CONCLUSION

We found that low or declining serum cholesterol concentrations were associated with death from suicide. Mechanisms that might link cholesterol concentrations to suicide should be thoroughly studied.

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Commentary: Having too much evidence (depression, suicide, and low serum cholesterol)

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Another observational study on low serum cholesterol concentration and suicide appears in this week's *BMJ*,[1] complementing other *BMJ* publications in the past two years.[2-4] These papers all take as their premise that the controversy on low serum cholesterol, depression, and accidents and suicide remains unresolved. They conclude that it remains unresolved.

The past two years have also seen the publication of two large randomised controlled trials of cholesterol reduction using hydroxymethyl glutaryl coenzyme A reductase inhibitors ("statins").[5 6] These drugs produce large reductions in serum cholesterol concentration (20-30%) and hence are particularly informative on safety. If smaller trials are taken into account as well, published randomised trials of statins have now accumulated 38 700 person years of observation on active treatment and 33 800 person years on placebo. With a total of 11 deaths from accidents and suicide in treated patients and 14 in controls in these trials, there is no indication of hazard. Most important, however, since one can never prove a negative, is the upper limit of the 95% confidence interval of the combined risk estimate from the numbers in these trials. The greatest likely hazard, if there were any, would be small—one death in about 5000 person years of treatment. Few such potent treatments have so much evidence of safety from randomised trials.

The older trials of cholesterol lowering (average reduction about 10%) are also reassuring. Concern relating to two trials that recorded more deaths from accidents and suicide in treated patients than controls (though neither difference was statistically significant) was resolved by the demonstration that the extra deaths occurred among men who had not taken their allocated tablets (active or placebo).[7] There had been a chance allocation of more patients with psychiatric illness on entry to active treatment than to placebo.[7 8] The rest of the older trials show no excess[8]; table 1 summarises the results.

The issue of low serum cholesterol and depression was directly examined in three randomised, placebo controlled trials of statins in which indices of depression were measured in all the participants—a total of 7400 people taking active treatment and 2400 taking placebo.[9-11] Depression was no more common among those taking active treatment.

With these trial results, why is there continued publication of observational studies that foster the view that the uncertainty persists? The observational and trial data have tended to be seen in isolation from each other. Some cross sectional studies show an association between low serum cholesterol concentration and depression,[12] and, given this, there is also an association between low serum cholesterol and suicide.[8] But the associations may arise because low serum cholesterol causes depression or because it is a consequence of depression (simply because depressed people eat less). Cross sectional studies cannot determine which is the cause and which the consequence. Other observational evidence indicates that the low cholesterol concentration is a consequence of the depression since (a) there was no excess mortality with low serum cholesterol in prospective studies of working men (less likely to have serious psychiatric illness on entry to the studies by virtue of being in work),[8] (b) the excess mortality in the prospective studies was short term with no significant excess after six years,[8] and (c) treating depression has been shown to increase serum cholesterol concentration.[13] The recent observational studies have merely introduced variations on the same theme: low serotonin concentrations (which accompany and may cause depression) are, not surprisingly, also associated with low cholesterol,[2 14] people who attempt suicide have low serum cholesterol concentrations,[3] and, in this week's issue, men with declining serum cholesterol concentrations are particularly likely to commit suicide.[1] If these were the only studies one could not distinguish cause from consequence. The randomised trials resolve the matter, providing compelling evidence that low

Table 1—*Deaths from accidents and suicide in randomised controlled trials of reduction of serum cholesterol concentration*

	Active treatment	Control
Trials of statin drugs (n = 13)	11	14
Trials of older drugs, diet, and ileal bypass surgery:		
The two trials that raised concern:	20	9
Patients who took allocated tablets	9	7
Patients who did not take allocated tablets	11	2
All other trials (n = 25)	78	77
Total:	109	100
Excluding patients who did not take tablets in the two trials	98	98

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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 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.