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A randomised controlled trial of extended anticoagulation treatment *versus* standard treatment for the prevention of recurrent venous thromboembolism (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, multicentred randomised controlled trial comparing extended *versus* limited duration anticoagulation following a first unprovoked VTE (proximal deep vein thrombosis or pulmonary embolism). 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. Two-hundred and eighty-one 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, adjusted hazard ratio (aHR) 0·20 (95% confidence interval (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: 0·81–11·05, $P = 0·10$)]. Outcomes of PTS and QoL 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 on anticoagulated patients.

Keywords: thrombosis (venous), anticoagulation, warfarin, post-thrombotic syndrome, D-dimer.

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

Anticoagulation therapy (AT) remains the mainstay of treatment for VTE. Clinical guidelines recommend a minimum of three months AT for proximal deep vein thrombosis (DVT) or pulmonary embolism (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 (Baglin *et al*, 2003; Keeling *et al*, 2011; NICE, 2012; Martinez *et al*, 2014; Kearon *et al*, 2016). 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

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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 one 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.

Post-thrombotic syndrome affects up to 50% of patients following DVT (Kahn 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 (International Normalised Ratio) 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 (six weeks *versus* six months) on risk for PTS in multivariate analysis (Schulman *et al*, 2006). However, there have been no previous studies to test whether extended anticoagulation duration (beyond six months) 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, multicentre, two-arm, parallel-group randomised controlled trial (RCT). Eligible patients were aged ≥18 years with a first unprovoked proximal DVT or PE who had completed a minimum of three 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. atrial fibrillation), 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 six monthly study follow-up clinic appointments for two years (five visits in total).

Blood samples

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

Outcomes

The primary outcome was the time to first recurrent 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 six monthly follow-up clinic appointments (Kahn 2009), bleeding events (major and clinically relevant non-major, CRNM) and QoL (VEINES-QOL and EQ-5D-3L) (Khan *et al*, 2006) at six monthly follow-up clinic appointments.

The relationship between VTE recurrence and baseline D-dimer results for all participants, and between VTE recurrence and 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 two-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 $\alpha = 0{\cdot}05$, 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's 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 two-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 cutoffs (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, >65 years). 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.

Venous thromboembolism recurrence rates are summarised by baseline D-dimer level (<0·5 and ≥0·5 μg/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 (Stata statistical software, London, UK) was used for all analyses.

Results

Participant recruitment

Figures 1A, 1 summarise the flow of patients from initial screening through recruitment, randomisation and follow-up. In all, 281 patients provided written informed consent to participate and were randomised between July 2011 and February 2015 (141 to the extended AT arm and 140 to discontinued AT). In the extended AT arm, only two 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 (four withdrawals, one protein S deficiency and one antithrombin deficiency) and two in the extended AT group (one withdrawal and one antiphospholipid syndrome) were excluded from the final ITT analysis by postrandomisation predefined exclusions.

Baseline characteristics

No differences were found in baseline characteristics (Table I). 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* seven events in seven patients (2·75 events/100PY) in the extended AT group [adjusted hazard ratio (aHR) = 0·20, 95% CI: 0·09–0·46, $P < 0{\cdot}001$] (Table II, Fig 2A). There was no evidence that sex or age group had a differential effect on the risk of VTE recurrence ($P = 0{\cdot}099$ and $P = 0{\cdot}267$ respectively Table III).

Secondary outcomes. There were three major bleeding events (1·18/100PY) in the discontinued AT group *versus* nine (3·54/100PY) in the extended anticoagulation group (aHR = 2·99, 95% CI: 0·81–11·05, $P = 0{\cdot}10$). There were 19 CRNM bleeding events (8·13/100PY) in the discontinued AT group, and 28 (12·50/100PY) in the extended AT group (aHR = 1·51, 95% CI: 0·84–2·71, $P = 0{\cdot}165$). These differences were not statistically significant (Table II, Figure 2B, 2). There was no evidence that sex or age group had a differential effect on the risk of major bleeding ($P = 0{\cdot}96$ and $P = 0{\cdot}19$ resp.) (Table III).

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, three patients had recurrent VTE and nine did not. A higher percentage of those with VTE recurrence had a baseline D-dimer ≥0·5 μg/ml (n = 3 of 38, 7·89% vs. n = 9 of 235, 3·83%) but this was not statistically significant (Table IV).

Similarly, 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 V). Patients randomised to warfarin overall had a TTR of 77% (recurrent VTE TTR = 84% vs. no recurrence = 76%).

Outcome measures of QoL and PTS were not different between the groups (Table VI). 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 VII).

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 three months *versus* no anticoagulation (Kearon *et al*, 1999; Agnelli *et al*, 2001; Agnelli *et al*, 2003; Campbell *et al*, 2007), two evaluated aspirin (Beccattini *et al*, 2012; Brighton *et al*, 2012) and four evaluated direct oral anticoagulants (DOACs) (Bauersachs *et al*, 2010; Romualdi *et al*, 2011; Agnelli *et al*, 2013; Schulman *et al*,

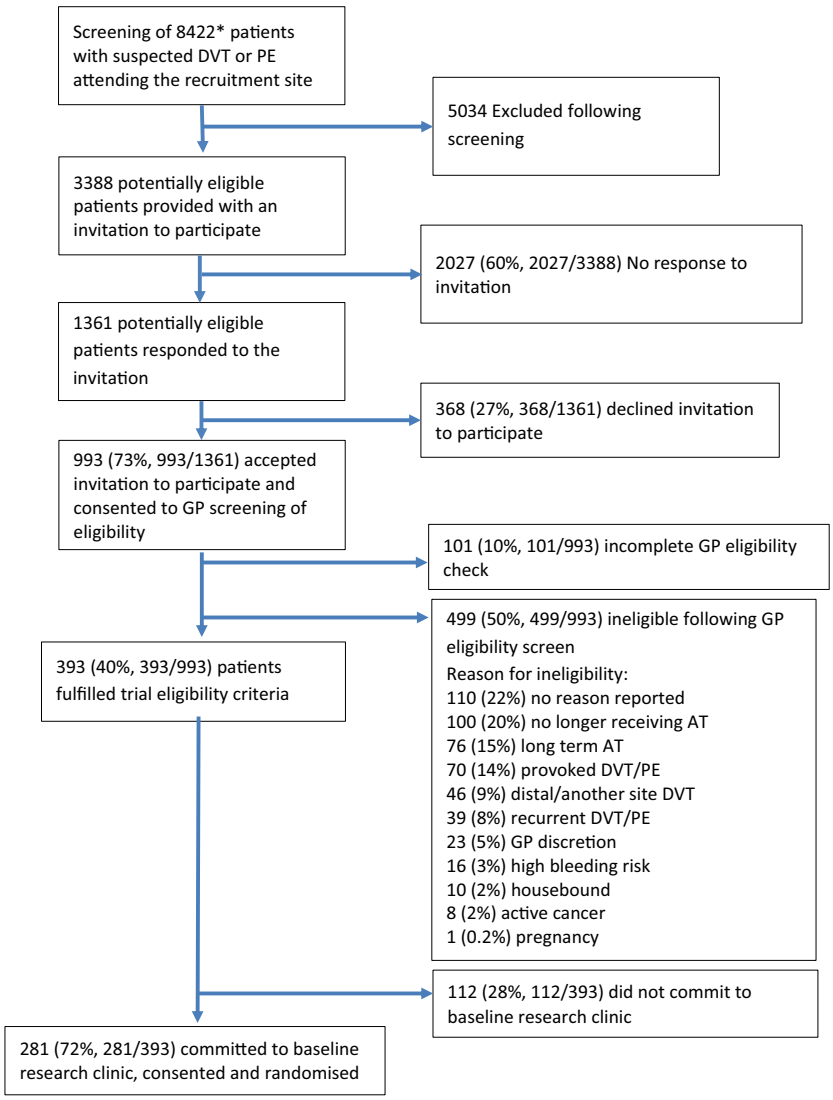

Fig 1. (A) Patient flow. *, data for suspected deep vein thrombosis (DVT) or pulmonary embolism (PE) are taken from site screening logs and are therefore only estimates of the total number with DVT or PE. (B) Patient flow following randomisation. *, includes four participants who withdrew consent to use their data; **, includes one participant who withdrew consent to use their data; ***, includes two patients receiving rivaroxaban therapy. A, anticoagulation therapy; GP, general practitioner. [Colour figure can be viewed at wileyonlinelibrary.com].

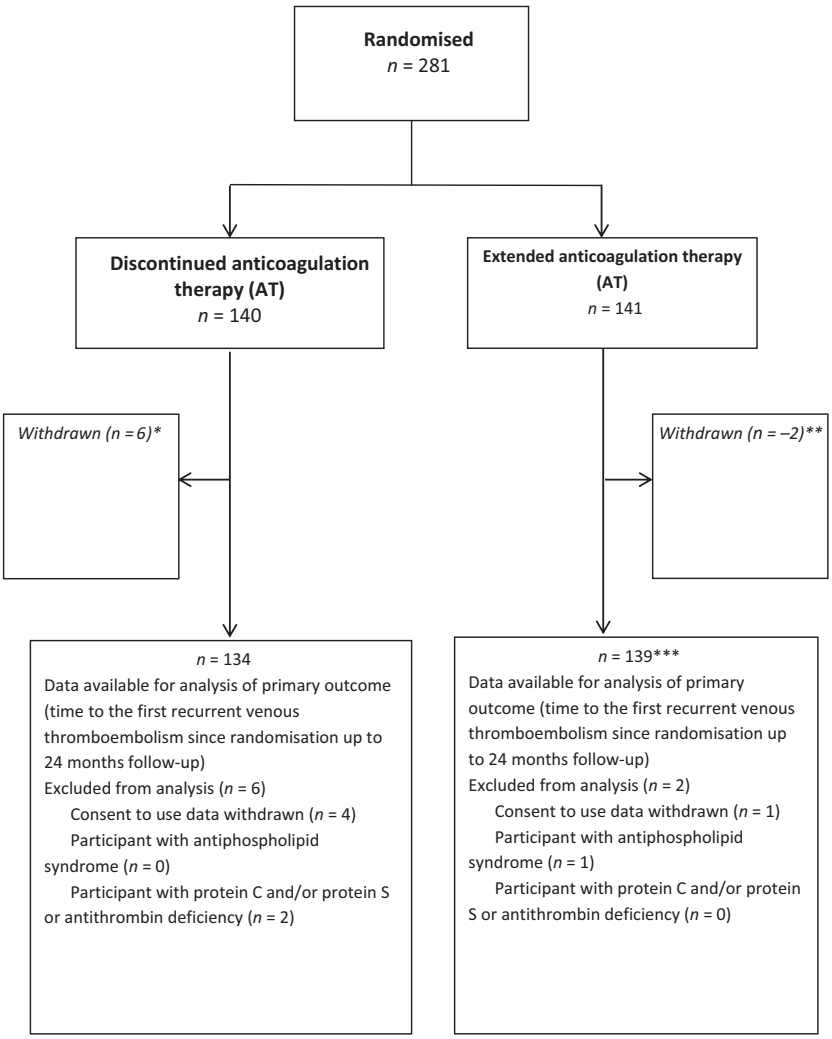

Fig 1. (Continued)

2013; Wells *et al*, 2016; 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 three 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 2·5 mg 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 threefold increase in major bleeding events in patients >65 years 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

Table I. Baseline characteristics.

Characteristic	Discontinued AT n = 134	Extended AT n = 139	Total n = 273
Age at time of randomisation			
Mean (SD)	63·3 (12·7)	62·2 (13·0)	62·7 (12·8)
Median (IQR)	64·5 (55·6–74·0)	64·4 (53·3–72·4)	64·4 (54·4–72·7)
Sex, *n* (%)			
Female	44 (32·8)	45 (32·4)	89 (32·6)
Male	90 (67·2)	94 (67·6)	184 (67·4)
Diagnosis (DVT/PE)†, *n* (%)			
Unprovoked DVT	69 (51·5)	70 (50·4)	139 (50·9)
Unprovoked PE	65 (48·5)	69 (49·6)	134 (49·1)
Ethnicity, *n* (%)			
White	131 (97·8)	131 (94·2)	262 (96·0)
Mixed	1 (0·8)	0 (0·0)	1 (0·4)
Asian or Asian British	0 (0·0)	3 (2·2)	3 (1·1)
Black or Black British	2 (1·5)	5 (3·6)	7 (2·6)
Other ethnic groups	0 (0·0)	0 (0·0)	0 (0·0)
Smoking status, *n* (%)			
Non-smoker	63 (47·0)	60 (43·2)	123 (45·1)
Ex-smoker	48 (35·8)	60 (43·2)	108 (39·6)
Current smoker	19 (14·2)	18 (13·0)	37 (13·6)
Smokes occasionally	4 (3·0)	1 (0·7)	5 (1·8)
Alcohol consumption, *n* (%)			
No	44 (32·8)	51 (36·7)	95 (34·8)
Yes	90 (67·2)	88 (63·3)	178 (65·2)
BMI classification, *n* (%)			
Underweight (<18·5)	2 (1·5)	0 (0·0)	2 (0·7)
Normal range (18·5–24·99)	47 (35·1)	47 (33·8)	94 (34·4)
Overweight (25–29·99)	51 (38·1)	53 (38·1)	104 (38·1)
Obese (≥30)	33 (24·6)	37 (26·6)	70 (25·6)
Missing	1 (0·8)	2 (1·4)	3 (1·1)
Family history of VTE, *n* (%)			
No	102 (76·1)	102 (73·4)	204 (74·7)
Yes	32 (23·9)	37 (26·6)	69 (25·3)
Previous medical history			
Stroke, *n* (%)			
No	130 (97·0)	136 (97·8)	266 (97·4)
Yes	4 (3·0)	3 (2·2)	7 (2·6)
Transient ischaemic attack (TIA), *n* (%)			
No	129 (96·3)	138 (99·3)	267 (97·8)
Yes	5 (3·7)	1 (0·7)	6 (2·2)
Angina, *n* (%)			
No	129 (96·3)	136 (97·8)	265 (97·1)
Yes	5 (3·7)	3 (2·2)	8 (2·9)
Myocardial infarction (MI), *n* (%)			
No	133 (99·3)	134 (96·4)	267 (97·8)
Yes	1 (0·8)	5 (3·6)	6 (2·2)
Ischaemic heart disease (IHD), *n* (%)			
No	130 (97·0)	136 (97·8)	266 (97·4)
Yes	4 (3·0)	3 (2·2)	7 (2·6)
Peripheral vascular disease (PVD), *n* (%)			
No	134 (100·0)	134 (96·4)	268 (98·2)
Yes	0 (0·0)	5 (3·6)	5 (1·8)
PTS score (categorical), *n* (%)			
No PTS	70 (52·2)	66 (47·5)	136 (49·8)
Mild PTS	42 (31·3)	51 (36·7)	93 (34·1)
Moderate PTS	15 (11·2)	18 (13·0)	33 (12·1)

Table I. (*Continued*)

Characteristic	Discontinued AT n = 134	Extended AT n = 139	Total n = 273
Severe PTS	5 (3·7)	2 (1·4)	7 (2·6)
Missing	2 (1·5)	2 (1·4)	4 (1·5)
PTS score			
Mean (SD)	5·2 (4·2)	5·1 (3·8)	5·2 (4·0)
Median (IQR)	4·0 (2·0–7·5)	5·0 (2·0–8·0)	4·0 (2·0–8·0)
Missing	2	2	4
EQ-5D-3L			
Mean (SD)	0·8 (0·2)	0·8 (0·3)	0·8 (0·3)
Median (IQR)	0·8 (0·7–1·0)	0·8 (0·7–1·0)	0·8 (0·7–1·0)
Missing	0	4	4
VEINES-QOL score			
Mean (SD)	48·2 (10·7)	49·6 (9·9)	48·9 (10·3)
Median (IQR)	51·1 (41·1–57·6)	53·0 (44·6–56·7)	52·1 (43·3–57·5)
Missing	0	2	2
Health care utilisation due to PTS			
Patient receiving primary care treatment, *n* (%)			
No	124 (92·5)	128 (92·1)	252 (92·3)
Yes	9 (6·7)	11 (7·9)	20 (7·3)
Missing	1 (0·8)	0 (0·0)	1 (0·4)
Type of nurse patients were seen by, *n* (%)			
Practice	2 (1·5)	1 (0·7)	3 (1·1)
District	0 (0·0)	0 (0·0)	0 (0·0)
HCA	0 (0·0)	0 (0·0)	0 (0·0)
None	59 (44·0)	70 (50·4)	129 (47·3)
Other	0 (0·0)	0 (0·0)	0 (0·0)
Missing	73 (54·5)	68 (48·9)	141 (51·7)
Patient receiving treatment for a leg ulcer, *n* (%)			
No	66 (49·3)	71 (51·1)	137 (50·2)
Yes	1 (0·8)	2 (1·4)	3 (1·1)
Missing	67 (50·0)	66 (47·5)	133 (48·7)
Patient receiving secondary care treatment, *n* (%)			
No	131 (97·8)	135 (97·1)	266 (97·4)
Yes	1 (0·8)	4 (2·9)	5 (1·8)
Missing	2 (1·5)	0 (0·0)	2 (0·7)

BMI, body mass index; DVT, deep vein thrombosis; HCA, health care assistant; IQR, interquartile range; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life; SD, standard deviation; VTE, venous thromboembolism.
†Minimisation variable.

outcome and as this is the greatest source of morbidity and impaired QoL 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 *et al*, 2017). In addition, the consistently reported increased bleeding risk and need for interventional radiology makes this intervention only applicable to a minority of patients (Broderick *et al*, 2016). 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 & Shian, 2017), but it is not standard practice to screen and diagnose these as it does 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 two 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

Table II. Primary and secondary outcomes.

Outcome	Discontinued AT $n = 134$	Extended AT $n = 139$	Adjusted hazard ratio (95% CI)‡	*P*-value
Primary outcome				
Recurrent VTE				
No of participants with ≥ 1 event – *n* (%)	31 (23·1)	7 (5·0)	0·20 (0·09, 0·46)	<0·001
No. of events§	32	7		
No./100 person-years¶	13·54	2·75		
Secondary outcomes				
Major bleeding events			2·99 (0·81, 11·05)	0·100
No of participants with ≥ 1 event – *n* (%)	3 (2·2)	9 (6·5)		
No. of events	3	9		
No./100 person-years¶	1·18	3·54		
Clinically relevant non-major bleeding events				
No of participants with ≥ 1 event and non-missing event dates† – *n* (%)	19 (14·2)	28 (20·1)	1·51 (0·84, 2·71)	0·165
No of participants with ≥ 1 event† – *n* (%)	21 (15·7)	32 (23·0)		
No. of events†	25	43		
No./100 person-years¶	8·13	12·50		

AT: anticoagulation therapy; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
†Two participants in the discontinued AT group and seven in the extended AT group had two or more thrombotic events within the two -year follow-up period, resulting in 15 repeated occurrences in total. Among the 53 time to first events, six events (two in the discontinued AT group and four in the extended AT group) had their event time missing (all of which should have occurred before the end of two-year follow-up by checking the corresponding visit number); so only 47 events contributed to the calculation of the adjusted hazard ratio.
‡Adjusting for baseline diagnosis (DVT/PE).
§One participant in the discontinued AT group had two thrombotic events within the two-year follow-up period.
¶Number of events per 100 person-years was calculated only for the first events with a non-missing event time.

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 one month. Raised D-dimers at this time point have been associated with a higher risk of VTE recurrence (Palareti *et al*, 2002; Verhovsek *et al*, 2008). However, stopping anticoagulation for one month to enable testing is logistically complex and potentially harmful with risk of VTE recurrence whilst 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 one 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 five 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 cutoff, 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 cutoff threshold could be more informative for patients on anticoagulation. The HERDOO2 rule has been prospectively validated using a lower cutoff (250 mcg/l) and a different D-dimer assay (VIDAS) (Rodger *et al*, 2017). However, other investigators have not used this cutoff (e.g. Palareti *et al*, 2014; Kearon *et al*, 2015 and 2019). The optimal D-dimer cutoff 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 & Akl, 2014).

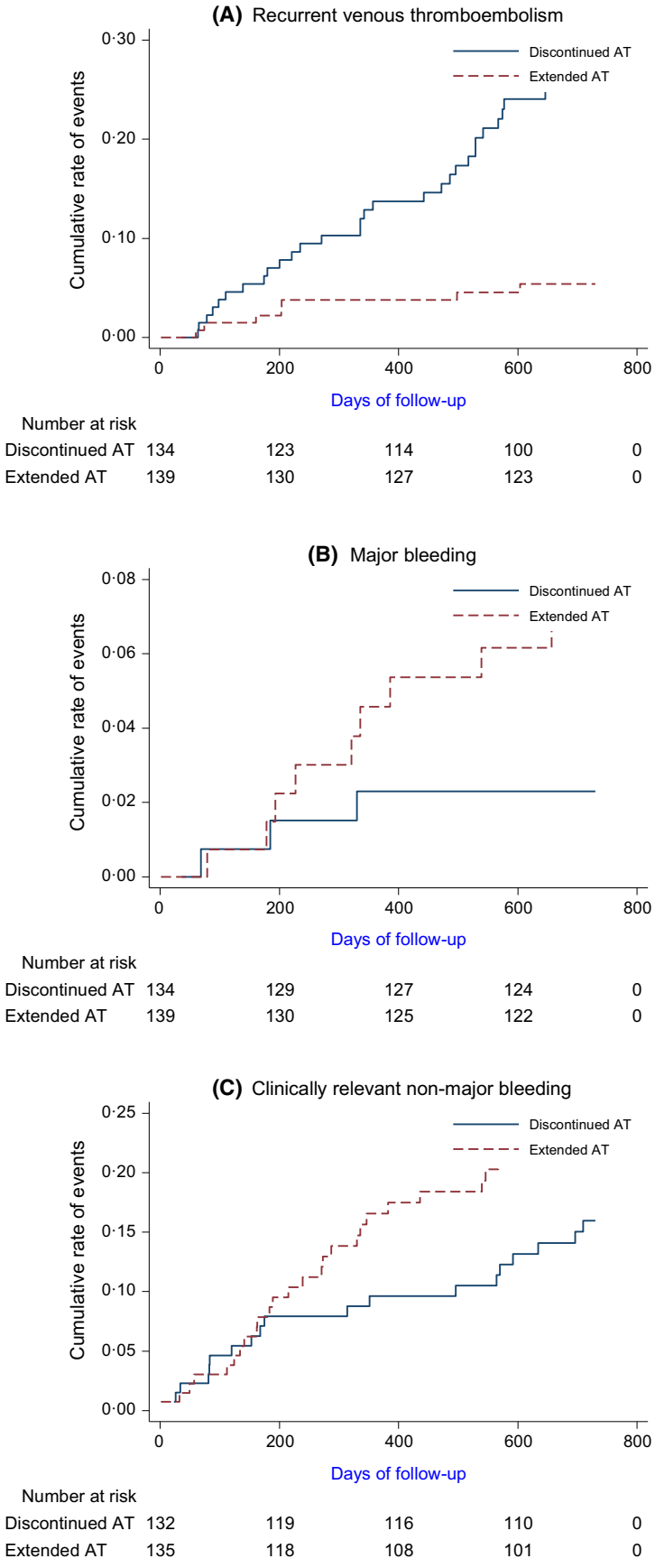

Fig 2. Cumulative risk of the primary outcome of time to first recurrent venous thromboembolism (A) and of the secondary outcomes of time to first major bleeding (B), and time to first clinically relevant non-major bleeding event (C) between discontinued and extended anticoagulation therapy (AT) groups. [Colour figure can be viewed at wileyonlinelibrary.com].

Table III. Subgroup analysis of primary and secondary outcomes.

	Discontinued AT n = 134		Extended AT n = 139			
Characteristic	n of events (%)	n/100 person-years	n of events (%)	n/100 person-years	Hazard ratio (95% CI)†	P-value for interaction
Recurrent VTE						
Sex						
Male	23 (25·6)	15·26	3 (3·2)	1·75	0·11 (0·03, 0·38)	0·099
Female	8 (18·2)	10·23	4 (8·9)	4·83	0·48 (0·14, 1·59)	
Age						
≤65 years	17 (23·3)	13·77	2 (2·8)	1·52	0·11 (0·03, 0·48)	0·267
>65 years	14 (23·0)	13·28	5 (7·5)	4·07	0·31 (0·11, 0·85)	
Major bleeding events						
Sex						
Male	2 (2·2)	1·18	6 (6·4)	3·57	2·92 (0·59, 14·48)	0·961
Female	1 (2·3)	1·18	3 (6·7)	3·49	3·13 (0·33, 30·12)	
Age						
≤65 years	2 (2·7)	1·45	2 (2·8)	1·50	1·01 (0·14, 7·17)	0·190
>65 years	1 (1·6)	0·86	7 (10·5)	5·79	6·89 (0·85, 56·03)	

AT: anticoagulation therapy; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism.
†Adjusting for baseline diagnosis (DVT/PE), the interaction between treatment and each of the two covariates (age and sex), separately, together with their main effects.

Table IV. Association of baseline D-dimer and risk of VTE recurrence.

D-dimer at baseline (μg/ml)	No recurrence (n = 235)	Recurrent venous thromboembolism (n = 38)	Total (n = 273)
Baseline D-dimer < 0·5 (%)	216 (86·74)	33 (13·25)	249
Baseline D-dimer ≥ 0·5 (%)	9 (75)	3 (25)	12
Missing	10	2	12

VTE, venous thromboembolism.

Table V. The Therapeutic Time in Range (TTR) for the Intervention group (extended AT) by the recurrence of venous thromboembolism (18 participants with zero TTRs were excluded).

TTR	No recurrence (n = 116)	Recurrent venous thromboembolism (n = 5)†	Total (n = 121)
Mean (SD)	76·27 (15·27)	83·93 (13·86)	76·59 (15·24)
Median (IQR)	77·03 (67·81–86·53)	76·95 (75·22–97·63)	77·02 (68·21–86·66)

AT, anticoagulation therapy; INR, International Normalised Ratio; IQR, interquartile range; SD, standard deviation.
†Two patients excluded, one patient received rivaroxaban and one patient did not attend for INR monitoring.

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 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 cutoff, in anticoagulated patients are unlikely to inform clinical decisions.

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Table VI. Secondary outcomes (continuous).

Outcome	Discontinued AT n = 134		Extended AT n = 139		P-value for time–treatment interaction
	n	Adjusted mean† (95% CI)	n	Adjusted mean† (95% CI)	
VEINES-QOL					
6 months	118	50·13 (48·98, 51·29)	126	49·87 (48·74, 51·00)	0·766
12 months	116	50·13 (48·97, 51·29)	124	50·34 (49·20, 51·48)	
18 months	112	50·74 (49·57, 51·91)	117	50·20 (49·04, 51·35)	
24 months	108	50·33 (49·14, 51·51)	120	50·30 (49·16, 51·45)	
EQ-5D-3L					
6 months	118	0·80 (0·76, 0·83)	126	0·81 (0·78, 0·84)	0·908
12 months	117	0·81 (0·77, 0·84)	124	0·81 (0·78, 0·85)	
8 months	113	0·82 (0·79, 0·86)	117	0·82 (0·79, 0·86)	
24 months	108	0·82 (0·79, 0·85)	120	0·81 (0·78, 0·85)	
Severity of PTS‡					
6 months	117	4·77 (4·24, 5·30)	126	4·73 (4·22, 5·25)	0·907
12 months	116	4·68 (4·14, 5·21)	123	4·88 (4·36, 5·40)	
18 months	111	4·73 (4·19, 5·28)	115	4·96 (4·43, 5·49)	
24 months	110	5·00 (4·45, 5·54)	120	5·09 (4·57, 5·62)	
	n	%	n	%	
Category of PTS‡					
6 months					
None (0–4)	66	49·25	71	51·08	
Mild (5–9)	42	31·34	36	25·90	
Moderate (10–14)	7	5·22	15	10·79	
Severe (≥15)	2	1·49	4	2·88	
12 months					
None (0–4)	67	50·00	71	51·08	
Mild (5–9)	38	28·36	38	27·34	
Moderate (10–14)	10	7·46	10	7·19	
Severe (≥15)	1	0·75	4	2·88	
18 months					
None (0–4)	63	47·01	63	45·32	
Mild (5–9)	39	29·10	37	26·62	
Moderate (10–14)	8	5·97	11	7·91	
Severe (≥15)	1	0·75	4	2·88	
24 months					
None (0–4)	66	49·25	65	46·76	
Mild (5–9)	29	21·64	37	26·62	
Moderate (10–14)	11	8·21	12	8·63	
Severe (≥15)	4	2·99	6	4·32	

AT: anticoagulation therapy; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QoL, quality of life.

†A linear mixed model was fitted adjusting for the corresponding baseline response, baseline diagnosis (DVT/PE), treatment, the time of assessments and the interaction between treatment and time.

‡Worst score from both legs.

Author contributions

The study was designed, and funding was 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.

Table VII. Secondary outcomes (continuous) – PTS for participants diagnosed at baseline with unprovoked DVT.

	Discontinued AT $n = 69$		Extended AT $n = 70$		
Outcome	*n*	Adjusted mean† (95% CI)	*n*	Adjusted mean† (95% CI)	*P*-value for time–treatment interaction
Severity of PTS‡					
6 months	62	5·19 (4·44, 5·93)	65	5·16 (4·44, 5·89)	0·576
12 months	63	4·76 (4·01, 5·50)	65	5·11 (4·39, 5·84)	
18 months	59	4·91 (4·15, 5·67)	62	5·64 (4·90, 6·38)	
24 months	59	5·41 (4·65, 6·17)	63	5·47 (4·74, 6·21)	
	n	%	*n*	%	
Category of PTS‡					
6 months					
None (0–4)	30	43·48	37	52·86	
Mild (5–9)	27	39·13	18	25·71	
Moderate (10–14)	3	4·35	7	10·00	
Severe (≥15)	2	2·90	3	4·29	
12 months					
None (0–4)	33	47·83	40	57·14	
Mild (5–9)	23	33·33	18	25·71	
Moderate (10–14)	7	10·14	4	5·71	
Severe (≥15)	0	0·00	3	4·29	
18 months					
None (0–4)	33	47·83	31	44·29	
Mild (5–9)	19	27·54	21	30·00	
Moderate (10–14)	7	10·14	7	10·00	
Severe (≥15)	0	0·00	3	4·29	
24 months					
None (0–4)	31	44·93	32	45·71	
Mild (5–9)	18	26·09	21	30·00	
Moderate (10–14)	8	11·59	8	11·43	
Severe (≥15)	2	2·90	2	2·86	

AT: anticoagulation therapy; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
†A linear mixed model was fitted adjusting for the corresponding baseline response, baseline diagnosis (DVT/PE), treatment, the time of assessments and the interaction between treatment and time.
‡Worst score from both legs.

Conflict of interests

CB has received speaker fees from BMS Pfizer, Novartis and Janssen, advisory fees from Ablynx and Novartis and funding to attend conferences from 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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