A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial

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Abstract

Objective—To compare aspirin with anticoagulation with regard to risk of cardiac death and reinfarction in patients who received anistreplase thrombolysis for myocardial infarction.

Design—A multicentre unblinded randomised clinical trial.

Setting—38 hospitals in six countries.

Subjects—1036 patients who had been treated with anistreplase for myocardial infarction were randomly assigned to either aspirin (150 mg daily) or anticoagulation (intravenous heparin followed by warfarin or other oral anticoagulant). The trial was stopped earlier than originally intended because of the slowing rate of recruitment.

Main outcome measure—Cardiac death or recurrent myocardial infarction at 30 days.

Results—After 30 days cardiac death or reinfarction, occurred in 11.0% (57/517) of the patients treated with anticoagulation and 11.2% (58/519) of the patients treated with aspirin (odds ratio 1.02, 95% confidence interval 0.69 to 1.50, $P=0.92$). Corresponding findings at three months were 13.2% (68/517) and 12.1% (63/519) (0.91, 0.63 to 1.32, $P=0.67$). Patients receiving anticoagulation were more likely than patients receiving aspirin to have had severe bleeding or a stroke by three months (3.9% v 1.7% (0.44, 0.20 to 0.97, $P=0.04$)).

Conclusion—No evidence of a difference in the incidence of cardiac events was found between the two treatment groups, though the trial is too small to claim treatment equivalence confidently. A higher incidence of severe bleeding events and strokes was detected in the group receiving anticoagulation, suggesting that aspirin may be the drug of choice for most patients in this context.

Introduction

Both aspirin¹ and oral anticoagulants^{2,3} have been shown in clinical trials to be effective in reducing reinfarction and death in the months after myocardial infarction. These trials were mostly conducted in the pre-thrombolytic era, and only one study has compared the two treatments since the widespread introduction of thrombolysis.⁴ Reinfarction is a major complication after thrombolysis and uncertainty remains about the relative efficacy and safety of the two regimens in this context. The AFTER (aspirin/anticoagulants following thrombolysis with eminease in recurrent infarction) study was undertaken to address this issue.

Patients and methods

This was a multicentre unblinded randomised controlled trial of aspirin and anticoagulation following anistreplase thrombolysis conducted in 38 hospitals in six countries. Central randomisation was performed by

telephone to the cardiac care unit of the Royal Sussex County Hospital, where random blocks of sealed envelopes were used for each participating centre. The primary objective was to compare the effect of these two regimens on cardiac events (cardiac death or recurrent myocardial infarction) at 30 days.

A recurrent infarction was diagnosed on the basis of the following evidence occurring more than 48 hours after the pre-randomisation presenting episode: (a) chest pain characteristic of myocardial infarction lasting at least 20 minutes unrelieved by nitrates and accompanied by autonomic symptoms; (b) new ST elevation in any leads; (c) a further rise in cardiac enzymes in any two consecutive 12 hourly blood samples; and (d) new electrocardiographic evidence of silent infarction—for example, new Q waves or reduced or absent R wave. Cardiac death was defined as death directly or indirectly related to myocardial infarction or ischaemic heart disease.

The secondary objective was to compare the effect on cardiac events and bleeding events of these agents at three months. A bleeding event was classified as severe if it was considered by the investigator to be of major clinical importance.

The intended sample size was based on the anticipated events rates at 30 days—1856 patients were needed to detect a difference of 8.5% versus 10.6% in cardiac event rates at 30 days, with type I and type II errors of 0.05 and 0.20 respectively. Allowing for a small proportion of patients lost to follow up, the intended total number of patients was set at 2000. An independent data monitoring committee was set up to examine interim results after 1000 patients had been evaluated at 30 days. This committee did not meet, however, as the steering committee decided to stop further patient entry after 1036 randomised patients because of the slowing rate of recruitment. This decision was made entirely blind of treatment specific outcome results.

Patients were considered for inclusion if they had been treated with anistreplase for myocardial infarction within six hours of the onset of symptoms. The electrocardiographic criterion for eligibility was ST elevation of at least 0.2 mV in two or more adjacent precordial leads or 0.1 mV in two or more standard leads. Patients were excluded from the study if anistreplase was contraindicated or if they had been treated with aspirin, non-steroidal anti-inflammatory agents, or oral anticoagulants before the event. After giving informed consent, patients were randomised either to an anticoagulant or to an aspirin regimen. Anticoagulation consisted of 1000 units/hour of intravenous heparin started six hours after anistreplase, followed by warfarin or other oral anticoagulant within 24 hours and continued for three months; heparin was discontinued when the international normalised ratio exceeded 2. This ratio was subsequently maintained between 2 and 2.5. The aspirin regimen was started immediately, with 150 mg, and continued daily for three months.

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Results

The study recruited 1036 randomised patients; follow up data were available for 97% (1004) of the patients at 30 days and 87% (901) at three months, with similar distributions of follow up time in the two randomised groups.

The patients in the two groups had similar characteristics at baseline (table 1). Compliance with the regimens was good, with an estimated 79% patients in the anticoagulation group and 76% in the aspirin group continuing with their treatment beyond 30 days.

Death and reinfarction rates were similar at 30 days and three months (table 2). The confidence interval at three months indicates that a difference of more than one third was virtually excluded. By three months stroke had occurred in seven patients in the anticoagulation group and in four in the aspirin group (difference not significant), while severe bleeding had occurred in 13 (2.5%) patients in the anticoagulation group and five (1.0%) in the aspirin group. Combining stroke with severe bleeding events showed that these were significantly less common in the aspirin group (odds ratio 0.44, 95% confidence interval 0.20 to 0.97, $P=0.04$). This difference largely arose in the first three days. If all bleeding events were included the three month difference was highly significant (24 and 56 in the aspirin and anticoagulation groups respectively (0.40, 0.24 to 0.65, $P=0.0002$)).

Discussion

Both oral anticoagulants and antiplatelet agents have been shown to reduce mortality in patients after myocardial infarction. Smith *et al* reported reductions of 24% in deaths, 34% in reinfarctions, and 55% in strokes in a study in the prethrombolytic era comparing warfarin and placebo.² In the ASPECT (anticoagulants in the secondary prevention of events in coronary thrombosis)

Table 1—Baseline characteristics of 1036 patients in trial randomised to two treatment groups

	Anticoagulation (n=517)	Aspirin (n=519)
Sex:		
No (%) of men	393 (76.0)	402 (77.5)
No (%) of women	123 (23.8)	117 (22.5)
No missing	1	0
Pulmonary oedema:		
No (%) present	66 (12.8)	61 (11.8)
No (%) absent	449 (86.8)	458 (88.2)
No missing	2	0
Age (years):		
Mean (SD)	60.3 (10.6)	60.3 (10.5)
No missing	8	10
No of hours till anistreplase:		
Median (interquartile range)	2.88 (2-4.17)	2.75 (1.83-3.88)
Missing	11	8

Table 2—Deaths and reinfarctions during follow up in both treatment groups. Values are numbers (percentages) of patients unless stated otherwise

Follow up time	Anticoagulation (n=517)	Aspirin (n=519)	Log rank P value	Odds ratio (95% confidence interval)
Cardiac death and/or reinfarction				
30 Days	57 (11.0)	58 (11.2)	0.92	1.02 (0.69 to 1.50)
3 Months	68 (13.2)	63 (12.1)	0.67	0.91 (0.63 to 1.32)
Deaths by cause				
30 Days:				
All causes	37 (7.2)	42 (8.1)	0.55	1.14 (0.72 to 1.81)
Cardiac	31 (6.0)	38 (7.3)		
Non-cardiac	6 (1.2)	4 (0.8)		
3 Months:				
All causes	42 (8.1)	46 (8.9)	0.65	1.10 (0.71 to 1.70)
Cardiac	34 (6.6)	40 (7.7)		
Non-cardiac	8 (1.5)	5 (1.0)		
Unknown		1 (0.2)		

Key messages

- Aspirin or anticoagulation are options after thrombolysis for myocardial infarction
- After anistreplase, aspirin (150 mg daily) resulted in a lower risk of bleeding and stroke than intravenous heparin followed by warfarin
- The rate of cardiac death or reinfarction at 30 days seemed similar for both treatments
- More evidence is needed, however, before therapeutic equivalence can be claimed confidently
- Aspirin is the drug of choice for most patients

study of oral warfarin (coumadin) versus placebo, in which 25% of the patients had received thrombolysis, there was a significant reduction in reinfarctions and strokes but not in deaths.³ The antiplatelet trialists overview found reductions of 13% in vascular deaths, 31% in reinfarctions, and 42% in non-fatal strokes.¹ The only study comparing oral anticoagulants, aspirin, and placebo after thrombolysis studied the effect of these agents on coronary reocclusion and recurrent ischaemia.⁴ Up to three months, there was an event free clinical course in 93% of patients taking aspirin, 82% taking warfarin (coumadin), and 76% taking placebo (aspirin *v* placebo, $P<0.001$; aspirin *v* coumadin, $P<0.05$). The authors concluded that, compared with placebo, aspirin significantly reduced reinfarction rate and revascularisation rate, improved event free survival, and better preserved left ventricular function, and that the efficacy of coumadin on these end points seemed poorer than that of aspirin. We understand that two trials are in progress comparing aspirin with anticoagulants in survivors of acute myocardial infarction, which will add substantially to our knowledge.⁵

Our study used a strategy of anticoagulation that incorporated both immediate intravenous heparin and subsequent warfarin compared with aspirin given over three months. The study was not big enough to establish clearly which regimen was better at preventing death or recurrent infarction. This issue is not resolved even if the results of the earlier study comparing anticoagulants and aspirin⁴ are taken into account because of the insufficient numbers of patients in the two studies. Nevertheless, it seems highly plausible that aspirin is as effective as anticoagulation in preventing ischaemic events. With regards to the incidence of the combined end points of stroke and bleeding, however, aspirin is unquestionably safer than anticoagulation. Furthermore, aspirin is easier to administer and cheaper. The higher incidence of bleeding in the anticoagulation group occurred during or soon after heparin administration to patients who had received thrombolysis and does not necessarily implicate warfarin. On the other hand, clinical situations such as pulmonary embolism or intraventricular thrombosis strongly indicate the need for an anticoagulant.

We conclude that aspirin rather than anticoagulation should be used routinely in the post-acute care of patients who have received thrombolytic drugs for myocardial infarction, with anticoagulation reserved for patients who have specific additional indications.

The members of the AFTER Study Group's steering committee are Professor D G Julian (chairman), Professor R Bernard, and Dr D A Chamberlain; and the staff at the statistical centre were Dr E J T Goetghebeur and Professor S J Pocock. The AFTER study participants are: United Kingdom—D Chamberlain (Royal Sussex County Hospital), L Borthwick (Lister Hospital, Stevenage), J Irving (Bangour General Hospital, West Lothian), W Murdoch (Heathfield Hospital, Ayr), J Pohl (Leicester General Hospital), D Wood

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Suicides after pregnancy in Finland, 1987-94: register linkage study

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Abstract

Objective—To determine rates of suicide associated with pregnancy by the type of pregnancy.

Design—Register linkage study. Information on suicides in women of reproductive age was linked with the Finnish birth, abortion, and hospital discharge registers to find out how many women who committed suicide had had a completed pregnancy during her last year of life.

Setting—Nationwide data from Finland.

Subjects—Women who committed suicide in 1987-94.

Results—There were 73 suicides associated with pregnancy, representing 5.4% of all suicides in women in this age group. The mean annual suicide rate was 11.3 per 100 000. The suicide rate associated with birth was significantly lower (5.9) and the rates associated with miscarriage (18.1) and induced abortion (34.7) were significantly higher than in the population. The risk associated with birth was higher among teenagers and that associated with abortion was increased in all age groups. Women who had committed a suicide tended to come from lower social classes and were more likely to be unmarried than other women who had had a completed pregnancy.

Conclusions—The increased risk of suicide after an induced abortion indicates either common risk factors for both or harmful effects of induced abortion on mental health.

Introduction

Childbirth has an impact on the mental health of women. Short term postnatal "blues" are experienced by 45-70% of women.^{1,2} An increased risk of non-psychotic depression after a delivery has been reported.^{3,4} The incidence of puerperal psychosis is 1.7 per 1000 live births.⁵ The initial stress effect of having a child, however, is transitional, and overall having a child has positive effects on women's mental health.⁶

Reports of mental complications after an induced abortion are controversial. Puerperal psychosis is rare (0.3 per 1000 abortions), but depression is more common (13-41%).⁷ Long term follow up studies, how-

ever, have documented more positive reactions and fewer undesirable feelings than short term studies.⁷

Less is known about the effects of miscarriage on mental health. A normal grief period is said to be from 6 to 12 months, but in some cases delayed, unresolved, and pathological grief may remain for years.⁸

There are only a few studies on suicides associated with pregnancy.⁹ The main reason may be the difficulty of getting reliable information on pregnancy before death¹⁰ and the relative rarity of suicides compared with other mental problems. The most reliable way to collect information on deaths related to pregnancy seems to be register linkage.¹¹

We determined the incidence of suicides up to one year after the end of a pregnancy by using national health registers. We analysed suicide rates by the type of pregnancy (birth, induced abortion, or miscarriage) and by background characteristics of the mothers.

Subjects and methods

Information on all deaths (n=9192) of women of childbearing age (15-49 years) in Finland in 1987-94 was extracted from the register of death certificates. Of these, 1347 had suicide as the main cause of death. No death had suicide as a contributing cause. The suicides were linked to the medical birth register (519 139 births in 1987-94), to the abortion register (117 139 abortions in 1986-94), and to the hospital discharge register (9 881 254 discharges in 1986-94) by using the mother's unique identification number to find evidence of termination of a pregnancy in the year before her death. The follow up period of one year was chosen according to the current definition of late maternal death.¹² We found 73 suicides associated with pregnancy. Ten violent and 16 non-violent deaths with unclear cause and 55 accidents associated with pregnancy were not included in the analysis.

The death certificate register, collected by Statistics Finland, is based on death certificates written by physicians. All the death certificates are checked by forensic specialists and by medical experts at Statistics Finland. Information on age, cause of death, residence, and occupation (in 1987) was gathered from the death certificates.

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