

**Articles****Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients***Fibrinolytic Therapy Trialists' (FTT) Collaborative Group\****Summary**

Large randomised trials have demonstrated that fibrinolytic therapy can reduce mortality in patients with suspected acute myocardial infarction (AMI). The indications for, and contraindications to, this treatment in some categories of patient are disputed, examples being late presentation, elderly patients, and those in cardiogenic shock. This overview aims to help resolve some of the remaining uncertainties.

From all trials of fibrinolytic therapy versus control that randomised more than 1000 patients with suspected AMI, information was sought and checked on deaths during the first 5 weeks and on major adverse events occurring during hospitalisation. The nine trials included 58 600 patients, among whom 6177 (10.5%) deaths, 564 (1.0%) strokes, and 436 (0.7%) major non-cerebral bleeds were reported. Fibrinolytic therapy was associated with an excess of deaths during days 0–1 (especially among patients presenting more than 12 h after symptom onset, and in the elderly) but this was outweighed by a much larger benefit during days 2–35. This “early hazard” should not obscure the very clear overall survival advantage that is produced by fibrinolytic therapy. Benefit was observed among patients presenting with ST elevation or bundle-branch block (BBB)—irrespective of age, sex, blood pressure, heart rate, or previous history of myocardial infarction or diabetes—and was greater the earlier treatment began. Among the 45 000 patients presenting with ST elevation or BBB the relation between benefit and delay from symptom onset indicated highly significant absolute mortality reductions of about 30 per 1000 for those presenting within 0–6 h and of about 20 per 1000 for those presenting 7–12 h from onset, and a statistically uncertain benefit of about 10 per 1000 for those presenting at 13–18 h (with more randomised evidence needed in this latter group to assess reliably the net effects of treatment). Fibrinolytic therapy was associated with about 4 extra strokes per 1000 during days 0–1: of these, 2 were associated with early death and so were already accounted for in the overall mortality reduction, 1 was moderately or severely disabling, and 1 was not.

This overview indicates that fibrinolytic therapy is beneficial in a much wider range of patients than is currently given such treatment routinely.

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**Introduction**

Randomised trials, involving in aggregate several tens of thousands of patients with suspected acute myocardial infarction (AMI), have demonstrated that fibrinolytic therapy can, in many circumstances, reduce mortality.<sup>1–9</sup> As a result, the routine use of such treatment has increased rapidly during the past few years. Even so, there is wide variation, both between and within countries, in the extent to which fibrinolytic therapy is used.<sup>10–14</sup> This may reflect the limited evidence available from individual studies about benefit in specific categories of patient (eg, those without ST elevation on their presenting electrocardiogram [ECG],<sup>15–18</sup> those presenting more than 6 h after the onset of symptoms,<sup>19,20</sup> elderly patients,<sup>21–24</sup> and those in cardiogenic shock<sup>25</sup>). Physicians also have to consider the possible risks (in particular, haemorrhagic strokes and major non-cerebral bleeding) so concerns about safety among certain types of patients, such as the elderly or those with high blood pressure (BP) or diabetes, may also have influenced the extent to which fibrinolytic therapy is used.<sup>26–30</sup>

A single trial may need to randomise several thousand patients before it can assess the overall effects of fibrinolytic therapy in the aggregate of the many different types of patient that it studies. Even then, it may well fail to yield statistically reliable evidence in a specific type of patient because to get such evidence several thousand patients of that type may need to be randomised, unless indirect arguments are used (see below).<sup>4</sup> Such large numbers are not often achieved in individual trials but may be in an overview of all—or of a large unbiased subset of all—trials.<sup>31,32</sup> We present here a systematic overview of the effects of treatment on mortality and on major morbidity in various patient categories in those trials designed to randomise more than 1000 patients with suspected AMI between fibrinolytic therapy and control. There are nine such trials: GISSI-1,<sup>1</sup> ISAM,<sup>2</sup> AIMS,<sup>3</sup> ISIS-2,<sup>4</sup> ASSET,<sup>5</sup> USIM,<sup>6</sup> ISIS-3 (“uncertain indication” group),<sup>7</sup> EMERAS,<sup>8</sup> and LATE.<sup>9</sup> Interpretation of the combined results of these trials may help to resolve some of the remaining uncertainties about fibrinolytic therapy and to ensure that it is used as widely as is appropriate.<sup>33–37</sup>

**Materials and methods***FTT Collaborative Group*

The aim of the FTT Collaborative Group is periodically to obtain collaboration between the coordinators of all unconfounded, randomised trials in which fibrinolytic therapy has been compared with control or in which one fibrinolytic regimen has been compared with another in patients with suspected AMI or unstable angina. The overview reported here, however, brings together only those trials<sup>1–9</sup> randomising more than 1000 patients between

Design feature	Trial								
	GISSI-1	ISAM	AIMS	ISIS-2	ASSET	USIM	ISIS-3*	EMERAS	LATE
<b>Fibrinolytic regimen</b>									
Dose	SK, 1.5 MU	SK, 1.5 MU	APSAC, 30 U	SK, 1.5 MU	tPA 100 mg	UK, 1 MU × 2	SK, 1.5 MU; tPA, 0.6 MU/kg; or APSAC, 30 U	SK, 1.5 MU	tPA, 100 mg
Duration	1 h	1 h	5 min	1 h	3 h	Bolus repeated at 60 min	1 h; 4 h; 3 min	1 h	3 h
<b>Control</b>	Open	Placebo	Placebo	Placebo	Placebo	Open	Open	Placebo	Placebo
<b>Routine antiplatelet</b>	No	Aspirin (single iv bolus)	No	Aspirin (50%)	No	No	Aspirin	Aspirin	Aspirin
<b>Routine heparin</b>	No	Yes, iv	Yes, iv at 6 h	No	Yes, iv	Yes, iv	50%, sc	No	64%, iv
Dose		5000 U + 800–1000 U/h	1000–1500 U/h		5000 U + 1000 U/h	10 000 U + 1000 U/h	12 500 U bd		5000 U (× 1 or 2) + 1000 U/h
Duration		72–96 h, then oral anticoagulant	Until effective oral anticoagulation		24 h	48 h	7 days		48 h
<b>Recruitment period</b>	Jan 1984–Jul 1985	Mar 1982–Mar 1985	Sept 1985–Oct 1987	Mar 1985–Dec 1987	Nov 1986–Feb 1988	Apr 1986–Sep 1988	Sept 1989–Jan 1991	Jan 1988–Jan 1991	Apr 1989–Feb 1992

\*In ISIS-3, 37 000 patients considered to have a "certain" indication for fibrinolytic therapy were randomised between SK, tPA, and APSAC, and are not part of present report, which is restricted to those in whom indication was "uncertain". The latter were allocated half to fibrinolytic (1/3 SK, 1/3 tPA, 1/3 APSAC; all taken together in this report) and half to open control.

Table 1: Design characteristics of trials that randomised more than 1000 patients between fibrinolytic therapy and control

fibrinolytic therapy and control. Trials were to be included only if believed to have been both randomised in a manner that precluded prior knowledge of the next treatment to be allocated (eg, alternation or odd/even dates would not suffice), and unconfounded, such that one group differed from another only in the treatment of interest (eg, a trial of fibrinolytic therapy plus heparin versus same heparin regimen alone was to be included whereas a trial of fibrinolytic therapy plus heparin versus no heparin was not).

#### Individual patient data sought

Data were sought for individual randomised patients on certain features recorded before randomisation (including entry ECG classification, hours from symptom onset, age, sex, systolic BP [SBP], heart rate, and history of MI or diabetes). Delay from symptom onset to randomisation was rounded to the nearest hour wherever possible, producing slight changes from the published results of some studies. Deaths during days 0–35 and major adverse events (ie, strokes or major non-cerebral bleeds) in hospital up to day 35 were also sought, along with the day of occurrence. (For the LATE study,<sup>9</sup> however, all non-fatal events during days 0–35, before and after hospital discharge, were included.) Strokes were to be subdivided into "haemorrhage" (including probably haemorrhagic) and "other" (including both probably ischaemic and unknown aetiology). "Major" bleeds were defined as non-cerebral bleeds that required transfusion or were otherwise life-threatening, severely disabling, or fatal. Studies often define non-fatal outcomes differently but retrospective reclassification would have been both impracticable and potentially biased so the definitions preferred by the original investigators were usually retained. The resulting heterogeneity of definition does not invalidate the overview.<sup>38,39</sup> Data were checked for internal consistency of individual patient records, for consistency with the summary tabulations sought for each trial and with the published results, for balance of treatment group sizes overall and subdivided by baseline characteristics, and for other indications of possible anomalies.<sup>32</sup> Queries were sent to the principal investigators, as were requests for missing data, so that unbiased, intention-to-treat analyses could be done.

#### Trial data available

The nine controlled trials of fibrinolytic therapy that planned to include more than 1000 patients were of streptokinase (SK), anistreplase (APSAC), tissue plasminogen activator (tPA; alteplase or duteplase), or urokinase (UK).<sup>1,9</sup> Follow-up of patients randomised was very complete except for one study<sup>6</sup> in which about 300 patients were excluded after randomisation, generally

because MI was not confirmed. Individual patient data were available from all but two studies,<sup>5,9</sup> and for these two tabular data were provided for inclusion in the overall and day-of-event analyses and in the analyses of mortality subdivided by baseline characteristics. For one study<sup>6</sup> in which individual patient data were available only for mortality, limited tabular data for strokes and bleeds were available from the study publication.

### Statistical methods

#### Proportional and absolute mortality reductions

The medical principles that underly an overview of randomised trials and the statistical methods<sup>38,39</sup> are summarised only briefly here. Within each separate trial (or subset of each trial) the standard quantity "observed minus expected" (O-E) for the numbers of events among patients randomised to fibrinolytic therapy is calculated, together with its "variance". E corresponds to the average experience of both the treatment and the control groups. So, in an evenly randomised trial with a favourable result (ie, with fewer events in the treatment group), O-E would be negative and equal in size to half the number of events that seem to have been avoided by fibrinolytic therapy. To combine information from several trials the O-E values for each trial are simply added up. If treatment did nothing then, by chance alone, each trial result could equally well appear slightly bad or slightly good, so each separate O-E value could equally well be positive or negative and their grand total would likewise differ only randomly from zero. If, on the other hand, treatment did reduce the risk of an adverse outcome in these trials then any individual O-E value would be likely to be negative, so that when all of them are added up the grand total may be clearly negative. For the grand total (GT) of several individual O-E values, the variance (VT) is the sum of their individual variances, and the standard deviation (SD) is the square root of this variance. A grand total that differs from zero by 2 SD or more would be conventionally statistically significant ( $2p < 0.05$ ), while one that differs from zero by  $\geq 3$  SD would be highly significant ( $2p < 0.003$ ). Two-sided  $p$ -values ( $2p$ ) are used throughout, and values  $\geq 0.1$  are described as non-significant (NS).

In the assessment of fibrinolytic therapy what is needed is not only evidence that the treatment does something (ie, a test of the "null hypothesis") but also an estimate of how big the effect is likely to be (ie, a description of the "alternative hypothesis"). The "typical odds ratio", which indicates the ratio of the odds of an unfavourable outcome among treatment-allocated patients compared with that among controls can be estimated by use of the formula  $\exp(GT/VT)$ .<sup>38,39</sup> This formula provides appropriate weighting and stratification of the individual trial results. Such

Presentation features	Trial (and number randomised)									All trials (n=58 800)	
	GISSI-1 (n=11 802)	ISAM (n=1741)	AIMS (n=1254)	ISIS-2 (n=17 187)	ASSET (n=5012)	USIM (n=2201)	ISIS-3 (n=9158)	EMERAS (n=4534)	LATE (n=5711)	No	%
<b>Entry ECG</b>											
BBB	1	5	—	4	—	—	8	6	2	2146	4
ST elev, anterior	37	44	35	22	—	42	16	33	—	13 229	23
ST elev, inferior	34	48	47	25	—	47	11	27	—	16 203	28
ST elev, other	20	2	18	14	—	—	3	16	—	10 187	17
ST depression	4	—	1	7	—	—	19	4	12	4237	7
Other abnormality	5	1	—	25	—	10	25	12	30	9691	17
Normal	0	—	—	2	18	—	17	2	0	2907	5
<b>Hours from onset</b>											
0-1	11	9	3	4	6	24	3	1	—	3348	6
2-3	41	51	43	26	49	65	22	2	—	16 632	28
4-6	31	40	54	33	44	12	29	12	2	16 493	28
7-12	17	—	—	23	—	—	28	46	38	12 788	22
13-24	—	—	—	14	—	—	18	40	60	9339	16
<b>Age (yr)</b>											
<55	29	35	39	29	27	30	22	32	22	16 238	28
55-64	35	34	43	35	36	36	29	32	30	19 608	33
65-74	24	30	18	28	37	24	32	26	35	17 000	29
75+	11	1	—	8	—	10	17	11	13	5754	10
<b>Sex</b>											
Male	80	82	82	77	77	82	69	77	72	44 745	76
Female	20	18	18	23	23	18	31	23	28	13 855	24
<b>SBP (mm Hg)</b>											
<100	5	5	5	4	4	5	3	6	3	2466	4
100-149	60	60	66	63	56	62	60	70	62	36 052	62
150-174	29	27	24	27	29	26	28	20	28	15 907	27
175+	6	8	5	7	11	7	9	4	8	4175	7
<b>Heart rate (/min)</b>											
<80	—	52	55	69	58	—	50	46	50	25 865	58
80-99	—	34	35	19	30	—	33	35	35	12 518	28
100+	—	14	10	12	12	—	16	19	15	6214	14
<b>Prior MI</b>											
Yes	16	12	17	17	27	—	32	12	22	11 329	20
No	84	88	83	83	73	—	68	88	78	45 070	80
<b>Diabetes</b>											
Yes	—	12	—	7	7	—	13	17	13	4529	10
No	—	88	—	93	93	—	87	83	87	38 814	90

— = none; blank = not recorded in trial.

Table 2: Patient characteristics (%)

methods assume, not that the size of the treatment effect is the same in the different trials, but merely that any real effects probably point in the same direction. A convenient way of describing the statistical reliability of such an odds ratio (OR) is to give its 95% or, where many comparisons are being made,<sup>38,39</sup> 99% confidence interval (CI). Alternatively, the proportional reduction in odds can be described along with its SD: an odds ratio of 0.75, for example, would correspond to a 25% reduction in the odds of death.

Proportional reductions in mortality may be more widely generalisable to different medical circumstances than absolute reductions are. But in deciding whether the benefits of fibrinolytic therapy outweigh its risks, absolute differences may be more relevant clinically. A crude but simple method to describe the absolute difference in outcome is to add up the treatment groups, add up the control groups, and then to compare the two grand totals. Such an unstratified comparison may not be ideal statistically<sup>38,39</sup> (and see below) but where, as here, all trials are approximately evenly randomised and the difference in outcome between treatment and control is very highly significant, such comparisons may well provide a description of the absolute effects of treatment that is sufficient for most practical purposes.

#### Effects in specific categories of patient

The very large numbers in trials of fibrinolytic therapy allow reasonably reliable *direct* assessment of the effects of treatment in some major subcategories of patient. However, even in an overview of several tens of thousands of patients, small subcategories in which treatment is especially advantageous or relatively ineffective can be difficult to identify. For, when there is clear overall evidence of benefit and a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several small subgroups in which treatment really is effective. In such circumstances, "lack of evidence of benefit" is not good "evidence

of lack of benefit",<sup>4</sup> and clearly significant overall results may provide strong indirect evidence of benefit in some small subgroups where the results, considered in isolation, are not conventionally significant—or even, perhaps, slightly adverse.

Paradoxically, therefore, the size of the net clinical benefit in a small specific category may best be estimated *indirectly* by applying the proportional reduction in mortality observed among all patients in these trials (most of which, of course, is cardiac mortality) to the absolute risk of death observed among control patients in that particular category and then comparing this with the absolute risk of treatment observed overall.<sup>38-40</sup> For example, in patients who would be at very low risk of cardiac death, any small benefits of fibrinolytic treatment may be outweighed by the risks of stroke. If, however, patient categories can be arranged in some meaningful order (eg, 0-3, 4-6, 7-12, 13-24 h from symptom onset) then direct assessment of the trend in the proportional reduction in mortality provides a relationship between the patient characteristics and the benefits of treatment that may be reasonably reliably informative about the absolute effects in these different categories.

## Results

### Features of trials and available data

In all nine trials of fibrinolytic therapy versus control that randomised more than 1000 patients the proportion of patients to be allocated to fibrinolytic therapy was one-half (table 1). The agent was SK in four, APSAC in one, tPA in two, UK in one, and a random choice of SK, tPA, or APSAC in one. Six trials were placebo-controlled, while three randomised patients between fibrinolytic therapy and "open" control (ie, both the physician and patient knew whether or not fibrinolytic therapy had been allocated).

Day of death	Deaths during days 0-35		Proportional reduction (95% CI)	Benefit per 1000 (95% CI)
	Fibrinolytic (29 315)	Control (29 285)		
Day 0	695 (2.4%)	554 (1.9%)	-26 SD 6 (-38% to -13%)	-5 SD 1§ (-7 to -2)
Day 1	475 (1.7%)	549 (1.9%)	13 SD 6 (2% to 25%)	3 SD 1* (0 to 5)
Days 2-7	847 (3.0%)	1100 (3.9%)	23 SD 4 (16% to 31%)	9 SD 2¶ (6 to 12)
Days 8-35	803 (2.9%)	1154 (4.3%)	32 SD 4 (24% to 39%)	13 SD 2¶ (10 to 16)
All in days 0-35	2820 (9.6%)	3357 (11.5%)	18% SD 2 (13% to 23%)	18 SD 3¶ (13 to 23)

\*, †, ‡, §, ¶ correspond to 2p < 0.05, < 0.01, < 0.005, < 0.001, < 0.00001.

Table 3: Proportional and absolute differences in mortality during days 0-35

Aspirin was to be given routinely to all patients in four trials and to half of the patients in one trial (where aspirin allocation was random). Heparin was intended to be given routinely to all patients in five trials by intravenous infusion and to half of the patients in one trial (where subcutaneous heparin allocation was random).

Three trials sought to include only patients with ST elevation and/or bundle-branch block (BBB) on the presenting ECG<sup>1-3</sup> and one trial sought to include only patients with some ECG abnormality.<sup>6</sup> Patients with suspected AMI were eligible for the other five trials even if the ECG was normal (table 2). Almost 60 000 patients were randomised in these nine trials: 4% had BBB, 68% ST elevation, 7% ST depression, 17% other abnormalities

(inverted T-waves or some other non-specific pattern suggestive of acute ischaemia), and 5% near-normal ECGs. A major eligibility criterion was the time from the onset of symptoms, with four trials including only patients presenting within 6 h,<sup>2,3,5,6</sup> one including only those presenting within 12 h,<sup>1</sup> and the other four including patients up to 24 h from the onset of symptoms: in the nine trials, 22% of patients presented at 7-12 h and 16% at 13-24 h. Three trials<sup>2,3,5</sup> explicitly aimed to exclude patients aged 75 years or more and there was underselection of this age group in other trials, so that only 10% of patients studied were aged 75+. Sex, SBP, heart rate, and history of previous MI or diabetes were not explicitly part of the entry criteria, and the distributions of these characteristics in the different trials were largely similar. In ISIS-3,<sup>7</sup> patients for whom the indication for treatment was considered by their physician to be "uncertain" were to be randomised between fibrinolytic therapy and control (whereas those in whom the indication was considered "certain" were randomised between SK, tPA, and APSAC and have been reported elsewhere<sup>7</sup>). During the period of recruitment into ISIS-3 (September, 1989, to January, 1991) this led to the inclusion of a large proportion of patients without ST elevation or BBB, particularly among those presenting early after the onset of symptoms.

Effects on 35-day mortality

Among all patients studied there were 2820 (9.6%) deaths during days 0-35 among 29 315 fibrinolytic-allocated

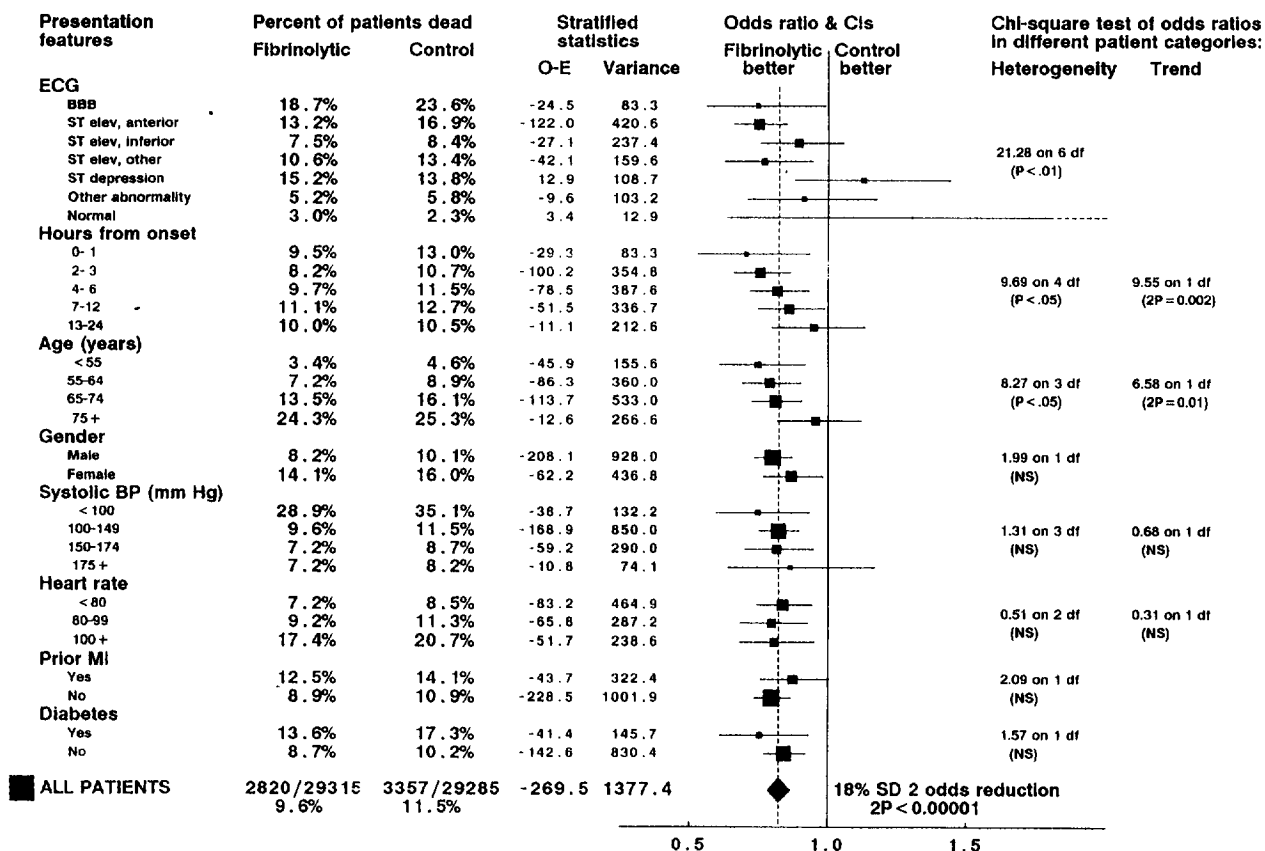


Figure 1: Proportional effects of fibrinolytic therapy on mortality during days 0-35 subdivided by presentation features

"Observed minus expected" (O-E) number of events among fibrinolytic-allocated patients (and its variance) is given for subdivisions of presentation features, stratified by trial. This is used to calculate odds ratios (ORs) of death among patients allocated to fibrinolytic therapy to that among those allocated control. ORs (black squares with areas proportional to amount of "statistical information" contributed by the trials<sup>39</sup>) are plotted with their 99% CIs (horizontal lines). Squares to left of the solid vertical line indicate benefit (significant at 2p < 0.01 only where entire CI is to left of vertical line). Overall result and 95% CI represented by diamond, with overall proportional reduction in the odds of death and statistical significance given alongside. Chi-square tests<sup>39</sup> for evidence of heterogeneity of, or trends in, size of ORs in subdivisions of each presentation feature are also given.

Presentation features	Patients		Deaths during days 0-1			Deaths during days 2-35			Deaths during days 0-35		
	Fibrinolytic	Control	Fibrinolytic	Control	Benefit per 1000 (SD)	Fibrinolytic	Control	Benefit per 1000 (SD)	Fibrinolytic	Control	Benefit per 1000 (SD)
<b>Entry ECG</b>											
BBB	1007	1025	82	96	12 (13)	106	146	43 (16)	188 (18.7%)	242 (23.6%)	49 (18)
ST elev, anterior	6587	6642	413	446	4 (4)	455	674	35 (5)	868 (13.2%)	1120 (16.9%)	37 (6)
ST elev, inferior	6556	6484	173	126	-7 (3)	320	416	15 (4)	493 (7.5%)	542 (8.4%)	8 (5)
ST elev, other	3053	3024	138	120	-6 (6)	186	284	34 (7)	324 (10.6%)	404 (13.4%)	27 (8)
ST depression	1779	1784	108	89	-11 (7)	163	158	-4 (9)	271 (15.2%)	247 (13.8%)	-14 (11)
Other abnormality	3988	3963	87	67	-5 (3)	122	163	11 (5)	209 (5.2%)	230 (5.8%)	6 (6)
Normal	995	990	12	5	-7 (4)	18	18	0 (2)	30 (3.0%)	23 (2.3%)	-7 (7)
<b>Hours from onset</b>											
0-1	1678	1670	78	83	3 (8)	81	134	34 (9)	159 (9.5%)	217 (13.0%)	35 (11)
2-3	8297	8315	302	339	4 (3)	381	550	21 (4)	683 (8.2%)	889 (10.7%)	25 (5)
4-6	8294	8195	325	307	-2 (3)	477	638	21 (4)	802 (9.7%)	945 (11.5%)	19 (5)
7-12	6478	6404	298	257	-6 (4)	421	556	22 (5)	719 (11.1%)	813 (12.7%)	16 (6)
13-24	4568	4701	167	117	-12 (4)	290	376	16 (6)	457 (10.0%)	493 (10.5%)	5 (6)
<b>Age (yr)</b>											
<55	8082	8158	113	137	3 (2)	165	236	9 (2)	278 (3.4%)	373 (4.6%)	11 (3)
55-64	9911	9678	291	288	0 (3)	418	576	18 (3)	709 (7.2%)	864 (8.9%)	18 (4)
65-74	8487	8496	459	434	-3 (3)	685	938	31 (5)	1144 (13.5%)	1372 (16.1%)	27 (5)
75+	2835	2953	307	244	-26 (8)	382	504	35 (11)	689 (24.3%)	748 (25.3%)	10 (13)
<b>Sex</b>											
Male	22 353	22 412	732	721	-1 (2)	1103	1537	20 (2)	1835 (8.2%)	2258 (10.1%)	19 (3)
Female	6962	6873	438	382	-7 (4)	547	717	27 (5)	985 (14.1%)	1099 (16.0%)	18 (6)
<b>SBP (mm Hg)</b>											
<100	1263	1182	237	261	33 (16)	128	154	42 (16)	365 (28.9%)	415 (35.1%)	62 (18)
100-149	17 979	18 063	699	648	-3 (2)	1032	1433	23 (3)	1731 (9.6%)	2081 (11.5%)	19 (3)
150-174	7907	8005	171	163	-1 (2)	398	531	16 (4)	569 (7.2%)	694 (8.7%)	15 (4)
175+	2166	2035	63	31	-14 (5)	92	136	24 (7)	155 (7.2%)	167 (8.2%)	11 (8)
<b>Heart rate (/min)</b>											
<80	12 922	12 965	358	311	-4 (2)	568	786	17 (3)	926 (7.2%)	1097 (8.5%)	13 (3)
80-99	6268	6221	235	204	-5 (3)	344	502	26 (5)	579 (9.2%)	706 (11.3%)	21 (5)
100+	3095	3126	228	238	2 (6)	309	408	33 (9)	537 (17.4%)	646 (20.7%)	33 (10)
<b>Prior MI</b>											
Yes	5719	5577	287	263	-3 (4)	430	521	19 (5)	717 (12.5%)	784 (14.1%)	15 (6)
No	22 468	22 635	842	794	-2 (2)	1151	1673	23 (2)	1993 (8.9%)	2467 (10.9%)	20 (3)
<b>Diabetes</b>											
Yes	2236	2260	117	121	1 (6)	186	270	38 (10)	303 (13.6%)	391 (17.3%)	37 (11)
No	19 423	19 424	693	607	-4 (2)	1004	1374	19 (3)	1697 (8.7%)	1981 (10.2%)	15 (3)
<b>All patients</b>	<b>29 315</b>	<b>29 285</b>	<b>1170 (4.0%)</b>	<b>1103 (3.8%)</b>	<b>-2 (2)</b>	<b>1650 (5.9%)</b>	<b>2254 (8.0%)</b>	<b>21 (2)</b>	<b>2820 (9.6%)</b>	<b>3357 (11.5%)</b>	<b>18 (3)</b>

Results for "uncertain" indication arm of ISIS-3 (see footnote to table 1), which have not been published separately, were included in all subdivisions: in summary, for patients with ST elevation or BBB in ISIS-3, the results were 84/782 fibrinolytic vs 97/760 control for delay 0-6 h, 69/586 vs 86/597 for 7-12 h, and 68/445 vs 59/431 for 13-24 h; and for patients with other ECG changes they were 104/1713 vs 65/1682 for 0-6 h, 47/694 vs 42/674 for 7-12 h, and 28/381 vs 26/413 for 13-24 h.

Certain of the presentation features were not recorded in GISSI-1 (heart rate and diabetes), AIMS (diabetes), USIM (heart rate, prior MI, diabetes), and ASSET and LATE (these particular ECG categories), so data from these trials could not be included in subdivisions by these features. Where the value of some presentation feature was missing for a particular patient then that patient was excluded from subdivision of that feature.

Table 4: Absolute differences in mortality during days 0-35 subdivided, where possible, by presentation features

patients compared with 3357 (11.5%) deaths among 29 285 controls (table 3). This 18% (SD 2) proportional reduction in 35-day mortality is highly significant (95% CI of 13-23%;  $2p < 0.00001$ ), and corresponds to avoidance of about 18 deaths (SD 3) per 1000 patients allocated treatment. The combined analysis indicates, however, that fibrinolytic therapy was associated with a highly significant excess of 5 (SD 1) deaths per 1000 on the day of randomisation (day 0, which contributes an average of only 12 h of trial data), and with only a small benefit of 3 (SD 1) deaths per 1000 on the following day (day 1), so that during days 0-1 there was no significant net benefit from fibrinolytic therapy. Only subsequently did a definite benefit emerge, with highly significant reductions in mortality among the fibrinolytic-allocated patients both during the remainder of the first week (days 2-7) and during the subsequent 4 weeks.

#### Mortality effects subdivided by baseline characteristics

**Presenting ECG** Subdivision by entry ECG does indicate some significant differences between both the proportional and the absolute mortality reductions observed (figure 1, table 4). Mortality was significantly reduced among patients with ST segment elevation (21% [SD 3];

$2p < 0.00001$ ) and among the smaller number with BBB (25% [SD 9];  $2p < 0.01$ ). The proportional reductions observed among patients presenting with ST elevation in anterior leads (25% [SD 4] reduction;  $2p < 0.00001$ ), in inferior leads (11% [SD 6] reduction; 99% CI of 24% reduction to 5% increase;  $2p = 0.08$ ), and in both anterior and inferior leads (ie, "other" ST elevation: 23% [SD 7] reduction;  $2p < 0.001$ ) were not significantly different from each other. The absolute benefits were, therefore, larger among the patients with evidence of anterior ST elevation, since they were at higher absolute risk than were patients with evidence of only inferior ST elevation (table 4).

No statistically significant mortality reductions were observed among patients presenting without ST elevation or BBB but with ST depression (13% [SD 10] proportional increase, but with 99% CI ranging from 12% reduction to 44% increase), even though such patients were at high risk of death. Nor were significant reductions observed among patients presenting with other ECG abnormalities (9% [SD 9] reduction; 99% CI of 29% reduction to 17% increase) or with "normal" ECGs (30% [SD 32] increase; 99% CI of 36% reduction to 165% increase), who were at relatively low risk of death from MI. However, the numbers of deaths observed among the patients studied in each

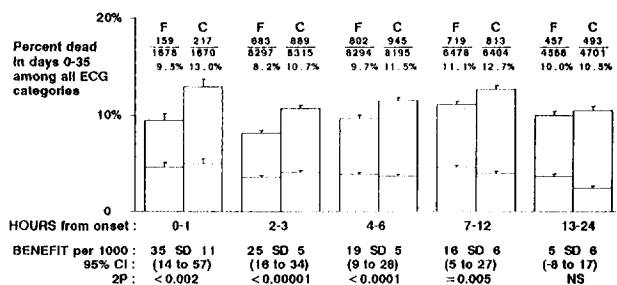


Figure 2: Absolute effects of fibrinolytic therapy on mortality during days 0-35 subdivided by delay from symptom onset

Unstratified percentages dead during days 0-35 among all those allocated fibrinolytic therapy and all those allocated control in these trials are plotted ( $\pm 1$  SD), subdivided by time from symptom onset. Portion below horizontal line within each column represents deaths during days 0-1; portion above line represents deaths during days 2-35.

of these three categories were small (and the CIs for the observed effects were wide) so moderate beneficial effects cannot be ruled out (see Discussion).

**Delay from symptom onset** There were significant trends towards greater proportional and absolute mortality reductions among patients treated earlier after symptom onset (both  $p < 0.01$ ; figures 1 and 2, table 4). The mortality reduction was highly significant among patients presenting within 3 h of symptom onset (26% [SD 4] proportional reduction;  $2p < 0.00001$ ) and among those presenting 4-6 h from onset (18% [SD 5] proportional reduction;  $2p < 0.0001$ ). A retrospective subgroup analysis of GISSI-1 had suggested that fibrinolytic therapy might be especially effective very soon after the onset of symptoms (51% [SD 12] proportional reduction among those presenting within 1 h compared with 15% [SD 9] reduction among those presenting at 2-3 h and, counterintuitively, a larger reduction of 19% [SD 9] at 4-6 h). This "hypothesis generating" observation in GISSI-1 was not, however, supported by the other trials. The combined analysis of all the large trials now indicates no marked discontinuity at 0-1 h, and only a gradual diminution of benefit with delay (0-1 h: 30% [SD 9] proportional reduction; 2-3 h: 25% [SD 5] reduction; 4-6 h: 18% [SD 5] reduction; figure 1).

The possibility that fibrinolytic therapy might still be of value even for patients who do not reach hospital until several hours after symptom onset had been suggested in 1985 by an overview of only 6000 patients in small trials (each of fewer than 1000 patients)<sup>41</sup> but much more evidence was needed. In the present overview, 22 000 out of 60 000 patients were randomised more than 6 h after

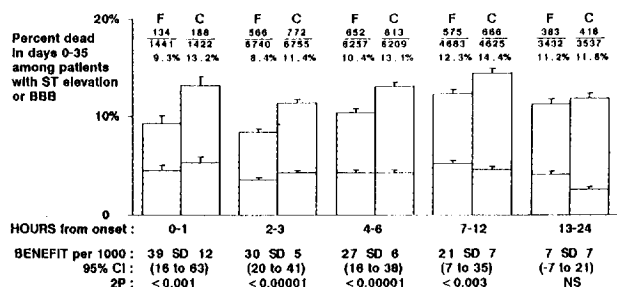


Figure 3: Absolute effects of fibrinolytic therapy on mortality during days 0-35 subdivided by delay from symptom onset, among patients with ST elevation or BBB

Legend as for figure 2. (All patients in ASSET and LATE were included because the tabular information available from these trials subdivided by delay was not subdivided by ECG.)

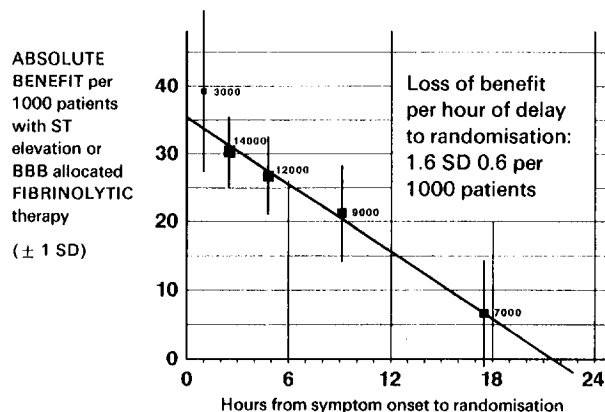


Figure 4: Absolute reduction in 35-day mortality versus delay from symptom onset to randomisation among 45 000 patients with ST elevation or BBB

(All patients in ASSET and LATE are included, see figure 3 legend.) For patients whose delays were recorded as 0-1, 2-3, 4-6, 7-12, and 13-24 h, absolute benefit ( $\pm 1$  SD) from figure 3 is plotted against mean recorded delay time (0.98, 2.50, 4.79, 9.11, and 17.48 h, respectively). Area of black square and extent to which it influences line drawn through five points is approximately proportional to number of patients it is based on. (Formally, area is inversely proportional to variance of absolute benefit it describes, and slope is inverse-variance-weighted least squares regression line.)

symptom onset. Fibrinolytic therapy produced a highly significant mortality reduction among the 13 000 presenting at 7-12 h (14% [SD 5] proportional reduction;  $2p = 0.005$ ), with non-significantly favourable results even among the 9000 who presented after more than 12 h (figure 1). In figure 2, the total height of the bars gives the 35-day mortality; the lower part shows mortality during days 0-1 and the upper part mortality during days 2-35 (when the overall benefits are seen; table 3). The length of the delay between the onset of symptoms and the time of randomisation is associated with a substantial increase in the excess of deaths on day 0-1 but, surprisingly, seems to have little effect on the size of the benefit during days 2-35 (figure 2, table 4).

**Presenting ECG and delay from symptom onset** In each period of delay from symptom onset, the absolute benefit appears slightly larger if attention is restricted to patients with ST elevation or BBB (figure 3). For the five time periods used, regression analysis of the absolute benefit versus the mean delay from symptom onset indicates an approximately straight-line relationship (figure 4), with every additional hour of delay being associated with a reduction in the benefit by about 1.6 (SD 0.6) lives per 1000 patients. This suggests that, for patients with ST elevation or BBB, the absolute mortality reduction would be about 30 per 1000 for those presenting 0-6 h from symptom onset, about 20 per 1000 for those presenting at 7-12 h, and perhaps about 10 per 1000 for those presenting 13-18 h from onset. Because the net effects of treatment after a delay of more than 12 h appear to be the sum of a substantial early hazard and a substantial later benefit (figure 3), more directly randomised evidence is still needed to assess the net effects of fibrinolytic therapy in this time period.

**Age** Older patients were at higher absolute risk of death from AMI, so, although there was a significant trend towards larger proportional reductions in mortality among younger patients ( $2p = 0.01$ ; figure 1), the absolute mortality reductions seem much the same among younger and older patients (figure 5, table 4). The early excess of

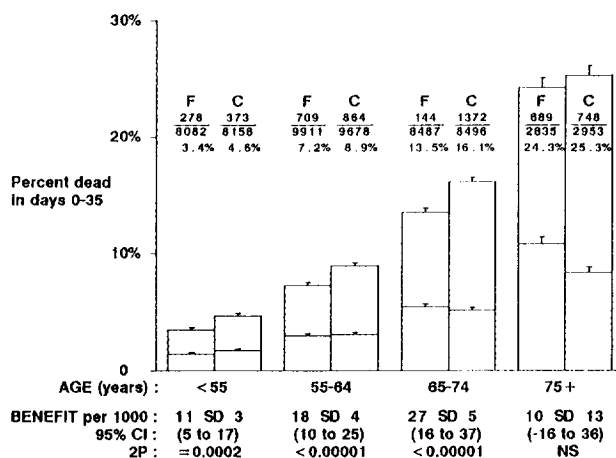


Figure 5: Absolute effects of fibrinolytic therapy on mortality during days 0-35 subdivided by age

Legend as for figure 2.

death on days 0-1 that is associated with fibrinolytic therapy increased with age, but so too did the benefits during days 2-35. (In this and in subsequent subgroup analyses, the absolute benefits would be expected to be slightly larger if attention were restricted to patients presenting with ST elevation or BBB within 12 h of symptom onset.)

**Sex** Fibrinolytic therapy reduced mortality significantly both among women and among men. The women studied were at higher absolute risk of death so, although the proportional reduction in mortality among women was slightly though non-significantly smaller (figure 1), the absolute reductions were similar for both sexes (table 4). The absolute excess of early deaths and the later absolute reduction with fibrinolytic therapy were both significantly larger among the women studied. This is similar to the pattern seen with increasing age and with treatment started later after the onset of symptoms, and may reflect the substantially older age of these women (44% of patients aged 75 or over were women compared with only 12% of those under 55) and their slightly longer average delay to treatment (7.0 h for women *vs* 6.2 h for men).

**Blood pressure and heart rate** The proportional reductions in the risk of death did not appear to be much influenced by the SBP or heart rate (figure 1). Patients with entry SBP less than 100 mm Hg or heart rate 100/min or more were, however, at very high risk of death, and the absolute benefits during the first 35 days seemed to be largest among such patients (eg, about 60 lives saved per 1000 patients with SBP under 100 mm Hg;  $2p < 0.001$ ; figure 6, table 4). The absolute excess of early deaths increased with increasing BP (and with decreasing heart rate), but even among those with raised BP there was a substantial later benefit.

**Previous myocardial infarction** Patients with a history of myocardial infarction are at increased risk of death after a subsequent infarction (table 4). The results in this subgroup of patients in GISSI-1 generated the hypothesis that fibrinolytic therapy might not be as effective among patients with a history of MI (previous MI in GISSI-1: 1% [SD 12] proportional reduction; no previous MI: 23% [SD 6] reduction). Even when the hypothesis-generating GISSI-1 trial is considered on its own, however, the absolute benefits of fibrinolytic therapy were not very significantly affected by the presence or absence of a history of MI, and the GISSI investigators were careful to point out that such a data-dependent observation might chiefly

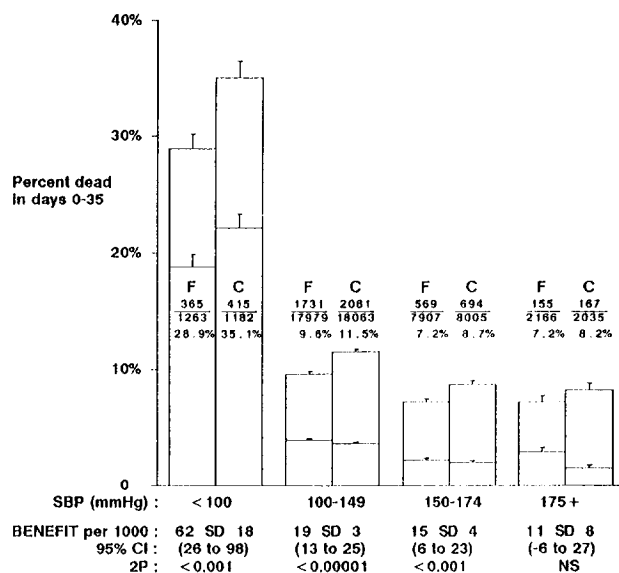


Figure 6: Absolute effects of fibrinolytic therapy on mortality during days 0-35 subdivided by entry SBP

Legend as for figure 2.

reflect the play of chance. In confirmation of this, fibrinolytic therapy has in the other large trials now produced a statistically definite benefit among patients with a previous MI. Even if GISSI-1 is included this benefit remains significant (figure 1, table 4), and there appears to be little difference between the mortality reduction observed among patients with a history of MI (13% [SD 5] proportional reduction, representing avoidance of about 15 [SD 6] deaths per 1000 patients;  $2p < 0.02$ ) and that among those without such a history (20% [SD 3] reduction or about 20 [SD 3] deaths per 1000).

**Diabetics** Diabetics are also at above-average risk of death after MI. The proportional reduction in mortality with fibrinolytic therapy was slightly, though non-significantly, greater among the diabetic patients studied (figure 1), so the absolute benefits of treatment appeared to be greater among diabetics (37 [SD 11] lives saved per 1000;  $2p < 0.001$ ; table 4) than among non-diabetics (15 [SD 3] lives saved per 1000;  $2p < 0.00001$ ).

**Strokes and non-cerebral bleeding with fibrinolytic therapy**  
**Strokes** Fibrinolytic therapy was associated with a small but significant excess of 3.9 (SD 0.8) extra strokes per 1000

Aetiology of stroke	Strokes during days 0-35		Excess per 1000 (SD)
	Fibrinolytic (29 315)	Control (29 285)	
<b>Days 0-1</b>			
Probable haemorrhage	78 (0.3%)	4 (0.0%)	2.5 (0.3)¶
Other (incl unknown)	88 (0.3%)	35 (0.1%)	1.8 (0.4)¶
Any in day 0-1	166 (0.6%)	39 (0.1%)	4.3 (0.5)¶
<b>Days 2-35</b>			
Probable haemorrhage	31 (0.1%)	11 (0.0%)	0.7 (0.2)‡
Other (incl unknown)	139 (0.5%)	172 (0.6%)	-1.1 (0.6)
Any in days 2-35	170 (0.6%)	183 (0.6%)	-0.4 (0.7)
<b>Days 0-35</b>			
Probable haemorrhage	111 (0.4%)	16 (0.1%)	3.2 (0.4)¶
Other (incl unknown)	229 (0.8%)	208 (0.7%)	0.7 (0.7)
Any in days 0-35	340 (1.2%)	224 (0.8%)	3.9 (0.8)¶

Unpublished results for the "uncertain" indication arm of ISIS-3 (strokes on day 0-1: 48 vs 6; strokes on days 2-35: 23 vs 15) included in each row and in all subdivisions of table 6. USIM data are included in days 0-35 subdivision only.

\*, †, ‡, §, ¶ correspond to  $2p < 0.05$ ,  $< 0.01$ ,  $< 0.005$ ,  $< 0.001$ ,  $< 0.00001$ .

Table 5: Strokes during days 0-35 (or prior discharge)

Presentation features	Patients		Strokes during days 0-1			Strokes during days 2-35			Strokes during days 0-35		
	Fibrinolytic	Control	Fibrinolytic	Control	Excess per 1000 (SD)	Fibrinolytic	Control	Excess per 1000 (SD)	Fibrinolytic	Control	Excess per 1000 (SD)
<b>Entry ECG</b>											
BBB	1007	1025	13	3	10.0 (3.9)	8	8	0.1 (2.0)	21 (2.1%)	11 (1.1%)	10.1 (5.5)
ST elev, anterior	6091	6203	29	7	3.6 (1.0)	34	52	-2.8 (1.5)	63 (1.0%)	59 (1.0%)	0.8 (1.8)
ST elev, inferior	6015	5984	29	8	3.5 (1.0)	32	29	0.5 (1.3)	61 (1.0%)	37 (0.6%)	4.0 (1.7)
ST elev, other	3053	3024	17	6	3.6 (1.6)	14	24	-3.4 (2.0)	31 (1.0%)	30 (1.0%)	0.2 (3.4)
ST depression	1779	1784	14	3	6.2 (2.3)	4	6	-1.1 (1.7)	18 (1.0%)	9 (0.5%)	5.1 (2.9)
Other abnormality	3897	3829	19	8	2.8 (1.3)	14	9	1.2 (1.3)	33 (0.8%)	17 (0.4%)	4.0 (1.8)
Normal	995	990	10	0	10.1 (3.2)	2	0	2.0 (1.4)	12 (1.2%)	0 (0.0%)	12.1 (3.5)
<b>Hours from onset</b>											
0-1	1252	1265	2	2	0.0 (3.5)	3	7	-3.1 (2.5)	5 (0.4%)	9 (0.7%)	-3.1 (2.9)
2-3	6354	6378	32	7	3.9 (1.0)	25	34	-1.4 (1.2)	57 (0.9%)	41 (0.6%)	2.5 (1.5)
4-6	6973	6924	45	10	5.0 (1.1)	37	48	-1.6 (1.3)	82 (1.2%)	58 (0.8%)	3.4 (1.7)
7-12	5333	5285	32	12	3.7 (1.2)	28	25	0.5 (1.4)	60 (1.1%)	37 (0.7%)	4.2 (1.8)
13-24	2925	2987	20	4	5.5 (1.6)	15	14	0.4 (1.8)	35 (1.2%)	18 (0.6%)	5.9 (2.4)
<b>Age (yr)</b>											
<55	6441	6517	8	4	0.6 (0.5)	10	25	-2.3 (0.9)	18 (0.3%)	29 (0.4%)	-1.7 (1.1)
55-64	7727	7582	50	8	5.4 (1.0)	33	35	-0.3 (1.0)	83 (1.1%)	43 (0.6%)	5.1 (1.5)
65-74	6310	6313	46	20	4.1 (1.3)	45	41	0.6 (1.4)	91 (1.4%)	61 (1.0%)	4.8 (1.9)
75+	2359	2427	27	3	10.2 (2.3)	20	27	-2.6 (2.9)	47 (2.0%)	30 (1.2%)	7.6 (3.7)
<b>Sex</b>											
Male	17 434	17 514	92	24	3.9 (0.6)	73	91	-1.0 (0.7)	165 (0.9%)	115 (0.7%)	2.9 (1.0)
Female	5403	5325	39	11	5.2 (1.3)	35	37	-0.5 (1.8)	74 (1.4%)	48 (0.9%)	4.7 (2.0)
<b>SBP (mm Hg)</b>											
<100	1036	950	10	1	8.6 (3.4)	3	8	-5.5 (3.3)	13 (1.3%)	9 (0.9%)	3.1 (5.0)
100-149	14 107	14 257	74	27	3.4 (0.7)	64	72	-0.5 (0.8)	138 (1.0%)	99 (0.7%)	2.8 (1.1)
150-174	6132	6162	31	6	4.1 (1.0)	35	38	-0.5 (1.4)	66 (1.1%)	44 (0.7%)	3.6 (1.7)
175+	1562	1470	16	1	9.6 (2.7)	6	10	-3.0 (2.7)	22 (1.4%)	11 (0.7%)	6.6 (3.7)
<b>Heart rate (/min)</b>											
<80	10 045	10 056	61	12	4.9 (0.8)	42	49	-0.7 (1.0)	103 (1.0%)	61 (0.6%)	4.2 (1.3)
80-99	4515	4501	31	11	4.4 (1.4)	25	27	-0.5 (1.7)	56 (1.2%)	38 (0.8%)	4.0 (2.1)
100+	2375	2382	15	4	4.6 (1.8)	16	21	-2.1 (2.6)	31 (1.3%)	25 (1.0%)	2.6 (3.0)
<b>Prior MI</b>											
Yes	4413	4309	22	4	4.1 (1.2)	36	17	4.2 (1.7)	58 (1.3%)	21 (0.5%)	8.3 (2.0)
No	18 424	18 530	109	31	4.2 (0.6)	72	111	-2.1 (0.7)	181 (1.0%)	142 (0.8%)	2.2 (1.0)
<b>Diabetes</b>											
Yes	1706	1730	17	7	5.9 (2.8)	15	16	-0.5 (4.0)	32 (1.9%)	23 (1.3%)	5.5 (4.2)
No	14 603	14 581	85	20	4.4 (0.7)	57	71	-1.0 (0.8)	142 (1.0%)	91 (0.6%)	3.5 (1.0)
<b>All patients</b>	<b>29 315</b>	<b>29 285</b>	<b>166 (0.6%)</b>	<b>39 (0.1%)</b>	<b>4.3 (0.5)</b>	<b>170 (0.6%)</b>	<b>183 (0.6%)</b>	<b>-0.4 (0.7)</b>	<b>340 (1.2%)</b>	<b>224 (0.8%)</b>	<b>3.9 (0.8)</b>

Certain of the presentation features were not recorded in GISSI-1 (heart rate and diabetes) and AIMS (diabetes), so data from these trials could not be included in subdivisions by these features. ASSET, LATE and USIM data were not available for any of these subdivisions.

Table 6: Strokes during days 0-35 (or prior discharge) subdivided, where possible, by presentation features

(340 [1.2%] fibrinolytic vs 224 [0.8%] control;  $2p < 0.00001$ ; table 5). All of this excess appeared on days 0-1 (166 [0.6%] vs 39 [0.1%]; 4.3 [SD 0.5] absolute excess per 1000;  $2p < 0.00001$ ), and where the aetiology could be ascertained this early excess was largely attributed to cerebral haemorrhage. Of the early strokes not attributed to cerebral haemorrhage, many were of unknown aetiology and may have been haemorrhagic. On days 2-35 there were slightly fewer total strokes among patients allocated to fibrinolytic therapy (170 [0.6%] vs 183 [0.6%]; 0.4 [SD 0.7] absolute reduction per 1000; not significant), but even in this later period a small but highly significant excess of haemorrhagic strokes was reported. Part of the overall excess of stroke was among patients who died in days 0-35 (145 [0.5%] vs 88 [0.3%]; 1.9 [SD 0.5] excess per 1000;  $2p < 0.001$ ) and so was already accounted for in the overall mortality reduction. Of the remaining excess of strokes about half were considered to be moderately or severely disabling and half were considered to have produced little or no disability.

Among patients aged under 55, the risk of stroke was low and the early excess with fibrinolytic therapy was small (table 6). The excess risk of early stroke that was associated with fibrinolytic therapy tended to increase with age. Age apart, however, no presentation feature significantly affected the absolute early stroke risk that was caused by fibrinolytic therapy, as long as due allowance is made for the number of subgroups studied (table 6; sum of seven chi-square values = 8.1, sum of degrees of freedom = 18;

not significant). Thus, although the early stroke hazard produced by fibrinolytic therapy may be greater for those with BBB or with a normal ECG, or for those with a low or a high SBP, these apparent deviations from the average hazard of about 4 per 1000 may be largely or wholly due to chance.

**Major non-cerebral bleeds** Non-cerebral bleeds were generally considered to be "major" if they required blood transfusion or were life-threatening. Fibrinolytic therapy was associated with a 7.3 (SD 0.7) per 1000 excess of such major bleeds (325 [1.1%] fibrinolytic vs 111 [0.4%] control;  $2p < 0.00001$ ; table 7). The size of this excess did not appear to differ much between any of the subgroups studied, including younger or older patients and those who presented with a high BP or a history of diabetes.

## Discussion

Several previous trials of fibrinolytic therapy in AMI have on their own been large enough to show that mortality during the first month or so can be reduced, and that these survival benefits persist.<sup>4,42-45</sup> This overview of the nine largest fibrinolytic trials<sup>1-9</sup> demonstrates that treatment is beneficial for a wide range of patients with suspected AMI, many of whom are still not routinely given fibrinolytic therapy.<sup>10-14</sup> Moreover, it has helped to characterise the early excess of deaths and of strokes associated with fibrinolytic therapy, and to show that this is outweighed in many types of patient by a much larger benefit during the next few weeks.

**Benefit among patients with ST elevation or BBB**

Fibrinolytic therapy appeared to reduce mortality among patients presenting with ST elevation irrespective of the site of infarction. Absolute benefits were largest among patients with anterior ST elevation, but there was still evidence of benefit among the somewhat lower-risk patients with inferior ST elevation. Fibrinolytic therapy was also significantly protective for patients with BBB, in whom the risk of death without treatment is substantial but where the likely site of infarction cannot be determined reliably. It remains unclear, however, whether there are any worthwhile benefits among patients presenting without ST elevation or BBB but with ST depression or other ECG abnormalities; the numbers of deaths among such patients were relatively small and data-dependent emphasis on the lack of a significant benefit in these subgroups may seriously mislead. Consequently, further trials of fibrinolytic therapy (and of other interventions) may still be warranted, especially among those with ST depression since their risk of death is high (but the pathophysiology may be different). Among patients with normal ECGs, however, it seems less likely that further study will demonstrate any net clinical benefit since these patients are usually at such low cardiac risk that the hazards associated with fibrinolytic therapy (notably, early stroke) may well not be outweighed by any reduction in cardiac deaths. Among patients with a normal or near-normal ECG, the few who are at real risk might be protected best by monitoring the ECG for several hours and

treating only if definite abnormalities develop that do indicate treatment with fibrinolytic therapy.

**Benefit among patients up to at least 12 h from onset**

For patients randomised within 6 h of the onset of symptoms, the earlier trials had left little doubt that fibrinolytic therapy reduced mortality. The present overview confirms this but also demonstrates that, although earlier treatment produces greater benefit, the decrease in the absolute benefit with increasing delay is not significantly steeper in the first few hours than in subsequent hours (figure 4). Each hour of delay recorded among patients with ST elevation or BBB was associated with a reduction in the benefit of about 1.6 deaths per 1000 patients. (The regression coefficient in figure 4 of 1.6 [SD 0.6] must have been diluted by the inaccuracies that are inevitable in the assessment of the duration of the delay.<sup>46</sup> Hence, the effect of actually treating an hour later is likely to be slightly greater, perhaps about 2 deaths per 1000. Direct assessment of this requires much larger randomised comparisons of earlier versus later treatment than have been conducted so far.)

Previously, the net effects on mortality among patients who present more than 6 h after pain onset were less clear, and the more recent trials (ISIS-3,<sup>7</sup> EMERAS,<sup>8</sup> and LATE<sup>9</sup>) were conducted to help address this question more reliably. The results in those trials are not significantly different from those of previous large studies,<sup>1,4</sup> and overall there is a highly significant mortality reduction ( $2p = 0.005$ ) among patients presenting within 7–12 h (figures 1 and 2), with somewhat greater benefit observed just among those patients presenting with ST elevation or BBB (corresponding to about 20 lives saved per 1000; figures 3 and 4). However, even after ISIS-3, EMERAS, and LATE, too few patients presenting after 12 h have been studied to determine directly whether the benefits outweigh the risks among any identifiable categories of such patients. The general pattern in figure 4 does, however, strongly suggest that worthwhile net benefits (perhaps about 10 lives saved per 1000) may await discovery among patients with ST elevation or BBB who present 13–18 h or so after onset.

Various explanations for the benefit of "late" fibrinolytic therapy have been offered.<sup>8,20,26,47,48</sup> This overview indicates that the gradual diminution in benefit with fibrinolytic therapy may be due to the association of later treatment with a larger excess of deaths on days 0–1, while the mortality reduction during days 2–35 appears to be surprisingly little affected by the time when patients are treated (figure 2, table 4). The causes of this "early hazard" are unclear (see below), but research should now be directed towards identifying these causes and preventing the hazard. If that could be achieved the benefits of fibrinolytic therapy might increase substantially, not just among patients presenting late where the early hazard is large but also among those presenting within 6 h, among whom, despite early thrombolysis, there seemed to be no net benefit on day 0 (2.1% deaths among fibrinolytic-allocated patients *vs* 1.9% among controls), perhaps reflecting an early benefit being opposed by an early hazard.

**Benefit among elderly patients**

The data do not provide evidence for withholding fibrinolytic therapy from patients on the basis of age (figure 5). The excess of deaths on days 0–1 increased with age but so did the reduction in deaths during days 2–35. This re-emphasises the need to reduce the early hazard if the full potential benefits of fibrinolytic therapy are to emerge for

Presentation features	Major bleeds during days 0–35		Excess per 1000 (SD)
	Fibrinolytic	Control	
<b>Entry ECG</b>			
BBB	13 (1.3%)	3 (0.3%)	10.0 (3.8)
ST elev, anterior	66 (1.1%)	19 (0.3%)	7.8 (1.4)
ST elev, inferior	88 (1.5%)	33 (0.6%)	9.1 (1.8)
ST elev, other	32 (1.0%)	13 (0.4%)	6.2 (2.2)
ST depression	19 (1.1%)	7 (0.4%)	6.8 (2.8)
Other abnormality	32 (0.8%)	3 (0.1%)	7.4 (1.5)
Normal	9 (0.9%)	2 (0.2%)	7.0 (3.2)
<b>Hours from onset</b>			
0–1	13 (1.0%)	3 (0.2%)	8.0 (3.1)
2–3	86 (1.4%)	27 (0.4%)	9.3 (1.7)
4–6	103 (1.5%)	38 (0.5%)	9.3 (1.6)
7–12	41 (0.8%)	8 (0.2%)	6.2 (1.3)
13–24	16 (0.5%)	4 (0.1%)	4.1 (1.5)
<b>Age (yr)</b>			
<55	47 (0.7%)	21 (0.3%)	4.1 (1.1)
55–64	106 (1.4%)	28 (0.4%)	10.0 (1.5)
65–74	81 (1.3%)	20 (0.3%)	9.7 (1.5)
75+	25 (1.1%)	11 (0.5%)	6.1 (2.6)
<b>Sex</b>			
Male	185 (1.1%)	53 (0.3%)	7.6 (0.9)
Female	74 (1.4%)	27 (0.5%)	8.6 (1.8)
<b>SBP (mm Hg)</b>			
<100	18 (1.7%)	1 (0.1%)	16.3 (4.4)
100–149	161 (1.1%)	44 (0.3%)	8.3 (1.0)
150–174	54 (0.9%)	27 (0.4%)	4.4 (1.4)
175+	26 (1.7%)	8 (0.5%)	11.2 (3.8)
<b>Heart rate (/min)</b>			
<80	121 (1.2%)	37 (0.4%)	8.4 (1.2)
80–99	87 (1.9%)	28 (0.6%)	13.0 (2.2)
100+	32 (1.3%)	15 (0.6%)	7.2 (3.0)
<b>Prior MI</b>			
Yes	51 (1.2%)	12 (0.3%)	8.8 (1.8)
No	208 (1.1%)	68 (0.4%)	7.6 (0.9)
<b>Diabetes</b>			
Yes	22 (1.3%)	6 (0.3%)	9.4 (3.2)
No	145 (1.0%)	46 (0.3%)	6.8 (0.9)
<b>All patients</b>	<b>325 (1.1%)</b>	<b>111 (0.4%)</b>	<b>7.3 (0.7)</b>

Unpublished results for the "uncertain" indication arm of ISIS-3 (42 vs 12 major bleeds) included in all subdivisions. Denominators and footnotes as in table 6.

**Table 7: Major bleeds during days 0–35 (or prior discharge) subdivided, where possible, by presentation features**

patients of all ages. The excess of early strokes was greater in old age than in middle age (with very small risks indeed among those under 55), but the excess of all strokes was not strongly related to age. Nor was the excess risk of major bleeds. Most of the elderly patients in the overview were in trials of SK, and directly randomised comparisons of different fibrinolytic regimens<sup>7,49,50</sup> have shown that tPA (and APSAC) regimens are associated with more strokes than is SK, and that these excesses increase with age. This may influence the choice of fibrinolytic regimen for older patients, but clearly age alone should no longer be considered a contraindication to fibrinolytic treatment.

*Benefit among patients with hypotension and/or tachycardia (and perhaps also in heart failure and shock)*

It has been suggested that primary coronary angioplasty should be used rather than fibrinolytic therapy in patients with cardiogenic shock, due to concerns that fibrinolytic therapy might be ineffective in such patients.<sup>25,51,52</sup> In GISSI-1, however, which is the only large trial where heart failure was systematically recorded, the proportional reduction in mortality observed among those patients with heart failure who were allocated SK was similar to that seen overall, suggesting a large absolute benefit. (Among the small number in GISSI-1 with cardiogenic shock there was little apparent effect, but the CI for the ratio of death among fibrinolytic-allocated patients with shock to that among controls was wide and consistent with a mortality reduction of 25–30%.) The other large trials did record hypotension at entry, which is quite closely correlated with heart failure or shock. (In GISSI-1, for example, about one-third of patients with SBP less than 100 mm Hg were in Killip class 3 or 4, while only 5% of those with higher BP were.) Figures 1 and 6 and table 4 indicate that the absolute reduction in mortality produced by fibrinolytic therapy is especially large among hypotensive patients. Similarly, patients with high heart rates at entry are at great risk of death, and among them fibrinolytic therapy also produced a larger than average mortality reduction. Patients with both SBP below 100 mm Hg and heart rate above 100/min were at very high risk, similar to that seen in Killip class 4 in GISSI-1. Among them there again appeared to be a larger than average absolute reduction in mortality (71 dead among 132 [53.8%] fibrinolytic-allocated *vs* 88 of 144 [61.1%] controls, corresponding to 73 lives saved per 1000), but these are small numbers and the difference is not significant. Overall, therefore, the large trials indicate that fibrinolytic therapy is especially effective among high-risk patients presenting with hypotension and/or tachycardia, many of whom would have been in heart failure or cardiogenic shock. Hypotension, heart failure, or even, perhaps, shock should not, therefore, be contraindications to fibrinolytic therapy or, indeed, other reperfusion strategies.

*Research implications*

This overview shows that fibrinolytic therapy reduces mortality in a wider range of patients than is generally treated at present, with net benefit for those presenting up to at least 12 h after symptom onset with ST elevation or BBB, irrespective of age, sex, BP, heart rate, or history of MI or diabetes. For any categories of patient where uncertainty remains about the benefits of treatment this should encourage further randomisation between fibrinolytic therapy and control. In particular, more reliable evidence is needed among patients presenting more than 12 h from pain onset, those with cardiogenic shock (in whom much larger direct comparisons of fibrinolytic

therapy versus primary angioplasty are also needed<sup>52</sup>), and those presenting without ST elevation or BBB but with other ECG abnormalities, such as ST depression, that imply a considerable risk of cardiac death.

We also need to know more about the causes of the excess deaths early after fibrinolytic therapy. (In many categories of patient this excess is too large to be due just to an excess of early stroke deaths and would appear to be due largely to cardiac causes.) This early hazard was observed in GISSI-1 during the first 6 h after randomisation and was largely attributed to electromechanical dissociation and heart failure.<sup>53</sup> The exact timing of deaths was not available in the other large trials, but review of deaths among the UK patients in ISIS-2 also suggested an excess of early deaths due to cardiac rupture or electromechanical dissociation, and this was supported by an excess in ISIS-2 as a whole of cardiac ruptures on days 0–1 (47 [0.5%] SK *vs* 29 [0.3%] control; personal communication). It has been suggested that this early hazard is due to various forms of reperfusion injury (such as arrhythmias, stunning, microvascular damage, necrosis, and myocardial haemorrhage<sup>54,55</sup>) and that an early excess of cardiac rupture increases with increasing delay to treatment<sup>56,57</sup> (though this has been disputed<sup>58</sup>). Further research may help to direct studies towards the most promising possibilities for avoiding this early hazard.

*Clinical implications*

The remaining uncertainties about fibrinolytic therapy should not be allowed to obscure the very clear evidence of overall benefit with fibrinolytic therapy in patients presenting with ST elevation or BBB up to at least 12 h from symptom onset. Among such patients, fibrinolytic therapy typically avoided about 20–30 deaths per 1000, and was associated with only about 4 extra strokes per 1000 (2 of these 4 strokes were associated with early death and so were already accounted for in the overall mortality reduction, 1 was non-fatal and moderately or severely disabling, and 1 was non-fatal with little or no disability). These survival benefits are increased further by concomitant antiplatelet therapy, such as low-dose aspirin, which also reduces the risks of reinfarction and of stroke (especially if it is not only given in the acute phase with the fibrinolytic agent but is also continued for some years afterwards).<sup>4,38</sup> The present overview indicates that fibrinolytic therapy is beneficial in a wide range of patients, especially those at high risk of cardiac death, many of whom are still not routinely treated because the benefits have not until now been shown convincingly to outweigh the risks.

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## Inactivated virosome hepatitis A vaccine

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### Summary

Immunopotentiating reconstituted influenza virosomes (IRIV) are efficient carrier systems for small virion particles such as hepatitis A virus (HAV). We evaluated immunogenicity and tolerability of an IRIV-HAV vaccine and the effectiveness of a booster by immunising 104 healthy HAV seronegative volunteers. A single dose was highly immunogenic, since 98% of volunteers had seroconverted after 2 weeks. Anti-HAV titres remained high, with 100% seroconversion rate 1 year later, when the booster was given. The vaccine was effective, with a 22-fold increase in geometric mean titres 1 month later. No serious adverse reactions were observed.

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### Introduction

Immune potentiation is used to make molecular vaccines sufficiently immunogenic, but remains one of the major problems in vaccinology. Aluminium precipitates are the main adjuvants used in human vaccines; their activity is partly related to inflammation created at the injection site, which can provoke side-reactions and local irritation. Unfortunately, such adjuvants are not sufficiently potent to enhance immune responsiveness to weak antigens. In addition, the use of aluminium-based adjuvants has been questioned because they can cause encephalopathies.<sup>1</sup> Other adjuvants, developed over the past few decades,<sup>2</sup> are not yet in use. A new type of adjuvant, immunopotentiating reconstituted influenza virosomes (IRIVs), are as safe, efficacious and easily prepared carrier systems for small virion particles, such as the hepatitis A virus (HAV).<sup>3</sup> IRIVs are spherical, unilamellar vesicles (diameter 150 nm)<sup>3</sup> that combine several components (haemagglutinin, neuraminidase, phospholipids) of influenza virus and adsorbed HAV particles. The essential feature of IRIVs is that as well as the HAV antigen their surface contains a fusion-inducing component, haemagglutinin, which facilitates antigen delivery to immunocompetent cells. Most adults have been exposed to influenza haemagglutinin, and so IRIVs recruit primed cells leading

to a rapid immune response. However, several studies have shown that enhanced immunogenicity by linking antigens to highly immunogenic carriers is not always effective.<sup>4,5</sup> Epitope suppression can occur when a host is immunised with an antigen conjugated to a vector to which the subject has been immunised. This carrier-induced epitopic suppression<sup>6</sup> would prevent a boosting effect for specific antigens, thus limiting the use of IRIVs as a vaccine delivery system. We challenged this hypothesis by giving IRIV-HAV as a single dose followed by a booster 12 months later. We then analysed hepatitis A antibody kinetics.

### Subjects and methods

After approval of the protocol by the ethics committee of the Hôpital Cantonal Universitaire de Genève, 119 healthy volunteers (medical students and health professionals) gave their written informed consent to participate. Our vaccine is derived from the RG-SB HAV strain purified from MRC-5 human diploid cell cultures, and inactivated in formalin (Swiss Serum and Vaccine Institute).<sup>3</sup> One dose of vaccine (0.5 ml) contains 500 RIA (Radio Immuno Assay) units of HAV antigens.

The vaccine was injected into the deltoid muscle. Each volunteer was asked to record all adverse reactions on a report sheet for 3 days after immunisation. Serum samples to assay HAV antibodies, liver enzymes, and routine biological tests were taken a week before immunisation and 14 days afterwards. HAV antibodies were also measured after 28 days, and 8, 12, and 13 months. A booster dose was given 12 months after the initial injection. Adverse reactions were recorded during the 4 days after second vaccination. HAV antibody titres were measured by sandwich enzyme linked immunosorbent assay (ELISA 1), with microtitre plates coated with hepatitis A RG-SB.<sup>7</sup> This test, called ELISA 1 in the text, is similar to the ELISA test used to evaluate the immunogenicity of the commercially available HAV vaccine.<sup>12</sup> Total antibody content was also determined with an automated sandwich ELISA test kit (ELISA 2) (Boehringer Mannheim) with antibody concentrations expressed as mIU/mL. For both tests, sera with titres below 20 mIU/mL were regarded as negative.

Statistical significance between geometric mean titres (GMT) was found with a paired *t* test; the correlation and *t* test were calculated from log titres. Differences between seroconversion rates were analysed by chi squared tests.

### Results

5 volunteers were excluded from the study (3 for personal reasons, 1 because of a pre-immunisation increase of liver enzymes, and 1 because of concomitant Epstein-Barr virus infection). Of the 114 remaining volunteers, 104 (91%) were seronegative (average age 23.6 [SD 5.2] years). There were

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## Fibrinolysis and MI

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### 'fibrinolytic therapy is beneficial in a much wider range of patients than currently receive such treatment routinely'

There can be little doubt that for most patients fibrinolysis reduces mortality after acute myocardial infarction (AMI). However, some subjects with AMI are not given fibrinolytic therapy because they belong to patient groups (eg, elderly, late presentation, cardiogenic shock) in whom the risk of this treatment is believed to outweigh the benefit. The Fibrinolytic Therapy Trialists (FTT) Collaborative Group has tried to resolve doubts about who should receive fibrinolysis with a meta-analysis of nine large randomised controlled trials (58 600 patients) of the treatment. Although fibrinolysis was associated with excess mortality during days 0–1, this "hazard" was outweighed by substantial benefit during days 2–35. Patients with bundle-branch block and ST elevation (45 000) showed significant reduction in mortality with fibrinolysis even if they presented as long as 12 h after the acute event (the benefit remains uncertain for the remaining patients because of small numbers). The collaborators conclude that age, hypotension, heart failure, and, perhaps, shock should not be contraindications to fibrinolytic therapy.

## New hepatitis A virus vaccine

page 322

### 'The inactivated IRIV-HAV vaccine appears safe and well tolerated. . . . reactions were mild and restricted to the first 24 hours'

One of the problems in development of a new vaccine is how to establish

enough immunogenicity for the vaccine to be successful. Loutan and colleagues used a new immune-stimulating technique to develop a vaccine for hepatitis A. They linked an epitope for the hepatitis A virus (HAV) to an adjuvant made from immunopotentiating reconstituted influenza virosomes (IRIVs). The unique feature of the IRIV-HAV vaccine is that the surface also contains haemagglutinin. The theory is that most adults have been exposed to influenza haemagglutinin and so IRIVs specifically stimulate immune cells and allow HAV to be delivered directly to them. Loutan et al claim that their vaccine is as good as, if not better than, a recently licensed hepatitis A vaccine, and will be of benefit to at-risk people such as travellers.

## Fat offspring of cold hearts

page 324

### 'parental neglect during childhood predicts a greatly increased risk of obesity in young adulthood'

Although the relations are complex, it seems clear that obesity in childhood has a genetic component. However, the strongest association reported so far for obesity in young adult life is with the support given to the child by the parents. Lissau and Sørensen report that children who were neglected by their parents were at least seven times more likely to become obese adults than were children whose relationship with their parents was "harmonious". Parental support was judged by the children's school teachers. The association was stronger than those found previously for other psychosocial risk factors—eg, socioeconomic status and school performance—or even for the genetic effect.

## Knocking Ph<sup>+</sup> ALL aside

page 331

### 'ablative therapy followed by bone marrow rescue is effective against Ph<sup>+</sup> ALL'

The outlook for children with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph<sup>+</sup> ALL) who do not have a sibling donor for a bone marrow transplant is poor. Aggressive induction/consolidation chemotherapy followed by a rotation of pairs of non-cross-resistant drugs in combination led to leukaemia-free survival in 4 of 11 Ph<sup>+</sup> ALL patients for, to date, 6–8 years. The investigators, from Memphis, USA, emphasise that the choice of cytotoxics to be used intensively is uncertain. However, their aggressive approach allows time for a search for an acceptable marrow donor.

## Vitamin K in the newborn

page 352

### 'the maximum number of expected cases [of HND] would have been 5. This contrasts with 10 documented cases, who had all received at least two oral doses of 1 mg vitamin K<sub>1</sub>'

The use of parenteral vitamin K to prevent haemorrhagic disease of the newborn (HND) is controversial, and has been replaced by oral administration in the UK and Germany, but not in the USA. However, von Kries and Göbel from Dusseldorf, Germany, report double the expected number of cases of late HND in babies given an oral product, with intracerebral haemorrhage in about three-quarters and evidence of cholestasis in half the affected babies. These workers speculate that use of a new micellar preparation might improve vitamin K absorption, and thus the efficacy of oral prophylaxis.