

Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial

I A Campbell,¹ D P Bentley,¹ R J Prescott,² P A Routledge,¹ H G M Shetty,³ I J Williamson⁴

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¹Llandough Hospital, Llandough, Cardiff CF64 2XX

²Department of Public Health Sciences, University of Edinburgh, Edinburgh

³University Hospital of Wales, Cardiff

⁴Royal Gwent Hospital, Newport, Gwent

Correspondence to: I A Campbell ian.campbell@cardiffandvale.wales.nhs.uk

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ABSTRACT

Objective To determine the optimum duration of oral anticoagulant therapy after an episode of deep vein thrombosis or pulmonary embolism, or both.

Design Multicentre, prospective, randomised study with follow-up for one year.

Setting 46 hospitals in United Kingdom.

Participants Patients aged ≥ 18 with deep vein thrombosis or pulmonary embolism, or both.

Interventions Three (n=369) or six months (n=380) of anticoagulation with heparin for five days accompanied and followed by warfarin, with a target international normalised ratio of 2.0-3.5.

Main outcome measures Death from deep vein thrombosis or pulmonary embolism; failure to resolve, extension, recurrence of during treatment; recurrence after treatment; and major haemorrhage during treatment.

Results In the patients allocated to three months' treatment two died from deep vein thrombosis or pulmonary embolism during or after treatment, compared with three in the six month group. During treatment deep vein thrombosis or pulmonary embolism failed to resolve, extended, or recurred in six patients in the three month group without fatal consequences, compared with 10 in the six month group. After treatment there were 23 non-fatal recurrences in the three month group and 16 in the six month group. Fatal and non-fatal deep vein thrombosis or pulmonary embolism during treatment, and after treatment thus occurred in 31 (8%) of those who had received three months' anticoagulation compared with 29 (8%) of those who had received six months' (P=0.80, 95% confidence interval for difference -3.1% to 4.7%). There were no fatal haemorrhages during treatment but there were eight major haemorrhages in those treated for six months and none in those treated for three months (P=0.008, -3.5% to -0.7%). Thus 31 (8%) of the patients receiving three months' anticoagulation experienced adverse outcomes as a result of deep vein thrombosis or pulmonary embolism or its treatment compared with 35 (9%) of those receiving six months' (P=0.79, -4.9% to 3.2%).

Conclusion For patients in the UK with deep vein thrombosis or pulmonary embolism and no known risk

factors for recurrence, there seems to be little, if any, advantage in increasing the duration of anticoagulation from three to six months. Any possible advantage would be small and would need to be judged against the increased risk of haemorrhage associated with the longer duration of treatment with warfarin.

Trial registration Clinical Trials NCT00365950.

INTRODUCTION

In 1992, the British Thoracic Society published the results of a multicentre prospective study, indicating that three months' anticoagulation should be given to patients with pulmonary venous thromboembolism (first episode or no episode for the previous three years).¹ This recommendation, however, has not been universally accepted, and authoritative sources in the United Kingdom, North America, and Europe continue to recommend six months or more. To obtain further evidence, the British Thoracic Society designed and conducted another multicentre study to compare the outcomes of two durations of anticoagulation, three and six months, with warfarin after initial heparin therapy.

METHODS

Patients

Eligible patients were aged ≥ 18 with suspected or proved deep vein thrombosis or pulmonary embolism, or both, whom the clinician intended to treat with anticoagulant. Categories of definite, probable (high or moderate probability), low probability, or negative were taken from the results of diagnostic tests. See bmj.com for list of excluding factors.

Design

Patients were randomised to three or six months of warfarin, the clinicians being asked to start warfarin on day one of the scheduled five days of heparin. Physicians used international normalised ratios to monitor anticoagulation with warfarin according to a standardised protocol.² The aim was to achieve ratios between 2.0 and 3.5.

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Clinicians were responsible for decisions about inpatient or outpatient management. They were asked to arrange follow-up appointments at three, six, and 12 months from the date of entry. Review forms were sent to the clinician before each follow-up date. These requested information on failure of resolution, extension or recurrence of deep vein thrombosis or pulmonary embolism, results of international normalised ratios, dates of start and completion of therapy with heparin and with warfarin, and adverse events.

Predetermined primary adverse outcomes were death from deep vein thrombosis or pulmonary embolism, failure during treatment (failure to resolve, extension, recurrence during treatment), recurrence after the end of treatment, and major haemorrhage during treatment.

We graded anticoagulation as good if the international normalised ratios were between 2.0 and 3.5 on at least two thirds of occasions, moderate if within that range on a third but less than two thirds of occasions, or poor if within that range for less than a third of occasions.¹ For patients in the six month group we applied these gradings separately for the first three months and for the second three months.

Haemorrhage was defined as major if the treating clinician deemed transfusion necessary, if the haemoglobin concentration fell by 20 g/l, if bleeding was intracranial or retroperitoneal, or if it was sufficiently serious for the clinician to discontinue anticoagulation.

Outcome at one year in patients with deep vein thrombosis or pulmonary embolism according to length of anticoagulation

	Three month group (n=369)	Six month group (n=380)
Deaths from PE during or after treatment	2 (0.5%)	3 (0.8%)
Deaths from haemorrhage during treatment	0	0
Deaths from known other causes during or after treatment	12	16*
Outcome at one year unknown	6	4
Non-fatal extensions, failures of resolution, or recurrences of DVT/PE	29 (8%)	26 (7%)*†
Major non-fatal haemorrhages during treatment	0	8 (2%)*†
Adverse outcome as a result of DVT/PE or its treatment	31 (8%)	35 (9%)

PE=pulmonary embolism; DVT=deep vein thrombosis.

*Includes one patient who died from haemorrhage after end of treatment, having had recurrence of DVT/PE and received further anticoagulation.

†Two patients had non-fatal extension, failure of resolution, or recurrence of DVT/PE as well major non-fatal haemorrhages.

Statistical analysis

We calculated that we would need 2400 patients to have 80% power to detect a difference, significant at the 5% level, between recurrence rates of 6% and 9%. After exclusion of ineligible patients we analysed the results by standard statistical methods according to the randomisation to define a full analysis population.

Type of anticoagulant

We offered centres a supply of a low molecular weight heparin (dalteparin) to use in the trial. Use of another low molecular weight heparin did not exclude these patients from the trial. The standard oral anticoagulant was warfarin, but clinicians could use an alternative coumarin if necessary.

RESULTS

From mid-September 1999 to the end of December 2002, 137 consultants from 46 hospitals entered 810 patients. After exclusions, 369 patients were randomised to three months and 380 to six months of treatment. Baseline characteristics were broadly similar, though a slightly higher proportion of men and of patients with pulmonary embolism were allocated to six months' treatment. The overall frequency of definite or probable diagnosis was 97% (see bmj.com).

Among those for whom we had the data, heparin was given for three to seven days in 74% of patients in the three month group and 77% of those in the six month group and warfarin as per protocol in 80% and 88% respectively (see bmj.com for details).

Control of warfarin therapy was good or moderate in most patients, but at the three month follow-up, 42 (13%) of 335 patients in the three month group with sufficient data were graded as poorly controlled, as were 37 (11%) of 340 in the six months group. Control improved between three and six months, and among those with sufficient data (n=313) only 11 (4%) were graded as poorly controlled.

During treatment four patients died from deep vein thrombosis or pulmonary embolism (one in the three month group, three in the six month group), and one patient in the three month group died from deep vein thrombosis or pulmonary embolism one month after completing treatment, an overall mortality of 0.7% (table).

Twelve patients in the three month group and 16 in the six month group died from causes other than deep vein thrombosis or pulmonary embolism during and after treatment. Of the 10 patients for whom we had no information on whether they were alive or had died by the end of their year in the trial, none had experienced any adverse outcome of deep vein thrombosis or pulmonary embolism or its treatment up to the time they were last reviewed.

Fatal and non-fatal failures during treatment plus recurrences after treatment occurred in 31 (8.4%) patients in the three month group and 29 (7.6%) in

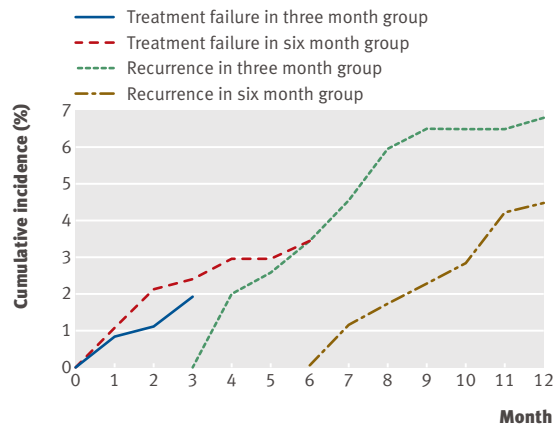


Fig 1 | Cumulative incidence of failure of treatment or recurrence of deep vein thrombosis or pulmonary embolism in the treatment groups

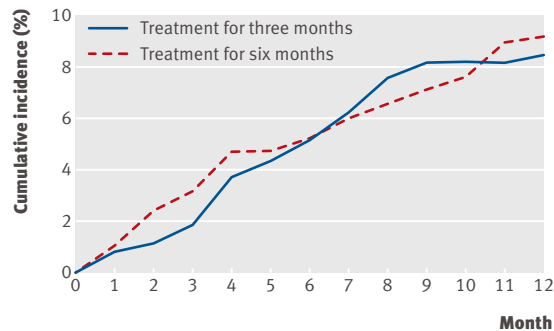


Fig 2 | Cumulative incidence of adverse outcomes in the two treatment groups

the six month group ($P=0.80$, 95% confidence interval for difference -3.1% to 4.7%) (fig 1).

During treatment no one in the three month group experienced major non-fatal haemorrhages, though eight (2%) in the six month group did (one in the second month, two in the third month, and five in the fourth month), one of whom also experienced failure during treatment and one experienced relapse after treatment ($P=0.008$, 95% confidence interval for difference -3.5% to -0.7%). None of these occurred when patients were receiving heparin.

Thus all adverse outcomes (deaths from deep vein thrombosis or pulmonary embolism, major haemorrhages during treatment, failures during treatment, and recurrences after treatment) as a result of deep vein thrombosis or pulmonary embolism or its treatment occurred in 31 (8%) patients allocated to three months' treatment and 35 (9%) patients allocated to six months' treatment (fig 2) ($P=0.79$, -4.9% to 3.2%).

In relation to outcome, there was no interaction between the duration of treatment and the original diagnosis (logistic regression $P=0.44$). See bmj.com for details.

The proportions of failures of resolution, extension, or recurrence of deep vein thrombosis or pulmonary embolism were similar in those who had received dalteparin (35/473; 7%), tinzaparin (22/243; 9%), and enoxaparin (3/22; 14%) ($\chi^2=1.5$, $df=2$, $P=0.47$).

DISCUSSION

In this trial, 8% of patients with deep vein thrombosis or pulmonary embolism experienced fatal and non-fatal failures of resolution, extension, or recurrence during and after three months of anticoagulation. The results were similar in those patients who had received six months' anticoagulation, but in this group 2% experienced major haemorrhages during treatment, whereas none of those treated for three months did. As we conducted the study across a wide range of acute hospitals in the UK, our results are likely to be representative of routine practice.

Previous randomised trials that included at least 100 patients with deep vein thrombosis or pulmonary embolism reported failures during treatment and recurrences after treatment for six months in 9-17% of patients.²⁻⁴ In 1992 the first British Thoracic Society study reported that 8% of patients who had received three months' anticoagulation experienced failure during treatment or recurrence after end of treatment, or both.¹ A study comparing three and six months' treatment found that both treatment times resulted in an 8% rate of failure during treatment or recurrence after the end of treatment.⁵ Another study randomised patients to six weeks' or six months' treatment and reported recurrence rates of 18% at two years with six weeks' treatment and 9% with six months' treatment.⁶ After six years, the recurrence rates rose to 28% in the six week group and 21% in six month group. The authors concluded that there was a cumulative risk of recurrence of 4-5% a year after the index event, independent of the initial duration of anticoagulation.⁷ After 10 years of follow-up there was no significant difference between the recurrence rates (31% and 27%).⁸ Another study following patients for two years found recurrence rates in those receiving three months' treatment varied between 12% and 16%, compared with 12% and 17% in those receiving 12 months' treatment. The authors concluded that prolonging anticoagulant therapy beyond three months simply delayed recurrence until anticoagulation was stopped.^{9,10} Another study compared three months' treatment with extended therapy, and concluded that patients with a first episode of idiopathic deep vein thrombosis or pulmonary embolism should be treated for longer than three months—although they did not say how much longer.¹¹

One year mortality from deep vein thrombosis or pulmonary embolism in previous clinical trials ranged from 0% to 2.2%,^{4,6,9-11} the previous study in 1992 reporting a rate of 1%,¹ whereas the 1996 and 2000 cohort studies each noted mortality of

WHAT IS ALREADY KNOWN ON THIS TOPIC

In patients with deep vein thrombosis or pulmonary embolism, or both, anticoagulation with heparin and warfarin reduces mortality and morbidity

Treatment for four to six weeks is usually enough for patients in whom the cause is transient
In other instances treatment for three months or more is necessary

WHAT THIS STUDY ADDS

For patients with deep vein thrombosis or pulmonary embolism in whom there are no persistent risk factors three months' anticoagulation is as effective as six months' treatment and is associated with a lower risk of major bleeding

0.5%.^{12,13} The 0.7% rate in the current study is well within this range.

A meta-analysis published in 2005 suggested that the risk of major bleeding was similar for patients receiving long term anticoagulation and those on short term regimens.¹⁴ Our results showed an overall rate of 1% in the trial as a whole, though the longer regimen of anticoagulation was associated with a 2% risk of major bleeding (none fatal) over the six month period of treatment. In the clinical trials between 1990 and 2005, deaths from major haemorrhage were reported in 0.1% to 0.4% of patients receiving three months' treatment compared with 0.1% in those receiving six months' treatment.^{1,5,6,9-11} In the cohort studies of 1996, 2000, and 2005 the death rate from major haemorrhage was 0.5% in those receiving three months' anticoagulation.¹²⁻¹⁵

Though we achieved a larger sample size than many other trials, it was disappointing relative to our planned sample (see bmj.com for reasons). The reduction in sample size increased the standard error of the differences for the primary outcome variables between the two periods of anticoagulation to 2% compared with an expected standard error with the original design of just over 1%. The observed differences for the primary outcome variables, however, are small, excluding substantial differences in favour of either length of treatment.

For patients with deep vein thrombosis or pulmonary embolism occurring in circumstances other than the presence of major thrombophilias or other persisting risk factors, our results do not affect the advice previously given in the British Thoracic Society guidelines.¹⁶ In terms of efficacy, three months' anticoagulation was associated with much the same benefit as six months' anticoagulant treatment but the shorter regimen seems to be associated with a lower incidence of haemorrhage during treatment.

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