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."

1 Zureik M, Courbon D, Ducimetière P. Serum cholesterol concentration and death from suicide in men: Paris prospective study I. *BMJ* 1996;**313**:649-51.
2 Steegmans PHA, Fekkes D, Hoes AW, Bak AAA, van der Does E, Grobbee DE. Low serum cholesterol concentration and serotonin metabolism in men. *BMJ* 1996;**312**:221.
3 Gallerani M, Manfredini R, Caracciolo S, Scapoli C, Molinari S, Fersini C. Serum cholesterol concentrations in parasuicide. *BMJ* 1995;**310**:1632-6.
4 Ryman A. Cholesterol, violent death, and mental disorder. *BMJ* 1994;**309**:421-2.
5 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;**344**:1383-9.
6 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;**333**:1301-7.
7 Wysowski DK, Gross TP. Deaths due to accidents and violence in two recent trials of cholesterol-lowering drugs. *Arch Intern Med* 1990;**150**:2169-72.
8 Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994;**308**:373-9.
9 Lines C. Hazards of reducing cholesterol. *BMJ* 1994;**309**:541.
10 Downs JR, Oster G, Santanello NC. HMG CoA reductase inhibitors and quality of life. *JAMA* 1993;**269**:3107-8.
11 Wardle J, Armitage J, Collins R, Wallendszus K, Keech A, Lawson A. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996;**313**:75-8.
12 Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. *Lancet* 1993;**341**:75-9.
13 Magni G, Garreau M, Orofiamma B, Palminteri R. Fengabine, a new GABAmimetic agent in the treatment of depressive disorders: an overview of six double-blind studies versus tricyclics. *Neuropsychobiology* 1988;**20**:126-31.
14 Engelberg H. Low serum cholesterol and suicide. *Lancet* 1992;**339**:727-9.
15 Cited in Wald NJ. *The epidemiological approach*. London: Wolfson Institute of Preventive Medicine, 1996.

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

Rory Collins, Stephen MacMahon, Marcus Flather, Colin Baigent, Lars Remvig, Svend Mortensen, Paul Appleby, Jon Godwin, Salim Yusuf, Richard Peto

BHF/MRC/ICRF Clinical Trial Service Unit, University of Oxford, Oxford OX2 6HE
Rory Collins, *professor of medicine and epidemiology*
Colin Baigent, *MRC research fellow*
Paul Appleby, *research fellow*
Jon Godwin, *research fellow*
Richard Peto, *professor of medical statistics and epidemiology*

Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand
Stephen MacMahon, *assistant professor of medicine*

Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London SW3 6NP
Marcus Flather, *director and honorary consultant*

Medical Department B, Rigshospitalet, Copenhagen, Denmark
Lars Remvig, *consultant*
Svend Mortensen, *consultant*

HGH-McMaster Clinic, Hamilton General Hospital, Hamilton, Ontario, Canada
Salim Yusuf, *professor of medicine*

Correspondence to:
Professor Rory Collins, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford OX2 6HE.

BMJ 1996;313:652-9

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 trials[4-30] 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 overviews[33-35] and considering separately the trials that assessed the effects of adding heparin to aspirin.

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" controls[36-43]) 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 intervention[44-55] 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*

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

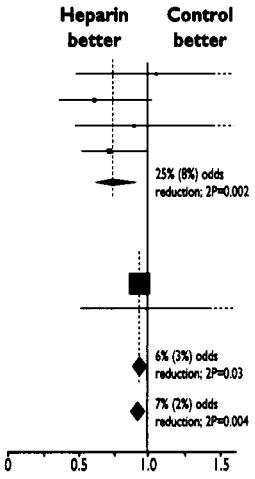
§In Carleton *et al* a high initial dose was specified with subsequent titration to aim for a coagulation time between 2 and 3 times control.

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

(a) Death

	Heparin	Control
Heparin in absence of aspirin:		
Low dose subcutaneous heparin	26/340 (7.6%)	25/347 (7.2%)
High dose subcutaneous heparin	54/463 (11.7%)	80/460 (17.4%)
High dose intravenous heparin	37/300 (12.3%)	42/306 (13.7%)
Heparin plus oral anticoagulant	167/1381 (12.1%)	231/1423 (16.2%)
Subtotal: no aspirin	284/2484 (11.4%)	378/2536 (14.9 %)
Heparin in presence of aspirin:		
Low dose subcutaneous heparin	—	—
High dose subcutaneous heparin	2900/33292 (8.7%)	3061/33332 (9.2%)
High dose intravenous heparin	32/676 (4.7%)	31/659 (4.7%)
Heparin plus oral anticoagulant	—	—
Subtotal: aspirin	2932/33968 (8.6%)	3092/33991 (9.1%)
All heparin trials†	3216/36452 (8.8%)	3470/36527 (9.5%)

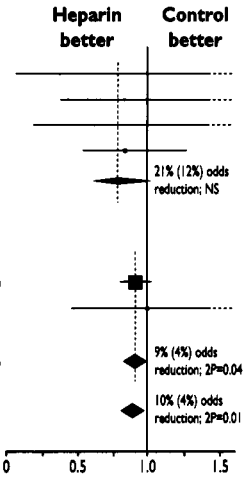


†Crude unadjusted control total = 3387/36136

Heterogeneity of odds reductions with heparin between:
26 trial strata: $\chi^2_{25} = 24.27$ (NS)
regimens in absence of aspirin: $\chi^2_3 = 3.02$ (NS)
regimens in presence of aspirin: $\chi^2_1 = 0.05$ (NS)
absence and presence of aspirin: $\chi^2_1 = 5.82$ (P<0.05)

(b) Reinfarction

	Heparin	Control
Heparin in absence of aspirin:		
Low dose subcutaneous heparin	3/179 (1.7%)	8/178 (4.5%)
High dose subcutaneous heparin	24/463 (5.2%)	28/460 (6.1%)
High dose intravenous heparin	8/195 (4.1%)	12/192 (6.3%)
Heparin plus oral anticoagulant	107/1287 (8.3%)	128/1326 (9.7%)
Subtotal: no aspirin	142/2124 (6.7%)	176/2156 (8.2 %)
Heparin in presence of aspirin:		
Low dose subcutaneous heparin	—	—
High dose subcutaneous heparin	986/33010 (3.0%)	1081/33027 (3.3%)
High dose intravenous heparin	23/676 (3.4%)	22/659 (3.3%)
Heparin plus oral anticoagulant	—	—
Subtotal: aspirin	1009/33686 (3.0%)	1103/33686 (3.3%)
All heparin trials†	1151/35810 (3.2%)	1279/35842 (3.6%)

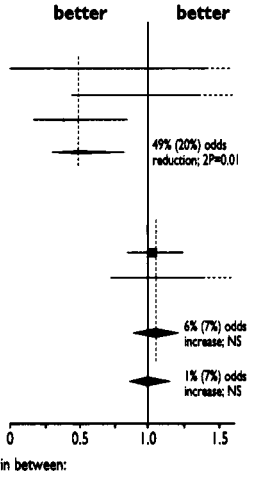


†Crude unadjusted control total = 1228/35451

Heterogeneity of odds reductions with heparin between:
19 trial strata: $\chi^2_{18} = 9.89$ (NS)
regimens in absence of aspirin: $\chi^2_3 = 1.76$ (NS)
regimens in presence of aspirin: $\chi^2_1 = 0.13$ (NS)
absence and presence of aspirin: $\chi^2_1 = 0.99$ (NS)

(c) Stroke

	Heparin	Control
Heparin in absence of aspirin:		
Low dose subcutaneous heparin	0/179 (0.0%)	0/178 (0.0%)
High dose subcutaneous heparin	0/360 (0.0%)	2/351 (0.6%)
High dose intravenous heparin	6/200 (3.0%)	2/201 (1.0%)
Heparin plus oral anticoagulant	17/1287 (1.3%)	40/1326 (3.0%)
Subtotal: no aspirin	23/2026 (1.1%)	44/2056 (2.1%)
Heparin in presence of aspirin:		
Low dose subcutaneous heparin	—	—
High dose subcutaneous heparin	385/33010 (1.2%)	371/33027 (1.1%)
High dose intravenous heparin	12/676 (1.8%)	4/659 (0.6%)
Heparin plus oral anticoagulant	—	—
Subtotal: aspirin	397/33686 (1.2%)	375/33686 (1.1%)
All heparin trials†	420/35712 (1.2%)	419/35742 (1.2%)

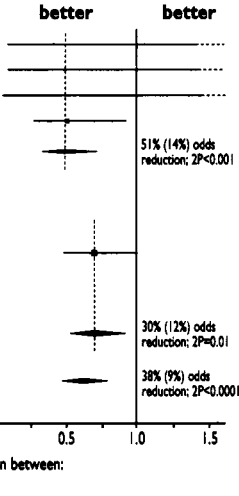


†Crude unadjusted control total = 410/35351

Heterogeneity of odds reductions with heparin between:
15 trial strata: $\chi^2_{14} = 24.50$ (P<0.05)
regimens in absence of aspirin: $\chi^2_2 = 7.42$ (P<0.05)
regimens in presence of aspirin: $\chi^2_1 = 3.51$ (NS)
absence and presence of aspirin: $\chi^2_1 = 6.98$ (P<0.01)

(d) Pulmonary embolism

	Heparin	Control
Heparin in absence of aspirin:		
Low dose subcutaneous heparin	3/331 (0.9%)	8/337 (2.4%)
High dose subcutaneous heparin	3/463 (0.6%)	6/460 (1.3%)
High dose intravenous heparin	2/127 (1.6%)	5/129 (3.9%)
Heparin plus oral anticoagulant	38/1368 (2.8%)	72/1409 (5.1%)
Subtotal: no aspirin	46/2289 (2.0%)	91/2335 (3.9%)
Heparin in presence of aspirin:		
Low dose subcutaneous heparin	—	—
High dose subcutaneous heparin	82/28824 (0.3%)	117/28826 (0.4%)
High dose intravenous heparin	0/64 (0.0%)	0/64 (0.0%)
Heparin plus oral anticoagulant	—	—
Subtotal: aspirin	82/28888 (0.3%)	117/28890 (0.4%)
All heparin trials†	128/31177 (0.4%)	208/31225 (0.7%)



†Crude unadjusted control total = 184/30834

Heterogeneity of odds reductions with heparin between:
14 trial strata: $\chi^2_{13} = 11.47$ (NS)
regimens in absence of aspirin: $\chi^2_3 = 0.19$ (NS)
regimens in presence of aspirin: Not applicable
absence and presence of aspirin: $\chi^2_1 = 2.16$ (NS)

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 part[28] and the international extension of GISSI-2[29]), 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 study[15]) 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 comparison 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 $\chi^2_2 = 1.49$; 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 ($\chi^2_3 = 1.76$ or, if the trials of low dose heparin are excluded, $\chi^2_2 = 0.32$; 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 ($\chi^2_2 = 7.42$; $P<0.05$).

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 *et al*[5]	14	13	NA		NA		NA		NA		1	2	0	0
Warlow *et al*[6]	73	73	6	5	NA		NA		0	1	2	11	0	0
Emerson and Marks[7]	38	43	0	1	NA		NA		0	3	2	14	NA	
Cade *et al*[8]	63	2 x 30	NA		NA		NA		NA		2	2 x 3	NA	
Remvig *et al*[9]	144	143	12	13	3	8	0	0	2	2	3	8	0	0
Zawilska *et al*[10]	50	53	5	6	NA		NA		0	1	2	10	0	0
High dose heparin (≥20 000 IU/day: mean 25 000) *v* no antithrombotic														
Carleton *et al*[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 *et al*[13]	30	30	2	3	NA		NA		0	2	0	7	1	0
Gueret *et al*[14]	46	44	NA		NA		NA		NA		NA		NA	
½ ISIS-2 pilot[15]														
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	
SCATI[17]														
Fibrinolytic	218	215	10	19	18	21	0	2	1	0	NA		4	2
No fibrinolytic	142	136	11	16	2	3					NA			
Bleich *et al*[18]	46	49	6	5	NA		2	0	0	0	NA		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 *et al*[21]	46	46	2	3	NA		NA		0	0	3	10	0	0
Pitt *et al*[22]	35	37	0	0	NA		NA		0	0	4	11	NA	
Nordrehaug *et al*[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 pilot[15]														
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-3[30]														
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 ECSG-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 similar 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.

HEPARIN IN THE PRESENCE OF ASPIRIN

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 activator[25] 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 aspirin[70]). The routine use of heparin is still encouraged by some authorities[71] 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]

Drs S Arvan, S Bleich, K Boscha, J Cade, R Carleton, J Col, R Collins (for the ISIS collaborators), D de Bono (for the ECSG collaborators), A Drapkin, R Ebert, P Emerson, MG Franzosi (for the GISSI collaborators), A Handley, J Nordrehaug, C O'Connor, M Ohman, A Pitt, P Prandoni, L Tavazzi, C Warlow, and R Wray provided additional information. We thank Gale Mead and Cathy Harwood for typing the manuscript and Mandy Ogier for administrative assistance. Rory Collins is supported by a British Heart Foundation endowed chair, Stephen MacMahon is supported by a Health Research Council of New Zealand senior research fellowship, Marcus Flather was supported by a British Heart Foundation junior research fellowship, and Colin Baigent is supported by a United Kingdom Medical Research Council training fellowship.

Funding: EC Biomed, British Heart Foundation, Medical Research Council.

Conflict of interest: None.

1 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; ii:349-60.
2 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106.
3 Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1996 (in press)
4 Handley AJ. Low dose heparin after myocardial infarction. *Lancet* 1972;ii:623-4.
5 Gallus AS, Hirsh J, Tuttle RJ, Trebilcock R, O'Brien SE, Carroll JJ, *et al.* Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med* 1973;**288**:545-51.
6 Warlow C, Terry G, Kenmure ACF, Beattie AG, Ogston D, Douglas AS. A double-blind trial of low doses of subcutaneous heparin in the prevention of deep-vein thrombosis after myocardial infarction. *Lancet* 1973;ii:934-6.
7 Emerson PA, Marks P. Preventing thromboembolism after myocardial infarction: effect of low dose heparin or smoking. *BMJ* 1977;i:18-20.
8 Cade JF, Andrews JT, Stubbs AE. Comparison of sodium and calcium heparin in prevention of venous thromboembolism. *Aust NZ J Med* 1982;**12**:501-4.
9 Remvig L, Mortensen SA, Als OS, Mentzel V, Holm G. Lav-dosis heparinbehandling som profylakse mod dyb venetrombose ved akut myokardieinfarkt. *Ugeskr Laeger* 1983;**145**:1053-6.
10 Zawilska K, Psuja P, Lewandowski K, Wroz M. Low-dose heparin in the prevention of thrombotic complications following acute myocardial infarction. *Cor Vasa* 1989;3:179-85.
11 Carleton RA, Sanders CA, Burack WR. Heparin administration after acute myocardial infarction. *N Engl J Med* 1960;**20**:102-5.
12 Steffensen KA. Coronary occlusion treated with small doses of heparin. *Acta Med Scand* 1969;**186**:519-21.
13 Handley AJ, Emerson PA, Fleming PR. Heparin in the prevention of deep vein thrombosis after myocardial infarction. *BMJ* 1972;ii:436-8.
14 Gueret P, Dubourg O, Ferrier A, Farcot JC, Rigaud M, Bourdarias J-P. Effects of full-dose heparin anticoagulation on the development of left ventricular thrombosis in acute transmural myocardial infarction. *J Am Coll Cardiol* 1986;**8**:419-26.
15 Collins R, Conway M, Alexopoulos D, Yusuf S, Sleight P, Brooks N, *et al* for the ISIS pilot study investigators. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. *Eur Heart J* 1987;**8**:634-42.
16 Diaz RA, Torres H. Valor de la anticoagulación precoz en la prevención de la trombosis intraventricular despues de un primer infarto del miocardio: estudio prospectivo y randomizado. *Rev Méd Chile* 1988;**116**:13-7.
17 SCATI (Studio sulla calciparina nell'angina e nella trombosi ventricolare nell'infarto) Group. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet* 1989;ii:182-6.
18 Bleich SD, Nichols TC, Schumacher RR, Cooke DH, Tate DA, Teichman SL. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;**66**:1412-7.
19 Drapkin A, Merskey C. Anticoagulant therapy after acute myocardial infarction. *JAMA* 1972;**222**:541-8.
20 Veterans' Administration. Anticoagulants in acute myocardial infarction: results of a cooperative clinical trial. *JAMA* 1973;**225**:724-9.
21 Wray R, Maurer B, Shillingford J. Prophylactic anticoagulant therapy in the prevention of calf-vein thrombosis after myocardial infarction. *N Engl J Med* 1973;**288**:815-7.
22 Pitt A, Anderson ST, Habersberger PG, Rosengarten DS. Low dose heparin in the prevention of deep vein thrombosis in patients with acute myocardial infarction. *Am Heart J* 1980;**99**:574-8.
23 Nordrehaug JE, Johannessen KA, Vonderlippe G. Usefulness of high-dose anticoagulants in preventing left ventricular thrombosis in acute myocardial infarction. *Am J Cardiol* 1985;**55**:1491-3.
24 Arvan S, Boscha K. Prophylactic anticoagulation for left ventricular thrombi after acute myocardial infarction: a prospective randomized trial. *Am Heart J* 1987;**113**:688-93.

25 De Bono DP, Simoons ML, Tijssen J, Arnold AER, Betriu A, Burgersdijk C, *et al* for the European Cooperative Study Group. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992;67:122-8.

26 Col J, Decoster O, Hanique G, Deligne B, Boland J, Pirenne B, *et al*. Infusion of heparin conjunct to streptokinase accelerates reperfusion of acute myocardial infarction: results of a double blind randomized study (OSIRIS). *Circulation* 1992;86(suppl I):259.

27 O'Connor CM, Meese R, Carney R, Smith J, Conn E, Burks J, *et al* for the DUCCS Group. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University clinical cardiology study (DUCCS) 1. *J Am Coll Cardiol* 1994;23:11-8.

28 Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: randomised trial of intravenous alteplase versus intravenous streptokinase in acute myocardial infarction. *Lancet* 1990;336:65-71.

29 International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between tissue plasminogen activator or streptokinase with or without heparin. *Lancet* 1990;336:71-5.

30 ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised trial of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753-70.

31 Peto R. Why do we need systematic overviews of randomized trials? *Stat Med* 1987;6:233-40.

32 Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. *Stat Med* 1987;6:245-50.

33 Chalmers TC, Matta RJ, Smith H, Kunzler A-M. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med* 1977;297:1091-6.

34 MacMahon S, Collins R, Knight C, Yusuf S, Peto R. Reduction in major morbidity and mortality by heparin in acute myocardial infarction. *Circulation* 1988;78(suppl II):98.

35 MacMahon S, Collins R, Flather M, Knight C, Remvig L, Mortensen S, *et al*. Heparin in the presence or absence of antiplatelet therapy: an overview of randomized trials in acute myocardial infarction. *Circulation* 1992;86(suppl I):259.

36 Prandoni P, Russo R, Pengo V, Boschello M, Casara D, Maddalena F, *et al*. Prevenzione della trombosi venosa profonda con eparina a basse dosi in pazienti con infarto miocardico acuto non complicato. *Minerva Cardioangiologica* 1986;34:653-7.

37 Wasserman AJ, Gutterman LA, Yoe KB, Kemp VE Jr, Richardson DW. Anticoagulants in acute myocardial infarction. The failure of anticoagulants to alter mortality in a randomized series. *Am Heart J* 1956;71:43-9.

38 Bjerkelund CJ. Effect of long-term treatment with dicoumarol in myocardial infarction. *Acta Med Scand* 1957;158(suppl 330):5-212.

39 Harvald B, Hilden T, Lund E. Long-term anticoagulant therapy after myocardial infarction. *Lancet* 1962;ii:626-30.

40 Loeliger EA, Hensen A, Kroes F, van Dijk LM, Fekkes N, De Jonge H, *et al*. A double-blind trial of long-term anticoagulant treatment after myocardial infarction. *Acta Med Scand* 1967;182:549-66.

41 Sorensen OH, Friis Th, Jorgensen AW, Jorgensen MB, Nissen NI. Anticoagulant treatment of acute coronary thrombosis. *Acta Med Scand* 1969;185:65-72.

42 Ruggiero HA, Caprissi LF, Neuman J, De Caprissi ES. Treatment of acute myocardial infarction with heparin at low doses. *Clin Cardiol* 1987;10:598-602.

43 Vakil RJ. Preinfarction syndrome—management and follow-up. *Am J Cardiol* 1964;14:55-63.

44 MacMillan RL, Brown KWG. Long-term anticoagulant therapy after myocardial infarction. *Can Med Assoc J* 1960;83:567-70.

45 Borchgrevink CF. Long-term anticoagulant therapy in angina pectoris and myocardial infarction. A clinical trial of intensive versus moderate treatment. *Acta Med Scand* 1960;168(suppl 359):5-52.

46 Brown KWG, MacMillan RL. Initial heparin therapy in acute myocardial infarction. *Can Med Assoc J* 1964;90:1345-8.

47 Lovell RRH, Denborough MA, Nestel PJ, Goble AJ. A controlled trial of long-term treatment with anticoagulants after myocardial infarction in 412 male patients. *Med J Aust* 1967;54:97-104.

48 Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. Assessment of short-term anticoagulant administration after cardiac infarction. *BMJ* 1969;i:335-42.

49 Habersberger PG, Pitt A, Anderson ST. Venous thrombosis in myocardial infarction. Comparison in heparin dosage. *Br Heart J* 1973;35:538-42.

50 Davis MJE, Ireland MA. Effect of early anticoagulation on the frequency of left ventricular thrombi after anterior wall acute myocardial infarction. *Am J Cardiol* 1986;57:1244-7.

51 Turpie AGG, Robinson JG, Doyle DJ, Mulji AS, Mishkel GJ, Sealey BJ, *et al*. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;320:352-7.

52 Topol EJ, George BS, Kereiakes DJ, Stump DC, Candela RJ, Abbottsmith CW, *et al* for the TAMI Study Group. A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989;79:281-6.

53 Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. Heparin-aspirin reperfusion trial (HART) investigators. *N Engl J Med* 1990;323:1433-7.

54 GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.

55 Van de Werf F, Topol EJ, Lee KL, Woodlief LH, Granger CB, Armstrong PW, *et al* for the GUSTO Investigators. Variations in patient management and outcomes, for acute myocardial infarction in the United States and other countries. Results from the GUSTO trial. *JAMA* 1995;273:1586-91.

56 Early Breast Cancer Trialists' Collaborative Group, *Treatment of early breast cancer.* Vol 1. *Worldwide evidence 1985-1990.* Oxford: Oxford University Press, 1990.

57 PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990;263:2753-9.

58 Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. *N Engl J Med* 1988;318:1162-73.

59 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;308:235-46.

60 Mahaffey KW, Granger CB, Collins R, O'Connor CM, Ohman EM, Bleich SD, *et al*. Overview of randomized trials of intravenous heparin in patients with acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 1996;77:551-6.

61 Ridker PM, Hebert PR, Fuster V, Hennekens CH. Are both aspirin and heparin justified as adjuncts to thrombolytic therapy for acute myocardial infarction? *Lancet* 1993;341:1574-7.

62 Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. *Arch Intern Med* 1991;151:333-7.

63 GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-22.

64 Granger CB, Califf RM, Hirsh J, Woodlief LH, Topol EJ, for the GUSTO Investigators. APTT's after thrombolysis and standard intravenous heparin are often low and correlate with body weight, age and sex: experience from the GUSTO Trial. *Circulation* 1992;86(suppl I):258.

65 Arnout J, Simoons M, de Bono D, Rapold HJ, Collen D, Verstraete M. Correlation between level of heparinization and patency of the infarct-related coronary artery after treatment of acute myocardial infarction with alteplase (rt-PA). *J Am Coll Cardiol* 1992;20:513-9.

66 Hsia J, Kleiman N, Aguirre F, Chaitman BR, Roberts R, Ross AM, for the HART Investigators. Heparin-induced prolongation of partial thromboplastin time after thrombolysis: relation to coronary artery patency. *J Am Coll Cardiol* 1992;20:31-5.

67 Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;90:1631-2.

68 Antman EM, for the TIMI 9A Investigators. Hirudin in acute myocardial infarction. Safety report from the thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9A trial. *Circulation* 1994;90:1624-30.

69 Neuhaus K-L, v Essen R, Tebbe U, Jessel A, Heinrichs H, Maürer W, *et al*. Safety observations from the pilot phase of the randomised r-hirudin for improvement of thrombolysis (HIT-III) study. *Circulation* 1994;90:1638-42.

70 Hennekens CH, O'Donnell CJ, Ridker PM. Current and future perspectives on antithrombotic therapy of acute myocardial infarction. *Eur Heart J* 1995;16(suppl D):2-9

71 Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 1. Heparin. *Circulation* 1994;89:1449-68.

72 Ellerbeck EF, Jencks SF, Radford MJ, Kresowik TF, Craig AS, Gold JA, *et al*. Quality of care for Medicare patients with acute myocardial infarction. A four-state pilot study from the cooperative cardiovascular project. *JAMA* 1995;273:1509-14.

(Accepted 21 June 1996)

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.)