

cholesterol concentration does not cause depression, accidents, or suicide.

As Sherlock Holmes observed, one can have too much evidence: "What was vital was overlaid and hidden by what was irrelevant."¹⁵ The randomised trial data are vital, but, given the trial evidence, observational data that are unable to distinguish cause from consequence have become irrelevant. It is all too familiar to find one vital piece of evidence that resolves an issue being drowned by much other data that serve only to obfuscate, leaving an overall impression of uncertainty. We should, like Holmes, "from all the facts presented to us, pick just those which we deem to be essential."

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Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials

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Abstract

Objectives—Most randomised trials of anticoagulant therapy for suspected acute myocardial infarction have been small and, in some, aspirin and fibrinolytic therapy were not used routinely. A systematic overview (meta-analysis) of their results is needed, in particular to assess the clinical effects of adding heparin to aspirin.

Design—Computer aided searches, scrutiny of reference lists, and inquiry of investigators and companies were used to identify potentially eligible studies. On central review, 26 studies were found to involve unconfounded randomised comparisons of anticoagulant therapy versus control in suspected acute myocardial infarction. Additional information on study design and outcome was sought by correspondence with study investigators.

Subjects—Patients with suspected acute myocardial infarction.

Interventions—No routine aspirin was used among about 5000 patients in 21 trials (including half of one small trial) that assessed heparin alone or heparin plus oral anticoagulants, and aspirin was used routinely among 68 000 patients in six trials (including the other half of one small trial) that assessed the addition of intravenous or high dose subcutaneous heparin.

Main outcome measurements—Death, reinfarction, stroke, pulmonary embolism, and major bleeds (average follow up of about 10 days).

Results—In the absence of aspirin, anticoagulant therapy reduced mortality by 25% (SD 8%; 95% confidence interval 10% to 38%; 2P = 0.002), representing 35 (11) fewer deaths per 1000. There were also 10 (4) fewer strokes per 1000 (2P = 0.01), 19 (5) fewer pulmonary emboli per 1000 (2P < 0.001), and non-significantly fewer reinfarctions, with about 13 (5) extra major bleeds per 1000 (2P = 0.01). Similar sized effects were seen with the different anticoagulant regimens studied. In the presence of aspirin, however, heparin reduced mortality by only 6% (SD 3%; 0% to 10%; 2P = 0.03), representing just 5 (2) fewer deaths per 1000. There were 3 (1.3) fewer reinfarctions per

1000 (2P = 0.04) and 1 (0.5) fewer pulmonary emboli per 1000 (2P = 0.01), but there was a small non-significant excess of stroke and a definite excess of 3 (1) major bleeds per 1000 (2P < 0.0001).

Conclusions—The clinical evidence from randomised trials does not justify the routine addition of either intravenous or subcutaneous heparin to aspirin in the treatment of acute myocardial infarction (irrespective of whether any type of fibrinolytic therapy is used).

Introduction

In the acute phase of myocardial infarction, antiplatelet therapy with agents such as aspirin has been shown to reduce the likelihood of death, reinfarction, and stroke and also to produce little increase in serious bleeding, even in patients who have received fibrinolytic treatment.¹⁻³ The second international study of infarct survival (ISIS-2) also showed that the combination of aspirin plus heparin was substantially (and highly significantly) more effective than heparin alone,^{1,3} but it did not address the question of whether aspirin plus heparin was more effective than aspirin alone. Consequently, although routine use of aspirin can be recommended for virtually all patients with suspected acute myocardial infarction (or unstable angina),^{1,2} it is not known whether other antithrombotic regimens might be more effective.

Since the 1970s, 26 randomised trials⁴⁻³⁰ in acute myocardial infarction have assessed the effects of anticoagulant therapy—heparin or, in some trials, heparin plus oral anticoagulants. Most were small studies conducted at a time when antiplatelet and fibrinolytic therapies were not used routinely. A few of the recent studies, however, were large trials in which all patients were to receive aspirin and most patients were to receive fibrinolytic therapy.²⁸⁻³⁰ The present paper provides a systematic overview^{31,32} of the results for death and other major clinical events from all randomised trials of early anticoagulation in patients with suspected acute myocardial infarction, updating the results of earlier overviews³³⁻³⁵ and considering separately the trials that assessed the effects of adding heparin to aspirin.

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Methods

SELECTION OF TRIALS AND ACQUISITION OF DATA

The intent was to obtain and analyse complete data on early deaths, reinfarctions, strokes, pulmonary emboli, and clinically important episodes of bleeding from all unconfounded properly randomised trials of anticoagulant therapy in the acute phase of suspected myocardial infarction. The literature was scanned by formal, computer aided searches; by scrutiny of reference lists; and by inquiry of other investigators and of pharmaceutical companies. Studies in which investigators could determine the treatment assignment before deciding whether to enter patients (for example, studies in which assignment was by alternation or those with retrospectively determined "historical" controls³⁶⁻⁴³) were not to be included, even if they were described as randomised, since such foreknowledge may introduce systematic differences between the types of patient

assigned to each treatment. Randomised trials were to be included only if they were "unconfounded"—that is, if they compared the effects of some standard treatment with the same standard treatment plus anticoagulant therapy. Trials that compared one anticoagulant regimen with another or that deliberately confounded the effects of anticoagulant therapy by some other intervention⁴⁴⁻⁵⁵ were to be excluded from the main analyses, although the largest^{54, 55} is considered in the Discussion. Some of the data thus collected did not include some randomised individuals or some relevant outcomes, and additional information was provided by investigators (see below).

STATISTICAL METHODS

The principles that underlie an overview of randomised trials and the statistical methods are described in detail elsewhere.^{2, 31, 32, 56} Within each sepa-

Table 1—Suspected acute myocardial infarction: summary design of all unconfounded randomised controlled trials of anticoagulant therapy

Trial or stratum	Year reported	Timing of entry	Heparin regimen studied			Routine therapy		No of subjects					
			Initial intravenous bolus (IU) or delay	IU/day (No of daily doses)	Duration (days) (+ oral anticoagulant)	Route	Anti-platelet	Fibrinolytic	Randomised	With mortality follow up*	Follow up (days)	Method of treatment allocation	Blinding
Low dose heparin (10 000-15 000 IU/day: mean 12 000) v no antithrombotic (807 randomised)													
Handley ⁴	1972	<4 h Adm	5000	15 000 (2)	7	SC	—	—	70	70	14	Envelopes	Open
Gallus <i>et al</i> ⁵	1973	<18 h Adm	—	15 000 (3)	Until mobile	SC	—	—	27	— [27]	11	Envelopes	Open
Warlow <i>et al</i> ⁶	1973	<12 h Onset	—	10 000 (2)	10	SC	—	—	146	146 [127]	10	Ampoules	Double
Emerson and Marks ⁷	1977	Not stated	5000	15 000 (2)	14	SC	—	—	81	81	14	Envelopes	Open
Cade <i>et al</i> ⁸	1982	Not stated	—	10 000 (2)	10	SC	—	—	93	— [93]	10	Ampoules	Double
Remvig <i>et al</i> ⁹	1983	<24 h Onset	—	10 000 (2)	10	SC	—	—	287	287	16	Ampoules	Double
Zawilska <i>et al</i> ¹⁰	1989	6-24 h Onset	—	10 000 (2)	14-21	SC	—	—	103	103	Hosp	Not stated	Open
High dose heparin (≥20 000 IU/day: mean 25 000) v no antithrombotic (1678 randomised)													
Carleton <i>et al</i> ¹¹	1960	<48 h Onset	—	35 000-100 000 (4)§	28	IV	—	—	125	125 [81]	28	Envelopes	Open
Steffensen ¹²	1969	Not stated	—	20 000 (2) + 10 000 (1)	16+8	SC	—	—	263	212	24	Ampoules	Double
Handley <i>et al</i> ¹³	1972	<24 h Onset	5000	40 000	14	IV	—	—	60	60	14	Envelopes	Open
Gueret <i>et al</i> ¹⁴	1986	<12 h onset	—	~24 000	4-7†	IV	—	—	93	— [90]	—	Not stated	Open
½ ISIS-2 pilot ¹⁵	1987	<24 h Onset	Delay 12 h	24 000	2	IV	—	67% SK	306	306	9	Telephone	Open
Diaz and Torres ¹⁶	1988	<12 h Onset	10 000	~24 000	Not stated	IV	—	—	25	20	Hosp	Not stated	Open
SCATI ¹⁷	1989	<24 h Onset	2000	25 000 (2)	Hosp	SC	—	~60% SK	711	711	Hosp	Telephone	Open
Bleich <i>et al</i> ¹⁸	1990	<6 h Onset	5000	~24 000	2-3	IV	—	tPA	95	95	Hosp	Envelopes	Open
High dose heparin (≥20 000 IU/day: mean 29 000) plus oral anticoagulants v no antithrombotic (2592 randomised)													
Drapkin and Merskey ¹⁹	1972	<24 Adm	5000	30 000 (3)	2 (+ Hosp)	SC	—	—	1286	1136	Hosp	Envelopes	Single
VA Coop ²⁰	1973	<72 h Onset	—	~20 000-30 000 (2-3)	Varied (+ 28)	SC	—	—	1037	1026 [999]	28	Envelopes	Single
Wray <i>et al</i> ²¹	1973	Not stated	—	40 000	2 (+ Hosp)	IV	—	—	100	92	Hosp	Not stated	Open
Pitt <i>et al</i> ²²	1980	<48 h Onset	5000	~40 000	2 (+ Unknown)	IV	—	—	115‡	72+36‡	7-10	Envelopes	Single
Nordrehaug <i>et al</i> ²³	1985	<12 h Onset	150/kg	~400/kg	Varied (+ 10)	IV	—	—	53	53	10	Envelopes	Double
Arvan and Boscha ²⁴	1987	<12 h Onset	5000	~24 000-72 000	Varied (+ Hosp)	IV	—	—	37	34	14	Envelopes	Open
High dose heparin (24 000-25 000 IU/day) plus aspirin v aspirin alone (68 090 randomised)													
½ ISIS-2 pilot ¹⁵	1987	<24 h Onset	Delay 12 h	24 000	2	IV	Aspirin	67% SK	313	313	Hosp	Telephone	Open
ECSG-6 ²⁵	1992	<6 h Onset	5000	24 000	2-5	IV	Aspirin	tPA	652	644	Hosp	Telephone	Double
OSIRIS ²⁶	1992	<6 h Onset	10 000	24 000	1	IV	Aspirin	SK	128	128	Hosp	Not stated	Double
DUCCS-1 ²⁷	1994	<12 h Onset	Delay 4 h	360/kg	4	IV	Aspirin	AP	250	250	14	Telephone	Open
GISSI-2 ^{28, 29}	1990	<6 h Onset	Delay 12 h	25 000 (2)	Hosp	SC	Aspirin	SK/tPA	20 891	20 748 [12 381]	Hosp	Telephone	Open
ISIS-3 ³⁰	1992	<24 h Onset	Delay 4 h	25 000 (2)	7	SC	Aspirin	90% SK /tPA/AP	45 856	45 856 [45 269]	Hosp	Telephone	Open

SC = subcutaneous; IV = intravenous; Adm = from admission; Hosp = until discharge; SK = streptokinase; tPA = tissue plasminogen activator; AP = anisoylated plasminogen streptokinase activator complex (anistreplase; APSAC).

*Square brackets indicate denominators for non-fatal events, except GISSI-2 where these are denominators only for pulmonary embolism.

†In Gueret *et al*, subcutaneous heparin was given for a further 20-50 days.

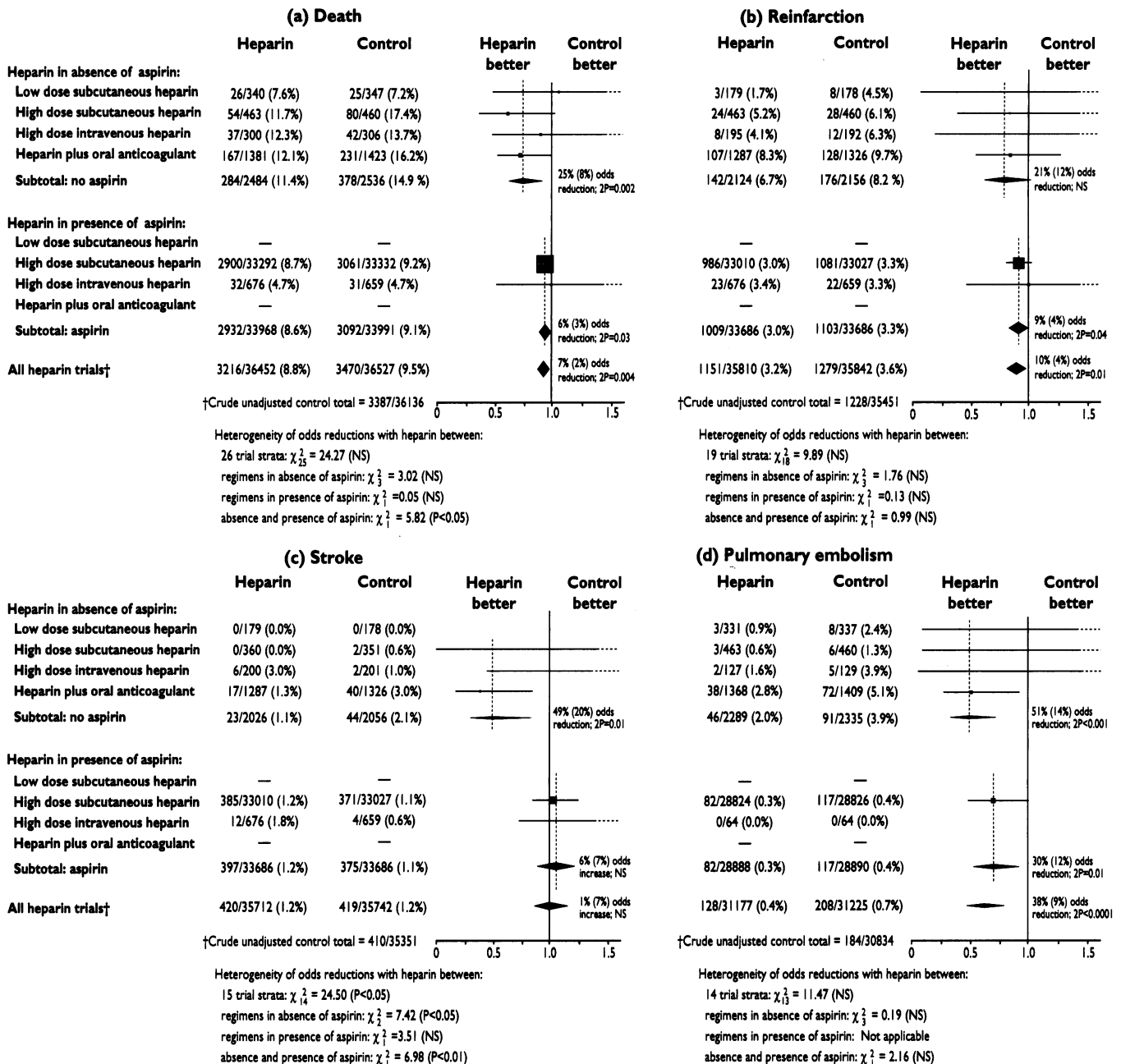
‡In Pitt *et al*, 7 patients were excluded after randomisation (3 deaths but no deep vein thrombosis or pulmonary embolism; treatment group not known), while 36 patients with follow up were allocated only 500 IU heparin for 2 days and do not contribute to the present analyses.

§In Carleton *et al* a high initial dose was specified with subsequent titration to aim for a coagulation time between 2 and 3 times control.

rate trial (or separate trial stratum) the number of events observed among patients randomised to the study treatment was compared with the average experience of both the treatment and the control groups. This comparison yields the statistic "observed minus expected" and its variance. To obtain an appropriately stratified combination of the information from several different trials, the separate observed minus expected results (one from each trial) are simply

added together. Likewise, the variance of this total is simply the sum of the separate variances. From these two totals an "odds ratio" can be calculated, which provides an appropriately weighted average of the apparent effects of treatment in these trials.^{2 56} A convenient way of describing the statistical reliability of such an odds ratio is to give its 95% confidence interval—or, where many comparisons are being made, its 99% confidence interval. Alternatively, the odds reduction can be

Effects of heparin in the absence and presence of aspirin



In most trials patients were allocated roughly evenly between treatment groups, but in some trials (see table 2) more patients were deliberately allocated to active treatment. To allow direct comparison between the percentages of patients in each group who had an event, adjusted totals have been calculated after conversion of any unevenly randomised trials to even ones by counting their control groups more than once. Statistical calculations are, however, based on the actual numbers from individual trials.

Solid squares represent stratified odds ratios (heparin:control) for combinations of

individual trials of particular anticoagulant regimens. Sizes of squares are proportional to the amount of "information" contributed; horizontal lines denote 99% confidence intervals.^{2 56} Diamonds represent stratified overviews (and 95% confidence intervals) of the results for all trials conducted in the absence and in the presence of routine aspirin; the difference in odds is given to the right of the solid vertical line. Black squares or diamonds to the left of the solid vertical line indicate additional benefit with heparin, but the result is significant ($2P < 0.01$ for horizontal lines and $2P < 0.05$ for diamonds) only when the entire confidence interval is to the left of the line.

described, along with its standard deviation: an odds ratio of 0.75, for example, would correspond to a 25% reduction in the odds of an event. From the odds reduction and its standard deviation the statistical significance can be calculated, and the abbreviation NS (not significant) is used to denote a two sided P value (2P) greater than 0.05.

Such 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 general direction. In principle, standard χ^2 tests of the heterogeneity of the treatment effects in different trials might be of interest. In practice, however, such tests are of limited value, partly because they are so insensitive to any real differences that may exist but chiefly because some heterogeneity is almost certain to exist no matter what a standard χ^2 test for heterogeneity may indicate.⁵⁶ A somewhat more sensitive measure of heterogeneity may be obtained by comparing groups of trials, but even this may be of limited value.

The odds reduction describes the proportional reduction in risk, which may be more widely generalisable to different medical circumstances than is the absolute reduction in risk. But in deciding whether the benefits of treatment outweigh its hazards, absolute differences in risk may be more relevant. A crude but simple method to describe the absolute difference in outcome is to add up the results in the treatment groups, add up those in the control groups, and then to compare the two grand totals. So, for example, an absolute risk reduction of 34 (11) per 1000 would indicate 34 fewer events among every 1000 patients allocated the treatment, with the standard deviation for this estimate being 11. (If any trial had deliberately allocated treatment unevenly—for example, two thirds of subjects to treatment and one third to the control group—then it was first “adjusted” to an evenly randomised comparison by counting the control group more than once.) This crude comparison, in conjunction with the properly stratified odds ratios described above, can provide a useful description of the effects of treatment.

Results

DESCRIPTION OF TRIALS IDENTIFIED

This overview includes data from 26 randomised trials involving a total of about 73 000 patients with suspected acute myocardial infarction—21 000 in GISSI-2 (which, throughout this report, includes both the Italian part²⁸ and the international extension of GISSI-2²⁹), 46 000 in ISIS-3,³⁰ and 6000 in various smaller trials.⁴⁻²⁷ The treatment regimens can be divided into four groups (table 1).

“Low dose” heparin in the absence of other antithrombotic therapy—Seven small trials among a total of fewer than 1000 patients studied the effects of daily heparin doses of 10 000 to 15 000 IU (weighted average 12 000 IU) given subcutaneously. Only two trials used an initial intravenous bolus dose.

“High dose” heparin in the absence of other antithrombotic therapy—Eight trials (one being half of the ISIS-2 pilot study¹⁵) among a total of fewer than 2000 patients studied the effects of daily heparin doses of 20 000 IU or more (weighted average 25 000 IU) administered either subcutaneously or by intravenous infusion.

“High dose” heparin plus oral anticoagulants in the absence of other antithrombotic therapy—Six trials among a total of fewer than 3000 patients studied the effects of daily heparin doses of at least 20 000 IU (weighted average 29 000 IU) given either subcutaneously or intravenously, plus an oral anticoagulant.

“High dose” heparin in the presence of aspirin—In GISSI-2 (21 000 patients), in ISIS-3 (46 000 patients), and in about 1000 patients from four smaller trials (one being the other half of the ISIS-2 pilot study) the com-

parison was of subcutaneous or intravenous high dose heparin (24 000-25 000 IU/day) plus aspirin versus aspirin alone.

Of the 26 trials, 10 (including 4000 patients) were double blind or single blind, and 16 (including 69 000 patients) were open. The average delay between the onset of symptoms and the administration of heparin in the trials is likely to have been more than 10 hours, for randomisation will itself have taken place several hours after the onset of symptoms, and in some of the largest trials heparin was not to be started for several hours after randomisation. The anticoagulant treatments in the trials were to be continued for an average of about eight days. Follow up of non-fatal events and of death was for at least the scheduled treatment period in all trials, and the average follow up was about 10 days.

HEPARIN IN THE ABSENCE OF ASPIRIN

For the 21 trials assessing anticoagulant therapy in the absence of aspirin, information was available on mortality from about 90% of all randomised patients and on reinfarction, stroke, and pulmonary embolism from about 75-85%. Several of the trials from which information is missing were designed primarily to assess the effects of low dose subcutaneous heparin on deep vein thrombosis, so the incompleteness may be due more to the missing outcomes not having been looked for (which would not bias an overview) than to data dependent unavailability of results for these outcomes (which could).

Death—Overall in the absence of aspirin, there were 284 (11.4%) deaths during an average of 10 days of follow up among 2484 patients allocated to anticoagulant treatment compared with 378 (14.9%) deaths among 2536 adjusted controls (fig 1(a): upper part). This 25% (SD 8%) proportional reduction in mortality is significant (95% confidence interval 10% to 38%; 2P = 0.002) and corresponded to avoidance of about 35 (11) deaths per 1000 patients allocated to anticoagulant therapy in the absence of aspirin. No apparent effect was found in the trials of low dose subcutaneous heparin, but few deaths were recorded. Among the trials of high dose heparin there was no significant difference between the effects observed with high dose subcutaneous heparin alone, high dose intravenous heparin alone, or high dose heparin plus oral anticoagulants. (The χ^2 test for heterogeneity between these three groups of trials was $\chi^2 = 1.49$; NS.)

Reinfarction—In the absence of aspirin, there was a non-significantly lower incidence of reinfarction among patients allocated anticoagulant therapy than among those not (142/2124 (6.7%) v 176/2156 (8.2%); 2P = 0.08). The 95% confidence interval for this apparent reduction of about one fifth in the odds of reinfarction was wide, ranging from about zero to nearly one half (fig 1(b): upper part). No significant heterogeneity was observed between the results with different anticoagulant regimens ($\chi^2 = 1.76$ or, if the trials of low dose heparin are excluded, $\chi^2 = 0.32$; both NS).

Stroke—In the absence of aspirin, the incidence of stroke was significantly lower among patients allocated anticoagulant therapy than among those not (23/2026 (1.1%) v 44/2056 (2.1%); 2P = 0.01). This approximate halving in the odds of stroke, with 95% confidence interval from about one sixth to about two thirds, corresponded to avoidance of strokes in about 10 (4) patients per 1000 treated (fig 1(c): upper part). No information on strokes was available from five of the low dose heparin trials, and no strokes were recorded in the two other low dose trials. Between the three other groups of trials there was marginally significant heterogeneity of the proportional effect ($\chi^2 = 7.42$; P < 0.05).

Venous thromboembolism—Pulmonary embolism can be difficult to diagnose clinically without special

Table 2—Suspected acute myocardial infarction: results of all unconfounded randomised trials of anticoagulant therapy

Trial or stratum	Number randomised with follow up*		Death		Reinfarction		Stroke		Pulmonary embolism		Deep vein thrombosis†		Major bleed**		
	Heparin	Control‡	Heparin	Control‡	Heparin	Control‡	Heparin	Control‡	Heparin	Control‡	Heparin	Control‡	Heparin	Control‡	
Low dose heparin (10 000-20 000 IU/day: mean 12 000) v no antithrombotic															
Handley ⁴	35	35	3	0	0	0	0	0	1	1	6	7	0	0	
Gallus <i>et al</i> ⁵	14	13		NA	NA	NA	NA	NA	NA	NA	1	2	0	0	
Warlow <i>et al</i> ⁶	73	73	6	5	NA	NA	NA	NA	0	1	2	11	0	0	
Emerson and Marks ⁷	38	43	0	1	NA	NA	NA	NA	0	3	2	14		NA	
Cade <i>et al</i> ⁸	63	2 x 30		NA	NA	NA	NA	NA	NA	NA	2	2 x 3		NA	
Remvig <i>et al</i> ⁹	144	143	12	13	3	8	0	0	2	2	3	8	0	0	
Zawilska <i>et al</i> ¹⁰	50	53	5	6	NA	NA	NA	NA	0	1	2	10	0	0	
High dose heparin (≥20 000 IU/day: mean 25 000) v no antithrombotic															
Carleton <i>et al</i> ¹¹	60	65	13	18	4	4		NA	2	3		NA	9	5	
Steffensen ¹²	103	109	33	45	4	4		NA	2	6		NA	0	0	
Handley <i>et al</i> ¹³	30	30	2	3		NA		NA	0	2	0	7	1	0	
Gueret <i>et al</i> ¹⁴	46	44		NA	NA	NA		NA	NA	NA		NA		NA	
½ ISIS-2 pilot¹⁵															
Fibrinolytic	104	100	7	11	3	6	1	1		NA		NA		1	0
No fibrinolytic	50	52	9	5	1	2	3	1		NA		NA		0	0
Diaz and Torres ¹⁶	10	10	0	0		NA		NA	0	0		NA			NA
SCAT¹⁷															
Fibrinolytic	218	215	10	19	18	21						NA			
No fibrinolytic	142	136	11	16	2	3		0	2		1	0		4	2
Bleich <i>et al</i> ¹⁸	46	49	6	5		NA		2	0	0	0	0		1	1
High dose heparin (≥20 000 IU/day: mean 29 000) plus oral anticoagulant v no antithrombotic															
Drapkin and Merskey ¹⁹	745	2 x 391	111	2 x 83	88	2 x 51	13	2 x 9	28	2 x 24		NA			NA
VA Coop ²⁰	513	513	49	58	17	24	4	19	10	24		NA		13	6
Wray <i>et al</i> ²¹	46	46	2	3		NA		NA	0	0	3	10		0	0
Pitt <i>et al</i> ²²	35	37	0	0		NA		NA	0	0	4	11			NA
Nordrehaug <i>et al</i> ²³	26	27	4	2	1	1	0	1	0	0		NA		0	0
Arvan and Boscha ²⁴	16	18	1	2	1	1	0	2	0	0		NA		2	0
High dose heparin (24 000-25 000 IU/day) plus aspirin v aspirin alone															
½ ISIS-2 pilot¹⁵															
Fibrinolytic	106	103	8	6	1	5	0	0		NA		NA		0	1
No fibrinolytic	54	50	2	3	1	2	1	0		NA		NA		0	0
ECSG-6 ²⁵	324	320	9	11	10	10	4	1		NA		NA		3	4‡
OSIRIS ²⁶	64	64	1	3	2	1	3	2	0	0		NA		6	4
DUCCS-1 ²⁷	128	122	12	8	9	4	4	1		NA		NA		14	7
GISSI-2 ^{28, 29}	10 361	10 407	884	932	282	303	115	119	8§	16§		NA		103	57
ISIS-3³⁰															
Fibrinolytic	20 656	20 643	1875	1954	645	707	261	240	70	88		NA		209	156
No fibrinolytic	2 275	2 282	141	175	59	71	9	12	4	13		NA		7	5

*See table 1 for total numbers with follow up for mortality or other outcome measures.

‡2 x = control groups counted twice in adjusted totals (but not in statistical calculations) to balance larger treatment groups in studies with 2:1 allocation ratio.

‡For ESCG-6, information was available on major bleeds only until coronary angiography, when study treatment was to stop.

§Pulmonary embolism available only for Italian part of GISSI-2 and not for international extension (see table 1).

¶Includes only deep vein thrombosis detected by radiolabelled fibrinogen or venogram.

**Requiring transfusion, for example.

investigations.⁵⁷ In most trials these were not performed routinely, so pulmonary emboli may well have been missed or misdiagnosed. But in any one trial this should apply approximately equally to both the treatment groups (especially in blinded studies). Hence, the chief effects of such diagnostic uncertainties are to make it more difficult to detect any real benefits^{58, 59} and to underestimate the absolute importance of any benefits that are detected. These effects would not, however, invalidate any clearly demonstrated proportional risk reductions from an appropriately conducted overview, even if this included trials with very different diagnostic methods.

Overall, in the absence of aspirin, a highly significantly lower incidence of pulmonary embolism was recorded among patients allocated anticoagulant therapy (46/2289 (2.0%) v 91/2335 (3.9%); 2P<0.001). This approximate halving, with 95% confidence interval from about one third to about two thirds, corresponded in these trials to a reduction of about 19 (5) per 1000 in the number of such emboli detected (fig 1(d): upper part). The proportional reductions seemed to be similar with each of the different types of anticoagulant regimen studied ($\chi^2_3 = 0.19$; NS). In principle the ascertainment of pulmonary embolism might have been influenced by knowledge of the allocated treatment group in open studies, but in practice a simi-

lar reduction was observed when such studies were excluded (50% (15%) reduction; 2P = 0.001). This reduction in pulmonary embolism is consistent with the very clear reduction in deep vein thrombosis (71% (12%); 2P<0.0001) in those of the trials that prospectively sought to identify venous thrombosis by radiolabelled fibrinogen scanning or venography (table 2). Similar sized reductions in deep vein thrombosis were indicated by the trials of low dose subcutaneous heparin (69% (15%); 2P<0.0001) and by those of high dose heparin with or without oral anticoagulants (75% (20%); 2P = 0.0001).

Major bleeding—The reporting of bleeding was generally incomplete, and the definitions and incidence of "major" bleeds (for example, those that required transfusion) differed substantially in the different trials. There was little evidence of any increased risk of major bleeding with low dose subcutaneous heparin (table 2). In the trials of high dose heparin there was reasonably consistent evidence of a doubling in the absolute risk of major non-cerebral bleeds (31/1322 (2.3%) v 14/1321 (1.1%); 2P = 0.01). Similar sized proportional increases were seen with the three different types of high dose anticoagulant regimen that were studied ($\chi^2_2 = 0.08$; NS). This doubling corresponded to an absolute excess of about 13 (5) major bleeds reported per 1000 patients treated with high dose heparin.

As aspirin is increasingly widely used for the treatment of acute myocardial infarction, the most relevant heparin comparisons now are of heparin plus aspirin versus aspirin alone. Of such comparisons, four small trials among a total of only about 1000 patients assessed high dose intravenous heparin and two very large trials (GISSI-2 and ISIS-3) assessed high dose subcutaneous heparin in a total of about 67 000 patients. Data were available on mortality, reinfarction, stroke, and major bleeding from 98-100% of randomised patients. Deep vein thrombosis was not sought by an objective method in any of these trials, and information on pulmonary embolism was sought from only 85% of the patients.

Death—There were 2932 (8.6%) deaths among 33 968 patients allocated heparin plus aspirin compared with 3092 (9.1%) among 33 991 allocated aspirin alone (fig 1(a); lower part). Despite these large numbers, this 6% (3%) proportional reduction in mortality is only just conventionally significant (0% to 10%; $2P = 0.03$) and corresponded to avoidance of about 5 (2) deaths per 1000 patients allocated heparin in addition to aspirin. This proportional reduction seems smaller than the reduction seen in the absence of aspirin ($\chi^2_1 = 5.82$; $P < 0.05$). GISSI-2 and ISIS-3 are the chief contributors to this overview, with a total of 8.7% dead among those allocated high dose subcutaneous heparin plus aspirin versus 9.2% dead among those allocated aspirin alone. No apparent effect was found in the trials of adding high dose intravenous heparin to aspirin, but very few deaths were recorded in those trials (32/676 (4.7%) intravenous heparin plus aspirin *v* 31/659 (4.7%) aspirin alone).

Reinfarction—The incidence of reinfarction with heparin plus aspirin was slightly lower than with aspirin alone (1009/33 686 (3.0%) *v* 1103/33 686 (3.3%); $2P = 0.04$). This reduction of about one tenth, with 95% confidence interval ranging from about zero to about one fifth, corresponded to avoidance of reinfarction in 3 (1.3) per 1000 patients (fig 1(b); lower part). As for mortality, no reduction was apparent in the small trials of high dose intravenous heparin (23/676 (3.4%) intravenous heparin plus aspirin *v* 22/659 (3.3%) aspirin alone), and all of the apparent effect was in the large trials of adding high dose subcutaneous heparin to aspirin. The number of reinfarctions in these intravenous heparin trials was small, however, and there was no significant heterogeneity of effect between the trials of subcutaneous and of intravenous heparin in the presence of aspirin ($\chi^2_1 = 0.13$, NS).

Stroke—In the absence of aspirin, anticoagulant therapy reduced stroke (fig 1(c); upper part). But aspirin itself also halves the risk of stroke,^{1,3} and the addition of heparin to aspirin seemed to produce no further reduction (397/33 686 (1.2%) aspirin plus heparin *v* 375/33 686 (1.1%) aspirin alone; NS) (fig 1(c); lower part). The beneficial effect of anticoagulant therapy in the absence of aspirin was significantly different from the lack of effect in the presence of aspirin ($\chi^2_1 = 6.98$; $P < 0.01$). Separate information on haemorrhagic strokes and on ischaemic strokes was not generally available. However, in GISSI-2 and ISIS-3 there was a small, non-significant excess of haemorrhagic stroke with the addition of heparin to aspirin (150 (0.45%) *v* 120 (0.36%)) and a non-significant shortfall of other strokes (226 (0.68%) *v* 239 (0.72%)).

Venous thromboembolism—Data on pulmonary embolism in the presence of aspirin were available only from the Italian part of GISSI-2, ISIS-3, and the small OSIRIS trial. The recorded incidence was much lower than in the previous studies (fig 1(d)). So, although there was a reduction of about one third in the odds of pulmonary embolism being detected among patients allocated heparin plus aspirin (82/28 888 (0.3%) *v* 117/28 890

(0.4%); $2P = 0.01$), which is only slightly less than the proportional reduction observed in the absence of aspirin, this corresponded to avoidance of such emboli in only about 1 (0.5) patient per 1000 treated. It may be that, with earlier ambulation after myocardial infarction and routine aspirin use,⁵⁹ the absolute risks of pulmonary embolism (and of deep vein thrombosis) really are much lower nowadays. But, there may have been substantial underascertainment of pulmonary emboli in GISSI-2 and ISIS-3, as these trials were not designed primarily to assess this outcome. If so, then the absolute reduction in pulmonary embolism when heparin is added to aspirin may well be greater than is suggested by these trial results.

Major bleeding—Adding high dose heparin to aspirin produced a highly significant increase of about 50% in the odds of having a major bleed reported (342/33 686 (1.0%) *v* 234/33 686 (0.7%); $2P < 0.0001$) (table 2). This corresponded to an absolute excess of about 3 (1) per 1000 patients treated with high dose heparin. Similar sized proportional increases were seen with high dose subcutaneous heparin and with intravenous heparin ($\chi^2_1 = 0.01$; NS).

Discussion

LACK OF EVIDENCE OF FURTHER BENEFIT FROM ADDING STANDARD HEPARIN REGIMENS TO ASPIRIN

Taken together, the trials in patients who were not routinely receiving aspirin (or fibrinolytic therapy) indicate that treatment with anticoagulants prevented some dozens of major vascular events per 1000 patients treated, which substantially outweighs the increased risk of bleeding. But assessment of anticoagulant therapy in the absence of aspirin is of somewhat limited relevance since aspirin should now be used routinely in acute myocardial infarction.³ Despite the inclusion of 68 000 patients in randomised trials that have directly addressed the effects of adding heparin to aspirin (with most patients also receiving fibrinolytic therapy),^{15 25-30} however, it remains uncertain whether such treatment is worth while. Any further reductions in death, reinfarction, or pulmonary embolism with the addition of heparin seem to be small (a few vascular events prevented per 1000 patients treated), are not statistically definite (as the lower confidence limits extend to about zero), and may be offset by an increase in major bleeds.

The absence of clear benefits in these trials suggests that little may be gained from adding heparin to routine aspirin and fibrinolytic therapy for acute myocardial infarction, unless some aspect of the design of the studies led to an underestimate of the effects of heparin. For example, almost all of the evidence comes from two megatrials in which heparin was to begin several hours (12 hours in GISSI-2 and 4 hours in ISIS-3) after the start of any fibrinolytic infusion that was given, and was subcutaneous, which caused some further delay.²⁸⁻³⁰ In the early hours, therefore, any differences in mortality chiefly reflect the play of chance, and only subsequently could any effects of heparin be expected to emerge. During the scheduled heparin treatment period in these trials there was some evidence of a reduction in mortality, suggesting avoidance of about 5 (2) deaths per 1000 patients allocated heparin. However, there was no significant effect of the heparin allocation on mortality at 35 days (2 (2) fewer deaths per 1000) or at 6 months (1 (3) fewer deaths per 1000).³⁰

LACK OF EVIDENCE OF ADDITIONAL BENEFIT WITH MORE INTENSIVE HEPARIN REGIMENS

Both GISSI-2 and ISIS-3 studied a high dose regimen of subcutaneous heparin, and an intravenous regimen could have produced more intensive anticoagulation. As is clear from the present overview (and elsewhere^{60 61}), very few patients have been studied in

Key messages

- Aspirin is of substantial value in acute myocardial infarction (and unstable angina), even when heparin is given, and should be used routinely
- Heparin seemed to be useful among patients with suspected acute myocardial infarction who, in the past, had received neither aspirin nor fibrinolytic therapy
- The available evidence from clinical trials does not justify the routine addition of intravenous or subcutaneous heparin to aspirin in the treatment of acute myocardial infarction (whether or not any type of fibrinolytic therapy is used)

trials of intravenous heparin plus aspirin versus aspirin alone, and so the unpromising results from just these small trials are inconclusive.

Further evidence about the effects of adding intravenous heparin to aspirin is provided by the large GUSTO-I trial in which—among patients allocated streptokinase—aspirin plus the ISIS-3 subcutaneous heparin regimen was directly compared with aspirin plus at least 48 hours of intravenous heparin.^{54 55} For those allocated intravenous heparin, an initial bolus of 5000 IU was to be followed by an infusion of 1000 IU/hour adjusted to aim for an activated partial thromboplastin time of 60–85 seconds.⁶² Despite randomisation of 20 000 patients in this GUSTO-I comparison, however, intravenous heparin was associated with slightly more deaths by 30 days (7.2% high dose subcutaneous heparin *v* 7.3% intravenous heparin), more strokes (1.2% *v* 1.4%), and more reinfarctions (3.5% *v* 4.2%; *2P*<0.01). Nor was there good evidence of any clinical difference in any particular subgroup, such as those with anterior myocardial infarction, that might have been expected to benefit particularly from more intensive anticoagulation.

So, despite the evidence of small improvements in coronary artery patency when intravenous heparin is added to adequate doses of aspirin after tissue plasminogen activator²⁵ or streptokinase,⁶³ the intravenous heparin regimen studied in GUSTO-I did not seem to confer any clinical advantage over high dose subcutaneous heparin plus aspirin—or, indirectly, over aspirin alone (taking into account the results of the present overview).³ However, intravenous heparin does seem to be associated with a small increase in major bleeding.

MORE BLEEDING WITH MORE INTENSIVE ANTICOAGULANT REGIMENS

In GUSTO-I, nearly half of the patients receiving the adjusted dose intravenous heparin regimen had an activated partial thromboplastin time below the prospectively defined “therapeutic range” of 60 to 85 seconds at 24 hours.^{54 64} As higher times are associated with higher coronary artery patency rates,^{65 66} a somewhat more intensive intravenous heparin regimen was studied in one arm of GUSTO-II (1300 IU per hour for patients of 80 kg or more, with the upper boundary of the target range increased to 90 seconds)⁶⁷ and in two other recent studies.^{68 69} Although an average of only about 20% more heparin was given, all three of these trials were stopped prematurely because of intracerebral haemorrhage and other major bleeds.^{67–69} This suggests that more intensive anticoagulation with heparin (or, perhaps, with other antithrombotics) may not be an appropriate strategy with fibrinolytic therapy.

ROUTINE HEPARIN USE IN ACUTE MYOCARDIAL INFARCTION IS NOT CLEARLY INDICATED

In conclusion, it seems that anticoagulant therapy was useful among patients with suspected acute myocardial infarction who, in the past, had received neither aspirin nor fibrinolytic therapy (and it might be found to be useful in patients not given fibrinolytic therapy who are given aspirin⁷⁰). The routine use of

heparin is still encouraged by some authorities⁷¹ and remains common in many European countries and in North America.⁷² But there is at present little evidence from randomised trials of any significant further net clinical benefit from adding either subcutaneous or intravenous heparin to the treatment of patients who are now already being given aspirin.³

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ONE HUNDRED YEARS AGO

WHISKY IN CENTRAL AFRICA.

Commissioner Sir H. Johnston, in his last report on trade in the British Central African Protectorate, calls attention to the alarming increase in the consumption of alcohol. Though he does not condemn wine and light lager beer, he declares the chief bane of that country to be whisky. Whisky, he says, is always noxious; and in those climates, even when much diluted with water, is "singularly prejudicial to health" when consumed daily

in considerable quantities. Of the highest importance to persons going to Africa is the emphatic statement that he who eschews spirit drinking is generally better able to resist the effects of malarial poisoning, and recovers rapidly from severe attacks of fever; while he whose system is permeated with alcohol has hardly a chance of recovery from malarial poisoning.

(*BMJ* 1896;ii:678.)