Prevention and treatment of venous thromboembolism in hospital and the community: a research programme including the ExACT RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

A research programme including the ExACT RCT

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Scientific summary

Background

The venous thromboembolism prevention and treatment programme (RP-PG-0608-10073) was designed to provide an evidence base to improve the prevention and treatment of venous thromboembolism in the NHS by addressing some of the existing gaps in the evidence. The programme consists of a series of studies, including a randomised controlled trial; a survey of stakeholders; qualitative interviews with patients, doctors, nurses and other stakeholders; cost-effectiveness analyses; a patient preference survey; and a number of economic modelling studies.

The three interconnecting work packages were:

1. a randomised controlled trial of extended anticoagulation treatment versus standard treatment for the prevention of recurrent venous thromboembolism and post-thrombotic syndrome [the ExACT (Extended Anticoagulation) trial]
2. a qualitative study to explore existing knowledge and barriers, across the spectrum of health care from patients to health-care professionals [the ExPeKT (Exploration of Patient knowledge and expectation) study]
3. a health economic modelling study to evaluate the most cost-effective methods of treating and preventing recurrence of venous thromboembolism.

Objectives

Work package 1

- To determine the protective effect of prolonged anticoagulation therapy on recurrent events of deep-vein thrombosis or pulmonary embolism.
- To establish the performance characteristics of D-dimer testing while still on treatment as a prediction tool for recurrence of venous thromboembolism in patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism.
- To establish factors that contribute to the recurrence of venous thromboembolism in patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism.

Work package 2

- To assess the level of existing knowledge of venous thromboembolism risk among a wide range of primary health-care professionals and patients.
- To assess current practice and the perceived role of primary care in thromboprophylaxis among primary health-care professionals and patients.
- To explore the interface between primary and secondary care in terms of thromboprophylaxis and the perceived role of primary care among acute trusts and other relevant organisations.
- To identify local organisations' perceived and actual clinical barriers to implementation of thromboprophylaxis for high-risk patients.
- To explore potential care pathways for high-risk patients prior to hospital admission in terms of assessment for thromboprophylaxis.
- To design effective education initiatives to ensure public and primary care engagement in venous thromboembolism preventative measures outside the hospital setting.

Work package 3

- To determine the costs and cost-effectiveness of different approaches to delivery of care and treatment for suspected thromboembolism.
- To determine patient preferences for extended versus standard treatment.
- To determine the cost-effectiveness of the measurement of levels of D-dimer and subsequent extended treatment with anticoagulation.
- To determine patient preferences and utilities with regard to extended anticoagulation treatment.

Methods

Work package 1

A prospective, multicentre, randomised controlled trial.

Setting

Patients were identified from anticoagulation clinics in hospitals and general practices across the Midlands, UK. Recruitment and follow-up took place in both hospital and primary care settings.

Participants

Patients aged $\geq$ 18 years with a first unprovoked deep-vein thrombosis or pulmonary embolism.

Work package 2

A two-stage, mixed-methods study that included a survey study and a qualitative interview study.

Participants

Primary health-care professionals, patients, acute trusts and other key stakeholders.

Work package 3

Analysis and decision model for alternative treatment pathways, and a patient preference study.

Results

Work package 1

A total of 281 patients were recruited, of whom 141 were randomly allocated to the intervention arm (group E) and 140 were randomly allocated to the control arm (group D) of the study. There were 32 recurrent venous thromboembolisms in 31 patients (13.54 events per 100 person-years) in the control group (group D) compared with seven events in seven patients (2.75 events per 100 person-years) in the intervention group (group E). This gave an adjusted hazard ratio of 0.2 (95% confidence interval 0.09 to 0.46; $p < 0.001$), meaning that patients who received extended anticoagulation therapy were 80% less likely to suffer a recurrent event than those patients who discontinued anticoagulation therapy. Age did not affect the rate of recurrence in either group, but males had numerically more recurrences of venous thromboembolisms off treatment than females.

There were three major bleeding events (1.18 events per 100 person-years) in the control group (group D) and nine major bleeding events (3.54 events per 100 person-years) in the intervention group (group E), which gave an adjusted hazard ratio of 2.99 (95% confidence interval 0.81 to 11.05; $p = 0.10$). There were 19 clinically relevant non-major bleeding events (8.13 events per 100 person-years) in the control group (group D) and 28 clinically relevant non-major bleeding events (12.50 events per 100 person-years) in the intervention group (group E), which gave an adjusted hazard ratio of 1.51 (95% confidence interval 0.84 to 2.71; $p = 0.165$). These differences were not statistically significant. In both groups, more people aged > 65 years experienced bleeding

The D-dimer levels pre-randomisation showed no difference in terms of risk of recurrence, but a higher percentage of those patients with venous thromboembolism recurrence had a baseline D-dimer level above 0.5 µg/l; this was not statistically significant.

Similarly, there was no significant difference in the time in the therapeutic range for patients on extended treatment between those with and those without recurrence (84% vs. 76%), but the numbers are small.

In terms of the quality of life and post-thrombotic syndrome outcomes, there were no differences between the groups.

Work package 2

Using a combination of questionnaire surveys and face-to-face qualitative interviews with patients, health-care professionals and other stakeholders identified five key areas that remain barriers to the effective implementation of preventative strategies for hospital-acquired thrombosis: communication, knowledge, role of primary care, education and training, and barriers to patient adherence.

Work package 3

The health economic model suggested that extended treatment with oral anticoagulants was only cost-effective at the £20,000-per-quality-adjusted life-year level if the annual venous thromboembolism recurrence rate was between 17.5% and 22.5%, depending on the drug acquisition costs. A patient preference study demonstrated a strong patient preference for extended treatment with anticoagulants based on a fear of recurrent venous thromboembolism over the risk of bleeding.

Limitations

Work package 1 did not achieve its recruitment target, which made it difficult to draw strong conclusions on the generalisability of these data. There are two similar studies currently being undertaken, one in Canada [DODS (the D-dimer Optimal Duration Study)] and the other in the Netherlands [the Venous thrombolSm: Tailoring Anticoagulant therapy duration (VISTA) study], and we have an agreement with those triallists to combine data.

Another weakness of this study was that there was no blinding for some of the end-point adjudication, particularly the evaluation of post-thrombotic syndrome. However, in terms of thrombosis and bleeding, an independent end-point adjudication committee was established.

Conclusions

This programme of work has added to the growing evidence that patients suffering a first unprovoked venous thromboembolism could be treated for longer than the standard 3–6 months, with a significant reduction in recurrence and only a small increase in major bleeding. Patients expressed a strong preference for extended treatment. The within-trial economic analysis and the model that extrapolated beyond the trial suggested that the extended strategy was cost-effective; however, further health economic modelling utilising a previously derived prognostic model suggested cost-effectiveness with novel oral anticoagulants only if the risk threshold for annual recurrence was between 17.5% and 22.5%. There was no effect on the rate or severity of post-thrombotic syndrome.

Significant barriers were identified to the successful implementation of thromboprophylaxis of hospital-acquired thrombosis, particularly at a primary care level.

Future research should focus on better identifying patients in whom it is safe to stop anticoagulation therapy early following a first unprovoked venous thromboembolism, on improving communication

and knowledge of hospital-acquired thrombosis (particularly at the primary care level), and the health economic model can be utilised with future data to better elucidate the cost-effectiveness of prolonged anticoagulation.

Trial registration

This trial is registered as ISRCTN73819751 and EudraCT 2101-022119-20.

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This report

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