, Worksop:* Blandford RL, Snell P; *Worthing:* Signy M, Lawson D; *Wrexham Maelor.* Sissons CE, Jones M; *Princess Alexandra, Wroughton:* Amroliwalla FK, Gilbert TJ; *Wycombe General:* Hendry WG, Collins S.

United States (5341 patients): *Brigham & Women's, Boston:* Hennekens C*, Bilodeau C, Buring J, Danielson E, deProsse S, Eberlein K, Goldhaber S*, Gordon D, LaMotte F, Reilly E, Ridker P; *William Beaumont, Royal Oak:* Timmis G*, Tollis CA; *NHLBI Clinical Trials Branch, Bethesda, MD:* Yusuf S*; *University of Chicago:* Meier P†; *Palt Momi Med Center, Atea:* Shikuma NK, Scura J; *Akron City:* Josephson R, Jasso DM; *Akron General Med Center.* Heiselman D, Hudock DK, Gordon T; *Allentown Osteopathic Med Center:* Starr HT, Stemmler CJ, *Island, Anacortes:* Rowe WW, Pfaff PJ, *Anderson Memorial:* Morse HG, Blackburn SA, Benson KK; *Anne Arundel Med Center, Annapolis:* Biern RO, Colburn L, *St Elizabeth, Appleton:* Rizzo JA, Gilsdorf MG; *Athens-Limestone, Athens:* Qureshi N, Wilson CJ; *Atlantic City Island:* Nascimento TR, Solomon E; *Sturdy Memorial, Attleboro:* DiCola JL, Nordstrom SM; *Aurora Community:* Gudapati RM, Kinder VA; *Humana, Aurora:* Battock DJ, Hornbaker AE; *Kern Med Center, Bakersfield:* Karunakar ARSR, Caldwell JW; *Maryland General, Baltimore.* Ennis L, Huber DJ; *St Agnes, Baltimore·* Bahr RD, Peacock H; *Sinai, Baltimore:* Effron MB, Aarons D; *Bay Med Center, Bay City:* Shrestha DD, Huston C; *Kaiser, Bellflower·* Bassan MM, Christianson J, *Berlin Memorial.* Carroll JJ, Beier KM; *Bloomsburg·* Kresock FD, Hess BL; *St Elizabeth's, Boston:* Wharton TP Jr, Otovic NA; *Brattleboro Memorial:* Tepfer BD, Johnson G; *Transylvania Community, Brevard:* Hermanny G, MacDonald S, *Bridgeport:* Babb JD, Yasick DL; *Melhan Med Center, Broken Bow:* Books NL, Rapp DD, *Bryn Mawr:* Robinson HJ, Gibson JE; *Med Center of Vermont, Burlington:* Langburd AB, Rowen M, *RL Thompson Strategic, Carswell AFB:* O'Donnell AE, Kennedy BM, *Valley View Med Center, Cedar City:* Alfaro E, Thompson J; *Presbyterian, Charlotte:* Niess GS, Phillips MW; *Erlanger Med Center, Chattanooga·* Hoback JW, Rhinehart DC, *Chelsea Community.* Yarows SA, Bravo PM; *Holy Cross, Chicago:* Streitmatter NI, Miernicki LM, *Weiss Memorial, Chicago:* Chiu C, Schneider JM; *Christ, Cincinnati:* Fry HF, Butler MA; *Good Samaritan, Cincinnati:* Razavi A, Longmuir LA; *Fairview General, Cleveland:* Watts RW, Camp BA; *MetroHealth Med Center, Cleveland:* Miller PE, Dziedzicki RE; *Clifton Springs:* Doling MJ, Carnevale L; *Samaritan North, Clinton:* Harb NH, Ryan JM; *Community Memorial, Cloquet·* Luehr D, Stevens N; *Baptist Med Center, Columbia.* Lide LD, Burks D; *Conway:* Sasser CG, Thorpe TR; *Cortland Memorial.* Gillim SW, Rodgers K; *Good Samaritan, Corvallis:* Marker TL, Veliotes C; *Newton General, Covington:* Crews TL, Scott AM; *Cullman Med Center:* Peinhardt WF, Howard JW; *Delano Regional Med Center:* Chang NSS, Carpio J; *Rose Med Center, Denver·* Battock DJ, VanDyke KA; *VA Med Center, Denver.* Hammermeister KE, Bott S; *Griffin, Derby:* Schwartz KV, Beres N, Shah JD; *Henry Ford, Detroit:* Gheorghiade M, Nowak RM, Wlodkowski MB; *St John, Detroit:* Formolo JM, Goldstein J, *Sinai, Detroit·* Goldberg MJ, Reinstein D; *Kent General, Dover:* Jarrell TN III, Moyer CE; *St Mary's Med Center, Duluth:* Thompson JI, Gressman A, *Hamot Med Center, Erie:* Nullett FR, Jaglowski AT; *Welborn, Evansville:* Young SH, Mann BS; *Farmington Regional Med Center:* Grix GJ, St Gemme SC; *St John's Episcopal, Far Rockaway:* Burnett V, Larosch KG; *Cape Fear Valley Med Center, Fayetteville:* Popio KA, Shearer M; *Ford Madison Community:* Cook TH, Lampe JA; *Franklin Regional Med Center:* Edwards WP, Hoobler S; *St Jude Med Center, Fullerton:* Choe AM, Kerr BL; *Callaway Community, Fulton: Nichols DA, Whittler-Bamber A; Thunderbird Samaritan, Glendale:* Saini JS, Farrell P; *St Mary's, Grand Rapids:* Foster RK, Lewis JA; *Marin General, Greenbrae:* Ogden PC, Jewell J; *United Community, Grove City:* Wilson FR, Kaspar PJ Jr, Swartz PE; *Mt Sinai, Hartford:* Riba AL, Waters KL, *St Francis Med Center, Hartford:* Therrien ML, Eltouney E; *Haverford, Havertown;* Resnick ME, Evans MT; *Margaret Pardee Memorial, Hendersonville:* Goodfield P, Goodfield T; *Mesabi Regional Med Center, Hibbing:* Dinter RW, Olson LL; *Queen's Medical Center, Honolulu:* Chesne EL, Warncke DL, *St Francis Med Center, Honolulu:* Dang WM, Thomas NJ; *Bath County, Hot Springs:* Redington JF, Howell BD; *Ryder Memorial, Humacao:* Rios ML, Rosado JA; *Daniel Freeman, Inglewood:* Frankle PS, Clay DA; *St John's, Jackson:* Sugden RG, Thomson JB; *Memorial Med Center, Jacksonville:* Venus B, Carter MC; *WCA, Jamestown:* Cirbus JJ, Yancey-Walton R; *Memorial Community, Jefferson City:* Sanders JS, Larson P; *Jersey City Med Center:* Goldman DS, Kozlowski KA, Wong P; *Oak Hill, Joplin:* Langevin GE, Langevin J; *Truman Med Center East, Kansas City:* Scarpinato L, Robertson D; *Kettering Med Center & Sycamore, Miamisburg:* Kiefaber RW, Lamb CC; *DePoo, Key West:* Calleja JF, Fletcher S; *Florida Keys Memorial, Key West·* Carraway RD, Rogan N; *Rappahannock General, Kilmarnock:* Price CD, Davis L; *Benedictine, Kingston:* Lader E, Kilgallon E; *Preston Memorial, Kingwood:* Saver D, Shannon CK, Riffle DS; *Univ Tennessee Med Center, Knoxville:* Scott JC, Reynolds FW; *Lakes Region, Lacoma:* Rosenfeld AS, Waldron K; *Lutheran, La Crosse:* Green RM, Kartman JL; *Rusk County Memorial, Ladysmith:* Charipar RM, Giebel SE; *Lakeland Regional Med Center:* Browne KF, O'Connor HE; *Lancaster Community:* Loss DM, Crawford LJ; *Lebanon Community:* Salisbury RA, Webster WL; *Witham, Lebanon:* Kunz RJ, McNabb C; *Leominster:* Robbins J, Trainque TL; *Beebe Med Center, Lewes:* Bolourchi H, Bradley D; *Central Maine Med Center & St Mary's General, Lewiston:* Weiss RJ, Rauscher AK; *Lewistown:* Suthar AL, Esterline V; *Lafayette Regional Health Center, Lexington:* Latif A, Youtsey CA; *Bryan Memorial General & St Elizabeth Community Health Center, Lincoln:* Weaver WF, Mahaffey TL; *North Lincoln, Lincoln City* Bohlman JE, Dunne P; *Lindsborg Community:* Loder BJ, Shields JA; *John McClellan VA, Little Rock:* Bissett JK, Ackerman DJ; *Littleton:* Pollak EM Jr, Buxton LL; *Valley Memorial, Livermore:* Kwee HH, Lasche PA; *Kaiser Hospital, Los Angeles:* Kapoor AS, Kennedy DL; *Westside, Los Angeles:* Karpman HL, Campbell J; *St Francis Med Center, Lynwood:* Tamboli KR, Shimada A; *Manchester Memorial:* Hanna JA, Eib DE; *North Shore University, Manhasset·* Morrison J, Ward M, Vogt S; *McDowell, Marion:* Whisenant MN, Teaster S; *Marshall Memorial:* Cash JQ, Schroeder KM; *McCook Community:* Cerbousek M, Messinger P; *Gottlieb Memorial, Melrose Park:* Shanes JG, O'Connor PM; *North Memorial Med Center, Minneapolis:* Hanovich GD, Antolick AB; *VA Med Center, Minneapolis:* Pierpont GL, Ewald S; *Lakewood, Morgan City:* Blereau RP, Bergeron P; *Grace, Morgantown:* Seagle RL, Macopson J; *Frick Community Health Center, Mt Pleasant:* Lynn RE, Pizzola LA; *Skagit Valley, Mt Vernon:* Feld JE, Meckstroth JA; *Muscatine General:* Weis RF, Batchelor DM; *VA Med Center, Muskogee:* Danisa K, Wescott BL; *Naples Community:* Alsbrook E Jr, Johnson VF, *St Thomas, Nashville:* Campbell WB, Norby JB; *Leonard Morse, Natick:* Pomfret DB, Tapley JA; *Theda Clark Med Center, Neenah:* Rizzo JA, Fuller KA; *Christiana, Newark:* Stillabower ME, Gale NN; *LSU Med Center, New Orleans:* Subramaniam PN, Kuss B; *Oschner Foundation, New Orleans:* White CJ, Covington KA; *Pendleton Memorial Methodist, New Orleans:* Breaux PC, Anderson C; *Beth Israel Med Center, New York:* Strain JE, Kelly AM; *Lenox Hill, New York:* Schiffer MB, Stiles D; *Sterling, New York.* Lockhart E, Weisman S; *Hoag Memorial Presbyterian, Newport Beach:* Kennelly BM, Meister FL, Hewett M; *Norton Community:* Joshi AR, Taylor SS; *Christ Med Center, Oak Lawn:* Cuadros HF, Krichbaum DW; *Methodist Med Center, Oak Ridge:* McLaughlin VW, Goforth C; *Community Memorial, Oconto Falls:* Artwich R, Bartel B; *Ojai Valley Community:* McManus JC, Howard S; *East Alabama Med Center, Opelika:* Davis WR, Stegall GC; *Oroville:* Smith RV, Mallette M; *McCullough-Hyde, Oxford:* Hunt TG, Combs JM ; *Arkansas Methodist, Paragould:* White RB, Clark C; *Memorial of Rhode Island, Pawtucket:* Khan AH, Barbour MM; *Good Samaritan Med Center, Phoenix:* Laufer N, Imming BJ; *Atlantic City Mainland, Pomona:* Dib H, Mott D; *Chilton Memorial, Pompton Plains:* Rosenthal MI, Shanoian BB; *Damas, Ponce:* Jovane JR, Orengo L; *Mercy & Scioto Memorial, Portsmouth:* Driedger HJ, Siegfried C, Smith CJ; *Pottstown Memorial Med Center:* Krantzler JD, Minnick S; *Utah Valley Regional Med Center, Provo:* Smith DR, Saldutte ME; *Quakertown Community:* Jenkins RH, Pack SP; *Burroughs Wellcome, Raleigh:* LittleJohn J; *Jefferson Memorial, Ranson:* Webb RF, Christie KL, *Dixie Regional Med Center, St George:* McDonnell MA, Musser L; *Jewish*

Hospital, St Louis: Rich MW, Crofton BJ; *United, St Paul:* Goldsteen DS, Tschida VH, Pitzen RM; *St Anthony's St Petersburg:* Pyhel HJ, Pippenger SB; *Methodist, Sacramento:* Vetter WR, Spinos CA; *Salem VA Med Center:* Lui CY, Mays L; *Peninsula General, Salisbury:* Agarwal BK, Porter SB; *LDS, Salt Lake City:* Anderson JL, Allen A; *Bonner General, Sandpoint:* Carlson RW, Allard NE; *Firelands Community & Providence, Sandusky:* Young DJ, Pulizzi MB, Reising J; *Chippewa Co War Memorial, Sault Ste Marie:* Hampton WB, Woodgate TK; *United General, Sedro Woolley:* Rowe WW, Naylor H; *Oktibbeha County, Starkville:* White R, Guyton CD; *Staten Island:* Costantino T, Bartolotta E; *Goddard Memorial, Stoughton:* Mazer MS, Lewis DK; *Kennedy Memorial, Stratford:* Papa LA, Talarico KM; *Allenmore Med Center & Tacoma General, Tacoma:* Lapin ES, McCarren CD; *Med College of Ohio, Toledo:* Fraker TD, Hiris S; *Tooele Valley Regional Med Center.* Sullivan WK, Miner J; *Greater Baltimore Med Center, Towson:* AliKhan M, Long ML; *Munson Med Center, Traverse City:* Kurtz RG, McGinnis T; *Wilham Beaumont, Troy:* Smiley WH, Brait DC; *Hillcrest Med Center, Tulsa:* Hagan AD, Madden J; *Magic Valley Regional Med Center, Twin Falls:* Emery JF, Allred D; *Mother Frances, Tyler:* Carney RJ, Murphy GA; *Uvalde Memorial:* Dimmitt DC, Koop J; *Valdese General:* Garrou BW, Smith LI; *Westchester County Med Center, Valhalla.* Weiss M, Baker J, Kanakaraj AM; *Wahiawa General:* Dang WM Jr, Luke BJ; *South County, Wakefield:* McGhee JR, Fay B; *John Muir Med Center, Walnut Creek:* Epstein MA, Epstein RE: *VA Med Center, Washington:* Papademetriou V, Bounds JA; *St Joseph's, West Bend;* Looze TE, Bertram S; *Humana, West Hills:* Blum RL, Laubenstein DM; *Noble, Westfield:* Kenia SN, Jones KF, Smith L; *VA Med Center, Wichita:* Pelletier LL Jr, Depler G; *Divine Providence, Williamsport:* Srinivasan V, Clark TR; *Rice Memorial Hospital, Willmar:* Anderson MT, Baker B; *St Francis, Wilmington:* Gordon RF, Sibert LN; *Wilmington:* Stillabower ME, Gale N; *Mt Ascutney, Windsor:* Conger B, Hamilton KM; *Winter Haven:* Willard EH, Schreiber MJ; *U Mass Med Center, Worcester:* Becker RC, Corrao JM; *York:* Petrovich LJ, Russell S; *East Pasco Med Center, Zephyrhills:* Pally MT, Wills M.

REFERENCES

1. Cairns JA, Collins R, Fuster V, Passamani ER. Coronary thrombolysis. *Chest* 1989; **95:** 73S–87S.
2. Braunwald E, Knatterud GL, Passamani E, Robertson TL, Solomon R for the TIMI Operations Committee. Update from the Thrombolysis in Myocardial Infarction Trial. *J Am Coll Cardiol* 1987; **10:** 970.
3. Sobel BE, Hirsh J. Principles and practice of coronary thrombolysis and conjunctive treatment. *Am J Cardiol* 1991; **68:** 382–88.
4. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; ii: 349–60.
5. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest* 1982; **69:** 1366–72.
6. Reilly IAG, FitzGerald GA. Inhibition of thromboxane formation in vivo and ex vivo: implications for therapy with platelet inhibitory drugs. *Blood* 1987; **69:** 180–86.
7. Clarke RJ, Mayo G, Price P, Fitzgerald G. Suppression of thromboxane A_2 but not of systemic prostacyclin by controlled-release aspirin. *N Engl J Med* 1991; **325:** 1137–41.
8. Berglund U, Wallentin L. Persistent inhibition of platelet function during long-term treatment with 75 mg acetylsalicylic acid daily in men with unstable coronary artery disease. *Eur Heart J* 1991; **12:** 428–33.
9. Gruppo Italiano per lo Studio della Streptochinasi nell'infarto miocardico (GISSI). GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990; **336:** 65–71.
10. The International Study Group. In-hospital mortality and clinical course of 20 891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990; **336:** 71–75.
11. de Bono DP, Simoons ML, Tijssen J, et al, for the European Cooperative Study Group (ECSG). Effect of early intravenous heparin on coronary patency, infarct size and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992; **67:** 122–28.
12. MacMahon S, Collins R, Knight C, Yusuf S, Peto R. Reduction in major morbidity and mortality by heparin in acute myocardial infarction. *Circulation* 1988; **78:** II–98.
13. GUSTO Coordinating Center. Heparin and GUSTO. *GUSTO Gazette,* January, 1992: 1–2.
14. Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991; **151:** 333–37.
15. Turpie AGG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989; **320:** 352–57.
16. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1986; **315:** 1109–14.
17. Doyle DJ, Turpie AGG, Hirsh J, et al. Adjusted subcutaneous heparin or continuous intravenous heparin in patients with acute deep vein thrombosis. *Ann Intern Med* 1987; **107:** 441–45.
18. The SCATI Group. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet* 1989; ii: 182–86.
19. GISSI. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; i: 397–402.
20. ISAM Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). Mortality, morbidity and infarct size at 21 days. *N Engl J Med* 1986; **314:** 1465–71.
21. ASSET Study Group. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988 ii: 525–30.
22. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. *Lancet* 1990; **335:** 427–31.
23. Mueller HS, Rao AK, Forman SA and the TIMI Investigators. Thrombolysis in Myocardial Infarction (TIMI): comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 1987; **10:** 479–90.
24. Topol EJ, George BS, Kereiakes DJ, et al. Comparison of two dose regimens of intravenous tissue plasminogen activator for acute myocardial infarction. *Am J Cardiol* 1988; **61:** 723–28.
25. Neuhaus K-L, Tebbe U, Gottwick M, et al. Intravenous recombinant tissue plasminogen activator (rt-PA) and urokinase in acute myocardial infarction: results of the German Activator Urokinase Study (GAUS). *J Am Coll Cardiol* 1988; **12:** 581–87.
26. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI IIA results. *JAMA* 1988; **260:** 2849–58.
27. Simoons ML, Arnold AER, Betrui A, et al for the ECSG for recombinant tissue-type plasminogen activator (rtPA). Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988; i: 197–203.
28. Malcolm A on behalf of ESPRIT Study Group. European Study of the Prevention of Reocclusion after Initial Thrombolysis (ESPRIT) with duteplase in acute myocardial infarction. 1992. Unpublished.
29. Grines CL, Karlsberg R, Stadius M for The Burroughs Wellcome Study Group. Infarct vessel patency and bleeding complications after weight-adjusted dosing of a double chain tissue plasminogen activator: final report. *J Am Coll Cardiol* 1990; **15:** 2A.
30. Kalbfleisch J, Kurnik P, Thadani U, et al for the Burroughs Wellcome Study Group. Infarct-artery patency and reocclusion rates after treatment with duteplase at the dose used in ISIS-3. 1992. Unpublished.
31. Koster RW, van Stralen R, McNeill AJ, et al. A randomized dose-ranging study of rt-PA in acute myocardial infarction. Effects on coronary patency and fibrinolytic parameters. *Eur Heart J* 1990; **11:** 730–39.
32. Anderson JL. Overview of patency as an end point of thrombolytic therapy. *Am J Cardiol* 1991; **67:** 11E–16E.
33. Sherry S, Marder VJ. Creation of the recombinant tissue plasminogen activator (rt-PA) image and its influence on practice habits. *J Am Coll Cardiol* 1991; **18:** 1579–82.
34. Wackers FJ, Terrin ML, Kaydon DS and the TIMI investigators. Quantitative radionuclide assessments of regional ventricular function after thrombolytic therapy for acute myocardial infarction: results of phase I thrombolysis in myocardial infarction (TIMI) trial. *J Am Coll Cardiol* 1989; **13:** 998–1005.
35. White HD, Rivers JT, Maslowski AH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator in left ventricular function after first myocardial infarction. *N Engl J Med* 1989; **320:** 817–21.
36. Magnani B for the PAIMS Investigators. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1989; **13:** 19–26.
37. Bassand JP, Cassagnes J, Machecourt J, et al. Comparative effects of APSAC and rtPA on infarct size and left ventricular function in acute myocardial infarction. A multicenter randomized study. *Circulation* 1991; **84:** 1107–17.
38. Peto R. Clinical trial methodology. *Biomédicine* (special issue) 1978; **28:** 24–36.
39. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Analysis and examples. *Br J Cancer* 1977; **35:** 1–39.
40. White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978; **37:** 849–57.
41. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull WHO* 1976; **54:** 533–40.
42. Patrono C. Aspirin and human platelets: from clinical trials to acetylation of cyclooxygenase and back. *Trends Pharmacol Sci* 1989; **10:** 453–58.
43. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM for the Heparin-Aspirin Reperfusion Trial (HART) Investigators. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1990; **323:** 1433–37.
44. Bleich SD, Nichols TC, Schumacher RR, Cooke DH, Tate DA, Teichman SL. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990; **66:** 1412–17.

45. Collins R, Flather M, Peto R. GISSI-2: 10% reduction in mortality with heparin in acute myocardial infarction? *Lancet* 1990; **336:** 439–40.
46. Collen D. Coronary thrombolysis: streptokinase or recombinant tissue-type plasminogen activator. *Ann Intern Med* 1990; **112:** 529–38.
47. Prins MH, Hirsh J. Heparin as an adjunctive treatment after thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1991; **67:** 3A–11A.
48. Tiefenbrunn AJ, Sobel BE. The impact of coronary thrombolysis on myocardial infarction. *Fibrinolysis* 1989; **3:** 1–15.
49. Scheidt S, Rogers W, Teifenbrunn A, Bleich SD, Collen D. ISIS-3 implications for American practice. Medical panel discussion. *CVR & R*, September, 1991: 37–61.
50. Roberts R, Aghababian R, Meister FL, Rogers WJ. ISIS-3 and other highlights of the ACC's 40th Annual Scientific Session. *Clinical Challenges in Acute Myocardial Infarction.* 1991; **1:** 1–10.
51. von Essen R, Vogt A, Roth M, Riess M, Tebbe U, Neuhaus KL for the TAPS Study Group. Early patency of infarct-related vessel after accelerated infusion of 100 mg rt-PA as compared to 30 mg APSAC: results of the TAPS Study. *Eur Heart J* 1991; **12** (abstr suppl): 30.
52. Anderson JL, Becker LC, Sorensen SG, et al for the TEAM-3 Investigators. A randomized, blinded comparison of anistreplase and alteplase in acute myocardial infarction: preliminary results of the TEAM-3 study. *Eur Heart J* 1991; **12** (abstr suppl): 97.
53. Verstraete M, Bernard R, Bory M, et al. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. *Lancet* 1985; i: 842–47.
54. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987; **76:** 142–54.
55. Lopez-Sendon J, Seabra-Gomes R, Santos FM, et al. Intravenous anisoylated plasminogen streptokinase activator complex (APSAC) versus intravenous streptokinase (SK) in myocardial infarction (AMI). A randomized multicenter study. *Eur Heart J* 1988; **9** (abstr suppl): 10.
56. Seabra-Gomes R, Silva JA, Aleixo A, et al. Evaluation of 2 intravenous thrombolytic agents (anisoylated plasminogen streptokinase activator complex versus streptokinase) in patients with acute myocardial infarction. *Drugs* 1987; **33** (suppl 3): 169–74.
57. Vogt P, Monnier P, Schaller MD, et al. Systemic thrombolysis in acute myocardial infarction: slow injection of APSAC versus infusion of streptokinase, interim results. *Eur Heart J* 1989; **10** (abstr suppl): 124.
58. Hogg KJ, Gemmill JD, Burns JMA, et al. Angiographic patency study of anistreplase versus streptokinase in acute myocardial infarction. *Lancet* 1990; **335:** 254–58.
59. Pacouret G, Charbonnier B, Curien ND, et al. Invasive reperfusion study II. Multicentre European randomized trial of anistreplase vs streptokinase in acute myocardial infarction. *Eur Heart J* 1991; **12:** 179–85.
60. Anderson JL, Sorensen SG, Moreno FL, et al and the TEAM-2 Study Investigators. Multicenter patency trial of intravenous anistreplase compared with streptokinase in acute myocardial infarction. *Circulation* 1991; **83:** 126–40.
61. Monrad ES. Thrombolysis: the need for a critical review. *J Am Coll Cardiol* 1991; **18:** 1573–78.

Identification by molecular cloning of an autoantigen associated with Addison's disease as steroid 17α-hydroxylase

KAI KROHN RAIVO UIBO EINARI AAVIK PÄRT PETERSON
KATJA SAVILAHTI

Idiopathic Addison's disease is characterised by a progressive failure in the synthesis of all classes of steroid hormones and by an immune response against the steroid-producing cells of the adrenal cortex; the nature of the adrenal autoantigens is not known. We have used molecular cloning and sequencing to identify the target antigens.

We screened a human fetal adrenal cDNA expression library in λ gt11 vector with serum samples from patients with Addison's disease as part of the type 1 polyendocrine autoimmunity syndrome. Samples from 3 patients, which had precipitating antibodies against two adrenal proteins detected by immunodiffusion and against five adrenal proteins of molecular mass 55, 48, 43, 39, and 19 kDa as judged by immunoblotting, were used to identify 60 immunoreactive clones. 39 of these were subcloned, inserted into the M13mp10 vector, and sequenced by the dideoxy method or identified by Southern and dot-blot hybridisation. All but 1 of the inserts showed more than 98·8% homology with the published sequence of steroid 17α-hydroxylase. This protein was expressed by insertion of 1 of the clones into the pGEMEX-1 vector. Only serum from patients with Addison's disease and type 1 polyendocrine autoimmunity syndrome that reacted with the 55 kDa adrenal protein recognised the recombinant 17α-hydroxylase protein on immunoblotting.

Our results show that one of the key enzymes in steroid biosynthesis, 17α-hydroxylase, is an autoantigen involved in the pathogenesis of adrenocortical failure.

Lancet 1992; **339**: 770–73.

Introduction

Some immune diseases are characterised by an autoimmune reaction against a specific organ, which results in structural and functional changes. In idiopathic Addison's disease, antibodies that react with the cytoplasm of cells from the adrenal cortex can be detected by immunofluorescence.[1] In patients with Addison's disease as part of the polyendocrine autoimmunity syndrome (the simultaneous occurrence of several organ-specific autoimmune diseases, such as hypoparathyroidism, pernicious anaemia, Addison's disease, and gonadal dysfunction[2]), there are also autoantibodies to the steroid-producing cells in the ovaries or testis[3] and precipitating antibodies against adrenal cortical proteins.[4]

The main function of the adrenal cortex is the synthesis of steroid hormones; Addison's disease is characterised by failure of steroid biosynthesis. It is therefore logical to propose that enzymes of the steroid-synthetic pathway might be target antigens in Addison's disease. We have shown previously[5] that serum antibodies from patients with Addison's disease react with a subcellular fraction that binds radioactive cholesterol and on incubation forms corticosteroid. Others[6] have found that the autoantibodies in Addison's disease react with the subcellular fraction of adrenal cortical tissue that contains cytochrome C reductase and 5'-nucleotidase.

Our strategy in identification of the adrenal autoantigens was to search in an adrenal cDNA expression library for

ADDRESSES: **Institute of Biomedical Sciences, University of Tampere, PO Box 607, Tampere SF-33101, Finland** (Prof K. Krohn, MD, R Uibo, MD, E. Aavik, MSc, P. Peterson, MSc, K. Savilahti, Cand Med), **and Institute of General and Molecular Pathology** (R. Uibo) **and Institute of Cellular and Molecular Biology** (P. Peterson), **Tartu University, Estonia.** Correspondence to Prof Kai Krohn.