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A Randomised Controlled Trial of Extended Anticoagulation Treatment Versus Standard Treatment for the Prevention of Recurrent VTE and Post-thrombotic Syndrome in Patients Being Treated for a First Episode of Unprovoked VTE (The ExACT Study)

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Summary

Venous thromboembolism (VTE) is prevalent and impactful, with a risk of death, morbidity and recurrence. Post thrombotic syndrome (PTS) is a common consequence and associated with impaired quality of life (QoL).

The ExACT study was a non-blinded, prospective, multi-centred RCT comparing extended versus limited duration anticoagulation following a first unprovoked VTE (Proximal DVT or PE). Adults were eligible if they had completed ≥3 months anticoagulation (remaining anticoagulated). The primary outcome was time to first recurrent VTE from randomisation. The secondary outcomes included PTS severity, bleeding, QoL and D-dimers.

281 patients were recruited, randomised and followed up for 24 months (mean age 63, Male:Female 2:1). There was a significant reduction in recurrent VTE for patients receiving extended anticoagulation (2.75 vs 13.54 events/100 patient years, aHR 0.20(95%CI:0.09 to 0.46, p<0.001)) with a non-significant increase in major bleeding (3.54 vs 1.18 events/100 patient years, aHR 2.99(95%CI:0.81 to 11.05,p=0.10)). PTS and QoL outcomes were no different between groups. D-dimer results (on anticoagulation) did not predict VTE recurrence.

In conclusion, extended anticoagulation reduced VTE recurrence but did not reduce PTS or improve QoL and was associated with a non-significant increase in bleeding. Results also suggest very limited clinical utility of D-dimer testing using a standard cut off on anticoagulated patients.

Key words

Thrombosis (venous), Anticoagulation, Warfarin, Post Thrombotic Syndrome, D-dimer

Introduction

VTE is a prevalent and severe disease with a risk of death, recurrence, psychological impact, and long-term morbidity resulting from PTS with impaired QoL (Martinez *et al* 2014, Cohen *et al* 2007, Noble *et al* 2014, Kahn *et al* 2008, 2016).

Anticoagulation therapy (AT) remains the mainstay of treatment for VTE. Clinical guidelines recommend a minimum of 3 months AT for proximal DVT or PE, with consideration of long-term, indefinite duration AT following an unprovoked VTE due to the higher risk of VTE recurrence than following a provoked VTE (Martinex *et al* 2014, Baglin *et al* 2003, NICE CG144, Kearon *et al* 2016, Keeling *et al* 2011). Guidelines also recommend weighing up individual additional risk factors for recurrence and bleeding with consideration of patient preference to inform anticoagulation duration decisions. A further consideration is the potential consequence of recurrence, with a higher risk of death with symptomatic PE than DVT (Douketis *et al* 2007) and recurrence as PE more likely if initial presentation was PE (Baglin *et al* 2010). Other factors associated with an increased VTE recurrence risk include male sex (Roach *et al* 2015), raised D-dimer after cessation of anticoagulation for 1 month (Palareti *et al* 2002, Verhovsek et al 2008) and PTS (Rodger *et al* 2008). Various scores exist to aid recurrence risk stratification and counselling of individual patients (e.g. DASH, Tosetto *et al* 2012) but anticoagulation duration decisions are sometimes challenging.

PTS affects up to 50% of patients following DVT (Kahn *et al* 2016) and is associated with significant morbidity and negative impact on QoL. PTS manifests as a spectrum of symptoms and signs of chronic venous insufficiency in the lower limb including chronic, persistent pain, swelling, skin changes and leg ulcers. PTS is burdensome and costly due to its prevalence, severity, and chronicity. At the current time, management remains unsatisfactory and there is no cure for PTS. In addition, there are no known effective strategies to prevent PTS following a DVT. Known risk factors for development of PTS include age >65 years, ipsilateral DVT recurrence and subtherapeutic INR results if on warfarin (>50% of time with INR<2.0)(Van Dongen *et al* 2005). Therefore, it is possible that extended duration AT may reduce risk of PTS by reducing risk of ipsilateral DVT recurrence (including subclinical recurrence) that may further damage the vascular pump. The 10-year follow-up of the DURAC 1 study with 545 evaluable patients showed no effect of initial anticoagulation

duration (6 weeks versus 6 months) on risk for PTS in multivariate analysis (Schulman *et al* 2006). However, there has been no previous studies to test whether extended anticoagulation duration (beyond 6m) can reduce the risk of PTS.

The ExACT study was designed to answer whether extended AT for unprovoked VTE, reduces VTE recurrence and/or the incidence and severity of PTS compared to limited AT. It also assesses whether extended AT is associated with increased bleeding and improved QoL. The relationship between VTE recurrence and baseline D-dimer results (all participants whilst still anticoagulated), and between VTE recurrence and Therapeutic Time in Range (TTR) for the extended AT group was also explored.

Methods

Trial design and participants

ExACT was a non-blinded, multi-centre, two-arm, parallel-group RCT. Eligible patients were aged ≥18 years with a first unprovoked proximal DVT or PE who had completed a minimum of 3 months AT (target INR 2-3 for those taking warfarin) and remained anticoagulated. Patients were excluded if they had another indication for long-term AT (e.g. AF), were at high risk of bleeding (e.g. additional antiplatelet) or very high risk of VTE recurrence (e.g. active cancer or antiphospholipid syndrome) or a life expectancy <5 years. The full list of exclusion criteria is available in the protocol (Tullett *et al* 2013).

Trial oversight was by a Trial Steering Committee (TSC) and an independent Data Monitoring Committee (IDMC). Ethics permission was granted by Trent Research Ethics Committee; reference 11/H0605/5. The trial is registered **(**ISRCTN:73819751 and EUDRACT:2101-022119-20).

Recruitment, randomisation and intervention

Patients were identified from UK NHS anticoagulant clinics. Patients who gave informed, written consent were randomised (1:1) to either extended AT for 24 months or discontinued

AT. Randomisation was performed within the web-based computerised clinical case report form. The software used random blocks randomisation (block size of 4) stratified by diagnosis (DVT or PE). All participants were asked to attend 6 monthly study follow-up clinic appointments for two years (5 visits in total).

Blood samples

D-dimers were tested at the baseline appointment (on anticoagulation) on Point of Care (POC) device (Cobas h 232, Roche Diagnostics). Patient and researcher were blinded to these results.

Outcomes

The primary outcome was the time to first recurrent venous thromboembolism (VTE) between randomisation and 24 months. The secondary outcomes were: measures of incidence and severity of PTS using the Villalta Scale applied to both legs at baseline and 6 monthly follow-up clinic appointments (Kahn *et al* 2009), bleeding events (major and clinically relevant non-major, CRNM) and QoL (VEINES-QOL (22) and EQ-5D-3L)(Khan *et al* 2006) at 6 monthly follow-up clinic appointments.

The relationship between VTE recurrence and baseline D-dimer results for all participants, and between VTE recurrence and Therapeutic Time in Range (TTR) for the extended AT group was also explored.

An Independent Adjudication Committee, blind to the intervention allocation, scrutinised all thrombotic and haemorrhagic events in order to obtain objective confirmation.

Statistical analysis

Sample Size:

The study was designed to compare 2-year VTE recurrence rates between participants in the extended versus discontinued AT arms, and also to compare these rates for a group of participants with a baseline raised D-dimer (Palareti *et al* 2002). A sample size of 352 (176 per arm) would be sufficient to detect a clinically important difference between the arms with minimum 86% power, two-sided alpha=0.05, assuming recurrence rates between 1.4% and 4.3% for the extended AT arm and 14.2% in the discontinued AT arm (Prandoni *et al* 2007). Recruitment was lower than expected and at the TSC request, the power calculation was re-estimated where it was determined that a sample of 270 participants (allowing for 10% loss to follow up) would provide at least 80% power to detect the planned effect sizes.

Analysis

All primary analyses (primary and secondary outcomes) were performed on an intention to treat basis (ITT).

Participant characteristics are summarised by treatment arm using descriptive statistics.

The number and percentage of participants with at least one recurrent VTE is presented by trial arm. Cox regression analysis was used to compare the time to first recurrent VTE between randomisation arms, censoring for deaths, losses to follow-up and withdrawals of consent to use data. The analysis was adjusted for diagnosis (DVT/PE) at baseline. The proportional hazards assumption was tested by cumulative log hazard plots and including a time by treatment covariate in the analysis. The treatment effect is presented as a hazard ratio, with the total number of events and the number of events per 100 patient years to aid interpretation of the data.

Analysis to compare the time to the first major and CRNM bleeding events (as separate outcomes) between randomisation arms was performed as per the primary outcome.

Repeated measures mixed modelling was used to compare the PTS score between arms over the 2 year follow up. The analysis allowed for the repeated nature of the data measured at 6,

12, 18 and 24 months, including an interaction term between treatment and time point. The worst score from both of the participant's legs was counted as the score for the participant. The model was adjusted for the baseline PTS score; assessment time and diagnosis (DVT/PE) at baseline were included as fixed effects. Model assumptions were checked for evidence of non-normality in the residuals. The adjusted mean PTS scores at each time point are presented by arm. The presence and severity of PTS is also reported, using frequencies and percentages, according to the following cut offs (0-4:no PTS, 5-9:mild PTS, 10-14:moderate PTS, ≥15:severe PTS).

Estimates of treatment effects are presented with 95%, two-sided confidence intervals and P values.

Subgroup analyses were limited to primary outcome (time to first VTE recurrence) and main secondary outcome (time to first major bleeding event) and the predefined subgroups sex and age (≤65, >65years). Each subgroup effect was independently assessed by the inclusion of a treatment arm by subgroup interaction term in the Cox model. Subgroup related estimates and 95% confidence intervals are presented with interaction results alongside.

VTE recurrence rates are summarised by baseline D-Dimer level (<0.5µg/ml and ≥ 0.5µg/ml) for all participants. TTR results are summarised for participants on warfarin in the extended AT group by whether or not a VTE recurrence occurred during follow-up.

Stata version 12 was used for all analyses.

Results

Participant recruitment

Figures 1A and 1B summarise the flow of patients from initial screening through recruitment, randomisation and follow up. Two hundred and eighty-one patients provided written informed consent to participate and were randomised between July 2011 and February 2015 (141 to the extended AT and 140 to discontinued AT). In the extended AT arm, only 2 patients continued on rivaroxaban and the others (n=139) remained on warfarin. All 281 trial participants attended visit 1, 273/281 (97%) attended visit 2, 263 (94%) attended visit 3 and 260/281 (93%) visit 4.

Six participants in the discontinued AT group (4 withdrawals, 1 protein S deficiency and 1 antithrombin deficiency) and two in the extended AT group (1 withdrawal and 1 antiphospholipid syndrome) were excluded from the final ITT analysis by post-randomisation pre-defined exclusions.

Baseline Characteristics

No differences were found in baseline characteristics (**Table 1**). The mean age of participants was 63, with a roughly even split between DVT and PE, whilst 67% of participants were male.

Primary outcome

Over 24 months follow up, there were 32 recurrent VTEs in 31 patients (13.54 events/100 patient years, PY) within the discontinued AT group versus 7 events in 7 patients (2.75 events/100PY) in the extended AT group (aHR=0.20,95% CI:0.09 to 0.46, p<0.001)(**Table 2A, Figure 2A**). In this study, there is no evidence that sex or age group had a differential effect on the risk of VTE recurrence (p=0.099 and p=0.267 respectively **Table 2B**).

Secondary outcomes

There were 3 major bleeding events (1.18/100PY) in the discontinued AT group versus 9 (3.54/100PY) in the extended anticoagulation group (aHR=2.99,95%CI: 0.81 to 11.05, p=0.10). There were 19 clinically relevant non-major bleeding (CRNM) events (8.13/100PY) in the discontinued AT group, and 28(12.50/100PY) in the extended AT group (aHR=1.51,95%CI: 0.84 to 2.71, p=0.165). These differences were not statistically significant (**Table 2A, Figure 2B and C**). In this study, there is no evidence that sex or age group had a differential effect on the risk of major bleeding (p=0.96 and p=0.19 resp.) (**Table 2B**).

D-dimers were tested at baseline in 273 patients and only 12 patients (4.4%) had D Dimer≥0.5 µg/ml and of these, 3 patients had recurrent VTE and 9 did not. A higher percentage of those with VTE recurrence had a baseline D-dimer≥ 0.5µg/ml (n=3 of 38, 7.89% vs n=9 of 235, 3.83%) but this was not statistically significant (**Table 3A**).

Similarly, time in therapeutic range (TTR) for patients on extended AT with warfarin was not significantly different between those with or without recurrence but the number of recurrences were small (**Table 3B**). Patients randomised to warfarin overall had a mean time in therapeutic range (TTR) of 77% (recurrent VTE TTR=84% vs no recurrence=76%).

Outcome measures of QoL and PTS were not different between the groups (**Table 4A**). An additional post-hoc analysis of patients only presenting with DVT at baseline, also showed no evidence of a difference in PTS outcomes with extended or discontinued AT (**Table 4B**).

Discussion

The ExACT study adds to accumulating evidence that extended AT reduces risk of VTE recurrence in patients with a first unprovoked VTE but also adds new perspective by assessing the additional clinically relevant outcomes of PTS and QoL. ExACT also explores the value of D-dimer testing on anticoagulated patients to predict VTE recurrence.

A recent Health Technology Assessment (Sterne *et al* 2017) reviewed all RCTs for VTE secondary prevention and found 10 multicentre phase III trials (total n=10,390 participants). Four studies evaluated therapeutic warfarin for varying durations beyond 3 months versus no anticoagulation (Campbell *et al* 2007, Agnelli et al 2001, Agnelli *et al* 2003, Kearon et al 1999), two evaluated aspirin (Beccattini et al 2012, Brighton et al 2012) and four evaluated direct oral anticoagulants (DOACs) (Agnelli et al 2013, Wells et al 2016, Romualdi et al 2011, Bauersachs et al 2010, Schulman et al 2013, Weitz et al 2017). All currently licensed DOACs for this indication (Apixaban, Rivaroxaban and Dabigatran) have been compared to placebo. Rivaroxaban has also been compared to aspirin and Dabigatran has also been compared to

warfarin. In addition, Rivaroxaban and Apixaban have been tested at lower "prophylactic doses" for VTE secondary prevention.

Taken together, the published evidence demonstrates that extended AT (warfarin or DOAC) beyond 3 months significantly reduces VTE recurrence but only whilst on anticoagulation and balanced against this is an increased risk of bleeding. Compared to Warfarin, Dabigatran was non-inferior in efficacy but with less major or CRNM bleeding events in the dabigatran arm. Compared to placebo, Dabigatran, Rivaroxaban and Apixaban all reduced the risk of VTE recurrence but resulted in increased bleeding, apart from the lower dose of apixaban 2.5mg bd which had equivalent bleeding risk to placebo. Compared to aspirin, rivaroxaban was more effective with equivalent bleeding risk.

The ExACT study is in alignment with this literature, demonstrating an 80% reduction in VTE recurrence risk for patients receiving extended AT following an unprovoked VTE. There were numerically more bleeding events in the extended AT arm, but not a statistically significant difference, likely due to the small number of events. Interpretation of subgroup analyses in the ExACT trial (age and sex) is also limited due to insufficient patient numbers (including only 1/3 female) and infrequent events. For example, the 3 fold increase in major bleeding events in >65 years patients on extended AT aligns with previous literature, but the small number of events meant statistical significance was not reached.

The TTR for the ExACT study was 77% which compares favourably with warfarin secondary prevention clinical trials (mean TTR: 64% in LAFIT, 65.3% in RE-MEDY and 81% in WODIT-DVT). Subtherapeutic INR has been associated with risk of VTE recurrence in previous studies (Nordstrom et al 2015) but in ExACT, the few recurrences that occurred on extended AT did not appear related to poor INR control (mean TTR=84% in those with VTE recurrence vs 76%).

Remarkably, none of the published 10 RCTs for VTE secondary prevention have included measurement of PTS as an outcome and as this is the greatest source of morbidity and impaired quality of life following a DVT, the inclusion of this assessment in the ExACT study is important and novel. Currently, there are no effective PTS prevention interventions that are broadly applicable to patients following a DVT. Although the CaVenT RCT demonstrated a

reduced risk of PTS with catheter directed thrombolysis for proximal DVT (Haig et al 2016), the ATTRACT study failed to demonstrate benefit (Vedantham 2017). In addition, the consistently reported increased bleeding risk and need for interventional radiology makes this intervention only applicable to a minority of patients. Compression stockings were long thought to reduce risk of PTS following DVT and were routinely used. However, recent data including large placebo controlled RCT have failed to demonstrate benefit of compression stockings to reduce risk of PTS following DVT(Subbiah *et al* 2016).

The ExACT study is the first to evaluate whether extended AT could reduce the incidence of PTS. It has previously been reported that the majority of patients with a PE diagnosis have an associated DVT (approximately 70%, Wilbur and Shian 2017), but it is not standard practice to screen and diagnose these as findings do not influence management. Consistent with this, patients recruited to the ExACT study with a PE were not routinely screened for DVT but PTS assessments were done for all patients (DVT and PE). By 2 years follow up, although over half of patients had developed some degree of PTS, only a minority of these were severe and there were no differences in frequency or severity between those patients randomised to extended versus discontinued AT. A post-hoc restricted analysis of patients only presenting with DVT also showed no evidence of a difference in PTS outcomes between groups. Previous data demonstrated that subtherapeutic INRs in the initial phase of AT is a risk factor for PTS (van Dongen *et al* 2005), which when combined with ExACT results, suggests optimising initial anticoagulation treatment is the priority to reduce PTS risk rather than extending the duration. It also suggests that the pathogenesis of PTS results from venous damage associated with the initial acute event rather than any ongoing further new thrombotic process. In addition, extending AT did not show evidence of an improved QoL as assessed by either generic or disease specific measures of QoL.

To-date, numerous clinical studies have evaluated D-dimer assays as a predictive biomarker for VTE recurrence but most studies have tested D-dimers after discontinuation of anticoagulation for 1 month. Raised D-dimers at this time point have been associated with a higher risk of VTE recurrence (Verhovsek *et al* 2008, Palareti *et al* 2002). However, stopping anticoagulation for 1 month to enable testing is logistically complex and potentially harmful with risk of VTE recurrence while awaiting testing.

Kearon et al assessed D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy in a cohort study (n=410). By far the majority (97%) of anticoagulated patients had a negative D-dimer. Of these, 85% continued to have negative D Dimers after stopping anticoagulation for 1 month but still remained at high risk of recurrent VTE (annual recurrence of 9.7% men and 5.4% women)(Kearon *et al* 2015). This highlights the reduced sensitivity of D-dimer testing in anticoagulated patients and the limitations of D-dimer testing to decide which patients can safely stop anticoagulation. Kearon et al have recently published an updated analysis of this cohort with extended follow up (median of 5 years) and demonstrated a continued high risk of VTE recurrence in male patients with a negative D-dimer (testing off anticoagulation, 7.5%/PY)(Kearon *et al* 2019). Similarly, in the ExACT study, only a small proportion (4.4%) of participants had positive D-dimers whilst on anticoagulation. Out of the 38 participants who went on to develop VTE recurrences, by far the majority (n=33, 87%) had negative D-dimer results. Therefore, D-dimer results using a standard cut off, on anticoagulated patients are not helpful to determine patients at low risk of VTE recurrence to stop anticoagulation. It is possible that a lower D-dimer cut off threshold could be more informative for patients on anticoagulation. The HERDOO2 rule has been prospectively validated using a lower cut off (250mcg/L) and a different D-dimer assay (VIDAS)(Roger et al 2017). However, other investigators have not used this cut off (e.g. Palareti et al Blood 2014, Kearon C 2015 and 2019). The optimal D-dimer cut off and specific assay to use in this context remains uncertain. In addition, it is unclear whether single testing or serial testing is better and how results should influence clinical management (Kearon and Akl 2014).

The limitations of the ExACT study include that nearly all patients in the extended AT arm received warfarin treatment whereas DOACs are now the preferred choice for VTE secondary prevention in the majority of patients. In addition, interpretation of bleeding outcomes and subgroup analyses (age and sex) are limited due to insufficient patient numbers (including 1/3 female) and infrequent events.

In summary, the ExACT study confirms that extended AT treatment for a first unprovoked VTE provides substantial protection in terms of recurrent VTE but does not reduce risk of PTS or improve QoL and is associated with a non-significant increase in bleeding. Finally, D-dimer results, using a standard cut off, in anticoagulated patients are unlikely to inform clinical decisions.

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Author Contributions

The study was designed, and funding were secured by DF, FDRH, CG, CH, and SJ. KF and DM undertook day-to-day management of the study and were responsible for data management and quality assurance. HS and GH undertook data collection. AR and PH provided senior quantitative methodological support for the design of the statistical analysis. AR and YS developed the statistical analysis plan, YS undertook the statistical analysis and contributed to the interpretation of findings. DM and KF contributed to the descriptive analysis. All authors contributed to data interpretation. CB and DF wrote the first draft of this paper and all authors were responsible for subsequent critical revision of the manuscript.

Declaration of interests

CB has received speaker fees from BMS Pfizer, Novartis and Janssen. Advisory fees: Ablynx and Novartis. Funding to attend conferences: Amgen and Bayer. FDRH has received occasional consultancy fees and expenses from BMS/Pfizer and Boehringer Ingelheim. None of the other authors have competing interests to declare.

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