Age, personal and family history are independently associated with venous thromboembolism following acute Achilles tendon rupture

AGE, PERSONAL AND FAMILY HISTORY ARE INDEPENDENTLY ASSOCIATED WITH VENOUS THROMBOEMBOLISM FOLLOWING ACUTE ACHILLES TENDON RUPTURE

William M. Oliver, LLB(Hons), MBBS(Hons), MRCSEd – william.m.oliver@doctors.org.uk

Samuel A. Mackenzie, MBChB, MRCSEd – samuel.mackenzie@nhs.scot

Lucia Lenart, BSc(Hons) – lenart.lusa@gmail.com

Conor J. McCann, BMedSci, MBChB – conor.mccann@nhslothian.scot.nhs.uk

Samuel P. Mackenzie, BSc(Hons), MD, FRCSEd(Tr&Orth) – sampmackenzie@gmail.com

Andrew D. Duckworth, FRCSEd(Tr&Orth), PhD – andrew.duckworth@ed.ac.uk

Nicholas D. Clement, FRCSEd(Tr&Orth), PhD – nickclement@doctors.org.uk

Timothy O. White, MD, FRCSEd(Tr&Orth) – twhite@rcsed.ac.uk

Julian F. Maempel, MD, MSc, FRCSEd(Tr&Orth) – julian.maempel@doctors.org.uk

All authors affiliated with:

Edinburgh Orthopaedics, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, Midlothian, EH16 4SA, UK

ADD also affiliated with: Centre for Population Health Sciences, Usher Institute, University of Edinburgh, 49 Little France Crescent, EH16 4SB, UK

JFM also affiliated with: Royal Prince Alfred Hospital, 50, Missenden Road, Camperdown, Sydney NSW 2050, Australia

Corresponding author:

- Name: William M. Oliver, Specialty Registrar in Trauma & Orthopaedic Surgery
- Institutional address: Edinburgh Orthopaedics, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, Midlothian, EH16 4SA, UK
- Phone: +44 131 242 3459
- Email: william.m.oliver@doctors.org.uk

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ABSTRACT

Purpose: The primary aim was to determine independent patient, injury and management-related factors associated with symptomatic venous thromboembolism (VTE) following acute Achilles tendon rupture (ATR). The secondary aim was to suggest a clinical VTE risk assessment tool for patients with acute ATR.

Methods: From 2010-2018, 984 consecutive adults (median age 47yrs, 73% [n=714/984] male) sustaining an acute ATR were retrospectively identified. Ninety-five percent (n=939/984) were managed non-operatively in a below-knee cast (52%, n=507/984) or walking boot (44%, n=432/984), with 5% (n=45/984) undergoing primary operative repair (<6wks post-injury). VTE was diagnosed using local medical records and national imaging archives, reviewed at a mean 5yrs (range 1-10) post-injury. Multivariate logistic regression was performed to determine independent factors associated with VTE.

Results: The incidence of VTE within 90 days of ATR was 3.6% (n=35/984; deep vein thrombosis 2.1% [n=21/984], pulmonary embolism 1.9% [n=19/984]), and the median time to VTE was 24 days (interquartile range 15-44). Age ≥50yrs (adjusted OR [aOR] 2.3, p=0.027), personal history of VTE/thrombophilia (aOR 6.1, p=0.009) and family history of VTE (aOR 20.9, p<0.001) were independently associated with VTE following ATR. These non-modifiable risk factors were incorporated into a VTE risk assessment tool. Only 23% of patients developing VTE (n=8/35) had a relevant personal or family history, but incorporating age ≥50yrs into the VTE risk assessment tool (alongside personal and family history) identified 69% of patients with VTE

(n=24/35). Non weight-bearing for ≥2wks after ATR was also independently associated with VTE (aOR 3.2, p=0.026).

Conclusions: Age ≥50 years, personal history of VTE/thrombophilia and a positive family history were independently associated with VTE following ATR. Incorporating age into our suggested VTE risk assessment tool enhanced its sensitivity in identifying at-risk patients. Early weight-bearing in an appropriate orthosis may be beneficial to all patients in VTE risk reduction.

Level of Evidence: Prognostic – Level III (retrospective cohort study)

Keywords: Achilles tendon rupture; venous thromboembolism; risk factors; thromboprophylaxis

HIGHLIGHTS

- The incidence of symptomatic venous thromboembolism (VTE) within 90 days of Achilles tendon rupture (ATR) was low: VTE 3.6%, deep vein thrombosis 2.1%, pulmonary embolism 1.9%.
- Age ≥50 years, a personal history of VTE/thrombophilia and a family history of VTE were non-modifiable risk factors for VTE following ATR.
- Non weight-bearing for ≥2 weeks post-injury was a modifiable risk factor for VTE following ATR in our analysis.

INTRODUCTION

Achilles tendon rupture (ATR) is a common soft tissue injury and the incidence is rising[1,2]. Venous thromboembolism (VTE) is a recognised complication of lower limb injuries in general, and ATR in particular[3–6], with potentially morbid sequelae including pulmonary embolism[7] and post-thrombotic syndrome[8]. The reported rate of VTE following ATR varies considerably[7,9–17], with some studies suggesting up to a half of patients are affected[18].

In light of the higher incidence of VTE observed among patients with ATR compared to other patients requiring lower limb immobilisation, guidance from the UK National Institute for Health and Care Excellence (NICE) has suggested that all patients with ATR should be offered chemical thromboprophylaxis unless contraindicated[19]. However, NICE acknowledged that the evidence underlying this guidance was heterogenous and of generally low quality, comprising a variety of injury types, surgical procedures, immobilisation regimes and thromboprophylactic measures[19]. Moreover, relatively few studies specifically analyse risk factors for VTE in the context of acute ATR[7,11,14,17,20], with only one study[7] involving more than 300 patients.

The primary aim of this study was to determine independent patient, injury and management-related factors associated with symptomatic VTE following acute ATR, in a large cohort of consecutive patients managed at a single centre. The secondary aim was to suggest a clinical VTE risk assessment tool for patients with acute ATR, based upon their non-modifiable risk factors, in order to rationalise thromboprophylaxis use in this group.

PATIENTS AND METHODS

Study cohort

Patients were identified from a retrospective search of electronic records held at the study centre. Nine hundred and eighty-four consecutive patients satisfied the inclusion and exclusion criteria (**Table I**). The study was registered with the local musculoskeletal quality improvement committee and underwent NHS Research Ethics Service assessment (reference NR/161AB6).

Patient and injury characteristics

Patient demographics and injury characteristics were obtained from electronic records. Patients with a first-degree relative with a history of venous thromboembolism (VTE) or thrombophilia were considered to have a positive family history. Regular medications were determined from electronic prescription data. For female patients, hormonal contraceptive status and the use of hormone replacement therapy were documented. Smoking status was recorded where available; this was known for 81.4% of patients (n=801/984). Body mass index (BMI) was determined from height and weight documented at the closest-available timepoint to injury; this was known for 60.7% of patients (n=597/984). Socioeconomic deprivation was determined for each patient according to the Scottish Index of Multiple Deprivation (SIMD), using their postal code at the time of injury[22].

Injury mechanism was classified into five domains (sport, dance, low-energy incident, direct trauma and not documented/unknown). 'Low-energy incidents' comprised any injuries sustained while standing, walking or falling from standing height or less. Direct trauma included patients who sustained their ATR in the context of an incised wound (n=1).

Management

All patients were placed into an equinus plaster of Paris backslab in the emergency department, instructed to remain non weight-bearing (non-WB) and referred to the fracture clinic. The eight-year duration of this study incorporated several distinct periods of ATR management at our institution. For patients sustaining ATR during the first three years of the present study (April 2010 to October 2013, n=363), cast immobilisation with prolonged non-WB for eight weeks was the standard treatment (i.e. four weeks non-WB in a full-equinus position, four weeks non-WB in semi-equinus and two weeks weight-bearing in a plantigrade position – a '4-4-2' regime). In November 2013, recruitment began for a single-centre randomised trial of adult patients (aged 16 to 60 years) with an acute ATR, who were allocated to either standard cast immobilisation (n=71) or early weight-bearing in a walking boot orthosis (n=69)[23]. Walking boot immobilisation comprised four weeks in a full equinus position, two weeks in semi-equinus and two weeks in a plantigrade position (a '4-2-2' regime) with full weight-bearing encouraged throughout. Once the preliminary results of this trial were available, functional rehabilitation with early weight-bearing in a walking boot was adopted as the standard treatment protocol. Details of operative and non-operative management and functional rehabilitation at our institution have previously been described in detail[23,24].

Ninety-five percent of patients (n=939/984) were managed non-operatively and 4.6% (n=45/984) underwent primary operative repair (within six weeks of ATR). Patients managed non-operatively underwent immobilisation in a below-knee cast (54.0%, n=507/939) or walking boot orthosis (46.0%, n=432/939). Median post-injury clinic follow-up was 2.5 months (interquartile range 2.3 to 3.5). Six patients (0.6%) failed to heal after at least 12 weeks of non-operative management, confirmed either clinically (n=3) or sonographically (n=3). Five of these

patients underwent late operative intervention, while the remaining patient (with multiple comorbidities and low functional demands) opted for continued non-operative management. The overall rate of tendon re-rupture was 5.1% (n=50/984).

Venous thromboprophylaxis

During the study period, VTE prophylaxis was prescribed on the basis of individual patient risk assessment. Our current policy is for patients to be counselled regarding the potential risk of VTE following ATR, and the effect of any personal or familial risk factors that may be present. Patients without contraindications to thromboprophylaxis are then given the option as to whether they receive a course of low molecular weight heparin (LMWH) injections. In the present cohort, eighty-two patients (8.3%) were taking anticoagulant medication prior to their ATR, of which eight (10%) were prescribed this for a prior VTE (**Table II**). Following ATR, 116 patients (11.8%) were taking some form of anticoagulant medication. Eighty patients (8.1%) continued their prior anticoagulant regime unchanged, two (who had been on anticoagulants for reasons other than prior VTE) received additional thromboprophylaxis, and 34 (3.5%) received a new prescription for VTE prophylaxis having not been on anticoagulants prior to injury.

Detection of venous thromboembolism

Local medical and national Picture Archiving and Communication System (Carestream Vue PACS, Carestream Health, Rochester, New York, USA) records were reviewed for all patients in this study at a mean of 5.1 years post-injury (range 1.1 to 10.6). Venous thromboembolism was defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE). The date at which VTE was diagnosed on Doppler ultrasound (DUS, for DVT) or CT pulmonary angiography

(CTPA, for PE) was recorded. These investigations were only performed in patients in whom there was a clinical suspicion of VTE. Overall, 67 patients (6.8%) underwent DUS for suspected DVT and 43 patients (4.4%) underwent CTPA for suspected PE. Occurrence of VTE up to six months following ATR was recorded, but only VTE occurring within 90 days of ATR were included in our statistical analyses.

The overall incidence of VTE within 90 days of ATR was 3.6% (n=35/984), rising to 3.7% (n=36/984) by 120 days. No further VTE occurred in this cohort between four and six months after injury. Of the 67 patients who underwent DUS, 21 (31%) were positive; the incidence of DVT within 90 days of ATR was 2.1% (n=21/984). Of the 43 patients who underwent CTPA, 19 (44%) were positive; the incidence of PE was 1.9% (n=19/984). The median time from injury to VTE diagnosis was 24 days (IQR 15 to 44). Seventeen VTE (47%) occurred within three weeks of injury, 21 (58%) within four weeks and 27 (75%) within six weeks (**Figure 1**).

Statistical methods

The relationship between categorical variables was assessed using the chi-squared test (CS), or the Fisher exact test (FE) if any cell value was <5. Parametricity of continuous data was determined using the Kolmogorov-Smirnov test and non-parametric data was assessed using the Mann-Whitney U test (MWU). Significance was set at $p \leq 0.05$[23].

All potential patient, injury and management-related risk factors for VTE were initially identified on unadjusted bivariate analysis. Risk factors for VTE that were trending towards significance on unadjusted analysis ($p<0.1$) were then entered into a multivariate binary logistic regression model, to identify variables independently associated with VTE adjusting for confounding factors. The age cut-off for prediction of VTE was determined using a receiver

operating characteristic (ROC) curve. Weight-bearing initiated within the first two weeks of injury is consistent with the definition of 'early functional weight-bearing' in the existing literature[25]. Sample size calculation for the regression model was limited due to the small number of VTE events observed (n=35), and was therefore restricted to four variables (i.e. 10 VTE events for each independent variable included)[26]. Additional forward and backward conditional modelling were used to verify model stability.

RESULTS

Patient and injury characteristics

The median age at injury was 47 years (interquartile range [IQR] 38 to 59) and 72.6% of patients (n=714/984) were male. Pre-existing medical comorbidities were documented in 56.2% of patients (n=553/984). Fifteen patients (1.5%) had a personal history of VTE (DVT 0.9%, n=9/984; PE 0.9%, n=9/984) and fourteen (1.4%) had a positive family history (VTE 1.4%, n=14/984; thrombophilia 0.3%, n=3/984). One-in-eight patients (12.6%, n=101/801) were cigarette smokers. The median BMI was 26.9kg/m^2 (IQR 24.2 to 30.3) and 27.1% (n=162/597) were classified as obese (BMI≥30 kg/m^2)[21].

The majority of ATRs were sustained through a sporting injury (54.3%, n=534/984). The diagnosis of ATR was confirmed clinically (69.8%, n=687/984) or following ultrasound assessment (30.2%, n=297/984). Most ruptures were left-sided (55.5%, n=546/984) and four patients (0.4%) had bilateral ruptures.

Unadjusted analysis: Factors associated with VTE

A personal history of thrombophilia (OR 19.11, p=0.011; FE) or VTE (OR 11.00, p=0.001; FE), family history of VTE (OR 24.34, p<0.001; CS) and patients taking prophylactic anticoagulant medication for prior VTE (OR 30.48, p<0.001; FE) were associated with developing a VTE within 90 days of ATR. The median age for patients who developed VTE after ATR was 53.6 years (IQR 44.9 to 66.1), compared to 47.3 years (IQR 38.2 to 59.0) for those who did not (p=0.036, MWU). There was a trend towards increased incidence of VTE among female patients taking the oral contraceptive pill at the time of injury (OR 24.67, p=0.088; FE). There was no demonstrable relationship between SIMD and the occurrence of VTE after ATR (p=0.851; **Table III**).

Patients sustaining their ATR during a low-energy incident were at increased risk of VTE compared to those with sporting or higher-energy mechanisms (OR 2.15, 95% CI 1.09 to 4.24, p=0.023; CS). There was a trend towards increased incidence of VTE in patients who remained non-WB for ≥2 weeks following their ATR (OR 2.47, 95% CI 0.95 to 6.44, p=0.056; CS; **Table IV**). Patients taking any post-injury VTE prophylaxis were also found to be at increased risk of VTE (OR 4.96, 95% CI 1.94-12.66, p<0.001; CS; **Table V**).

Adjusted analysis: Factors independently associated with VTE

Based on our bivariate analysis, eight variables were potentially suitable for inclusion in the regression model (p<0.1). 'Personal history of thrombophilia' was combined with 'personal history of VTE' to form a single 'personal VTE risk factors' variable for model purposes. 'Prophylactic anticoagulation for prior VTE' and 'post-injury VTE prophylaxis' were considered to be an indirect reflection of personal VTE risk and were therefore excluded from the model. There was a strongly negative correlation between injury energy (low *versus* higher) and patient age (median age for low-energy incident 62.2 years, median age for higher-energy incident 43.3 years, p<0.001, MWU; point-biserial correlation coefficient 0.511, p<0.001). Accordingly, injury energy was not considered to be independent of age and was excluded from the model. Age at injury, personal VTE risk factors, family history of VTE and initial non-WB ≥2 weeks were therefore entered into the regression model. ROC curve analysis demonstrated an age cut-off of 50 years had a sensitivity of 57.1% and specificity of 58.1% to predict VTE following ATR.

Regression modelling demonstrated that age ≥50 years (adjusted OR [aOR] 2.30, p=0.027), personal VTE risk factors (aOR 6.13, p=0.009), family history of VTE (aOR 20.90, p<0.001) and an initial non-WB period ≥2 weeks (aOR 3.22, p=0.026) were independently associated with VTE

within 90 days of ATR (**Table VI**). The model had a low sensitivity (8.6%) but a high specificity (99.7%) for prediction of VTE following ATR.

Suggested VTE risk assessment tool

A clinical VTE risk assessment tool was developed, based upon the non-modifiable independent risk factors identified in our analysis (**Figure 2**). Of patients who developed a VTE within 90 days of ATR (n=35), 14% (n=5/35) had personal VTE risk factors and 17% (n=6/35) had a family history of VTE. However, the majority of the cohort (97.3%, n=957/984) had neither of these risk factors and 77% of all VTE (n=27/35) occurred within this group. By comparison, 57% of patients sustaining a VTE (n=20/35) were aged ≥50 years, and incorporating age ≥50 years into the VTE risk assessment tool (alongside other non-modifiable risk factors) identified 69% of patients who developed a VTE (n=24/35; **Table VII**).

Of patients with none of the non-modifiable risk factors identified in this study (n=552), the majority (n=412) had been non-WB for ≥2 weeks and the observed VTE rate in this sub-group was 2.4% (n=10/412). In contrast, the rate of VTE in patients who began weight-bearing within two weeks of ATR was 0.7% (n=1/140, p=0.305; FE).

DISCUSSION

In this large retrospective review of consecutive patients managed at a single centre, the incidence of VTE within 90 days of ATR was 3.6% and the majority of cases occurred within four weeks of injury. Older age at injury, personal history of VTE/thombophilia and a positive family history were independent non-modifiable risk factors for VTE following ATR, but the majority of patients who sustained a VTE did not have a personal or family history of thromboembolic disease. Moreover, rates of VTE remained significantly higher in patients taking thromboprophylactic medications, suggesting that current treatment regimens may not negate the risk of this complication. Identification of at-risk patients, and effective strategies to reduce their VTE risk, remain challenging for surgeons managing ATR. However, incorporating age into VTE risk assessment tools may improve the identification of patients at risk following ATR, while early weight-bearing in an appropriate orthosis may also be protective for all patients.

Older age has previously been found to be associated with VTE risk in the wider population[27,28], as well as after lower limb injuries in general[3,5,29] and ATR in particular[7,14,20,30]. This phenomenon may be due to age-related loss of muscle tone, reduced mobility or degenerative vascular changes[31]. Although older age is considered a risk factor for VTE in generic clinical guidelines[19,32] and risk assessment tools[33–35], it is not identified as a risk factor for VTE in many current ATR management protocols[18,36,37]. Our findings suggest that being aged ≥50 years should be considered as a specific risk factor for VTE among patients with ATR, and incorporation into existing ATR protocols may enhance our ability to identify those at risk of VTE.

Similarly, personal or family history of VTE are associated with an increased risk of VTE among patients without ATR[28,38,39], and many generic VTE risk assessment tools use

screening questions pertaining to these factors to determine which patients are at the highest risk[19,32,33,40]. Although personal history of VTE has been demonstrated to be a risk factor for VTE after ATR[7,13], to our knowledge this is the first study to confirm family history as an independent risk factor for VTE in the ATR population. We suggest that a history of VTE in any first degree relative should form part of the VTE risk assessment for patients with ATR.

Over recent years, awareness of the potential for VTE to complicate lower limb injuries has increased, including those such as ATR that would ordinarily be managed on an outpatient basis[11,17,41]. Many modern ATR protocols seek to identify 'high risk' individuals using screening questions, including those based upon personal and family history of VTE, in order to selectively target prophylactic anticoagulants to this group of patients[17,18,36,37]. However, our findings highlight two limitations of this approach.

Firstly, although patients with a positive personal or family history were at increased risk of developing VTE in our study, over three-quarters of patients sustaining a VTE had no personal or family history of thromboembolic disease. This suggests that administration of prophylactic anticoagulation based solely on these risk factors may 'miss' many patients who go on to develop VTE after ATR[11]. One possible solution, as advocated in the most recent NICE guidance[19], is that prophylactic anticoagulation should be offered to all ATR patients (unless contraindicated). The authors of a retrospective audit of 208 patients with ATR (who were not risk-assessed and whose injuries were managed with prolonged non-WB immobilisation) suggested that routine administration of chemical thromboprophylaxis may be beneficial, although only one patient in that cohort had actually received prophylaxis[11]. A recent systematic review also advised routine chemoprophylaxis when there is prolonged lower limb immobilisation for any injury[41]. Another solution may to offer VTE prophylaxis to a wider (but nonetheless selected) group of patients,

including those aged ≥50 years. By including this group in our clinical risk assessment tool, we were able to improve our ability to correctly identify those patients who sustained a VTE from 23% to 69%. The risk assessment tool is summarised in **Figure 2** and facilitates estimation of VTE risk based on the presence or absence of the identified non-modifiable independent risk factors for VTE after ATR.

The second limitation is that the efficacy of current thromboprophylactic measures in the context of ATR are largely unknown. Of patients prescribed additional VTE prophylaxis in this study (as they had been deemed to be at increased risk), almost 6% went on to develop a VTE following their ATR. Although this study was not designed to determine the efficacy of anticoagulant medications in reducing VTE risk, our results suggest that placing at-risk patients on thromboprophylaxis will not remove the potential for this complication. Previous smaller studies have also demonstrated that thromboembolic events may occur following ATR despite the use of prophylactic anticoagulation[9,42,43], particularly in those with risk factors for VTE[17,36]. Lapidus *et al.* showed no difference in incidence of DVT after ATR with or without administration of LMWH for six weeks[9], although an earlier randomised study demonstrated reduced rates of VTE with chemical thromboprophylaxis in patients immobilised for lower limb injuries[44]. Moreover, opponents of routine thromboprophylaxis argue that anticoagulation may cause adverse bleeding events[13], although major bleeding complications appear to be rare[9,41]. Large, prospective studies of both general ATR populations and higher-risk sub-groups are required to assess the efficacy of thromboprophylactic agents, the risk profile associated with their use and whether any additional measures (such as intermittent pneumatic compression devices[30]) might help mitigate VTE risk.

In keeping with existing literature, we did not demonstrate any difference in VTE rates between patients managed non-operatively and operatively[10,13,24,45,46]. However, we found that patients who spent at least two weeks non-WB following their ATR were more likely to develop a subsequent VTE. Healy *et al.* suggested that studies should explore whether early weight-bearing after ATR reduces the risk of VTE[11], and Pedersen *et al.* hypothesised that occurrence of early VTE reported in some studies may suggest that an initial period of non-WB prior to commencement of functional rehabilitation led to an increased VTE risk[7]. A recent randomised trial of patients undergoing Achilles tendon repair reported that reduced weight-bearing during functional rehabilitation was an independent risk factor for VTE[20]. Early weight-bearing is considered to be beneficial to VTE risk after foot and ankle injuries[47], particularly those requiring immobilisation[29]. Although adequate weight-bearing may be difficult to achieve, even when immobilised in functional orthoses[20], our findings suggest this may be the most important modifiable risk factor for VTE in patients with ATR. Based upon our analysis, patients aged under 50 with no personal/family history of VTE, and who have begun weight-bearing in an orthosis within two weeks of their ATR, have a risk of developing VTE that is less than one percent.

Overall rates of VTE following ATR generally vary between 0% and 23%[7,11–17] but may be as high as 48% in studies where all patients underwent Doppler imaging[9,10,18]. However, this approach does not reflect routine clinical practice and the vast majority of VTE identified in such studies occurred below the knee and were asymptomatic[48]. The incidence of clinical VTE after ATR in our study is similar to smaller studies[11,17,49], as well as two prospective randomised trials at our institution conducted fifteen years apart[23,24]. Half of the reported VTE in this study occurred within the first three weeks and three-quarters within the first

six weeks following ATR, in keeping with previous studies[7,11]. Patients should be counselled regarding the importance of the symptoms and signs of VTE and should be instructed to present should these develop during the period of their treatment. This may be of greater importance given that current thromboprophylactic measures do not appear to mitigate VTE risk entirely in the ATR population[6,9,17,43].

Limitations of this study include retrospective data collection and the potential for VTE risk factors to have been documented more reliably in patients who ultimately developed VTE. For some risk factors, the number of positive responses was low and therefore likely to be unstable. Although we identified a trend towards increased VTE risk among women taking the hormonal contraceptive pill, we were unable to perform a sub-group analysis to assess the independent influence of this variable. While patients kept non-WB for at least two weeks post-injury were found to be at increased risk of VTE, we recognise that the median time spent non-WB for patients in this study was relatively high in both those who did and did not develop VTE. This may be the result of a substantial number of patients who were treated with prolonged non-WB immobilisation prior to the introduction of functional rehabilitation[23]. However, the rate of clinically relevant VTE (the primary focus of this study) is unlikely to be under-reported, since review of national patient imaging archives ensured any additional VTE diagnosed elsewhere were detected, and prospective series from our institution are consistent with the reported incidence here[23,24]. While our study is relatively large compared to many others in the literature[11,14,17], it may still be underpowered to detect rare events such as fatal pulmonary embolism[7].

CONCLUSIONS

The incidence of clinically relevant VTE within 90 days of ATR was 3.6%, and the majority occurred in the first six weeks following injury. Age ≥50 years, personal history of VTE/thrombophilia and a positive family history were the non-modifiable risk factors independently associated with VTE following ATR. The majority of patients who developed VTE had no personal or family history of the condition, but incorporating older age into our suggested VTE risk assessment tool enhanced the identification of at-risk patients. Being non-WB for ≥2 weeks post-injury was also independently associated with VTE. Early weight-bearing in an appropriate orthosis may be beneficial to all patients in VTE risk reduction, but further prospective randomised studies are warranted.

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TABLES

Table I: Inclusion and exclusion criteria for the study cohort

Inclusion criteria	**Exclusion criteria**
• Age ≥16 years • Acute ATR presenting within 2 weeks of injury • Injury between April 2010 and December 2018	• Associated injuries/fractures, polytrauma • Chronic ATR • Delayed presentation • Musculotendinous junction tears • Calcaneal tuberosity avulsions with intact Achilles tendon • Patients residing outwith the institution's catchment area who were followed-up elsewhere

ATR, Achilles tendon rupture

Table II: Summary of patients taking venous thromboprophylaxis prior to Achilles tendon rupture (ATR)

Age/sex	Medication	Indication (time prior to ATR)	ATR management	Additional prophylaxis	Post-ATR VTE
39/F	Warfarin	Postpartum DVT (10yrs)	Cast (NWB 72 days)	Nil	Nil
60/M	Warfarin	Unprovoked DVT x2 (18yrs, 13yrs)	Cast, boot (NWB 29 days)	Nil	Nil
67/M	Warfarin	Unprovoked DVT (1yr)	Cast (NWB 80 days)	Dalteparin	DVT (day 6)
81/F	Rivaroxaban	Unprovoked PE (5yrs)	Cast, boot (NWB 7 days)	Nil	PE (day 79)
67/M	Dalteparin	Unprovoked PE (2 months)	Boot (NWB 0 days)	Nil	Nil
39/M	Warfarin	Unprovoked DVT & PE (1yr)	Cast (NWB 54 days)	Dalteparin	PE (day 32)
48/M	Dabigatran	Unprovoked PE (3yrs) & DVT (2yrs)	Cast, boot (NWB 41 days)	Dalteparin	PE (day 17)
66/M	Warfarin	Unprovoked DVT x2 (16yrs, 9yrs)	Cast, boot (NWB 28 days)	Nil	Nil

ATR, Achilles tendon rupture; DVT, deep vein thrombosis; F, female; M, male; NWB, non weight-bearing; PE, pulmonary embolism; VTE, venous thromboembolism

Table III: Unadjusted analysis of patient-related risk factors for VTE within 90 days of ATR (n=984)

		No VTE (n=949)	**VTE (n=35)**	**OR (95% CI)**	**p-value (test)**
Gender (n, %)					
	Male	685, 95.9%	29, 4.1%	0.54	.165
	Female	264, 97.8%	6, 2.2%	(0.22-1.31)	(CS)
Age at injury (years)					
	Median (IQR)	47.3 (38.2-59.0)	53.6 (44.9-66.0)	-	**.036* (MWU)**
Medical comorbidities (n, %)					
	None	420, 97.4%	11, 2.6%	1.73	.133
	≥1	529, 95.7%	24, 4.3%	(0.84-3.58)	(CS)
Active malignancy (n, %)					
	No	927, 96.5%	34, 3.5%	1.24	.569
	Yes	22, 95.7%	1, 4.3%	(0.16-9.47)	(FE)
Thrombophilia (n, %)					
	No	946, 96.6%	33, 3.4%	19.11	**.011***
	Yes	3, 60.0%	2, 40.0%	(3.09-118.25)	**(FE)**
Previous VTE (n, %)					
	No	938, 96.8%	31, 3.2%	11.00	**.001***
	Yes	11, 73.3%	4, 26.7%	(3.32-36.50)	**(FE)**
Previous DVT (n, %)					
	No	943, 96.7%	32, 3.3%	14.73	**.003***
	Yes	6, 66.7%	3, 33.3%	(3.53-61.60)	**(FE)**
Previous PE (n, %)					
	No	943, 96.7%	32, 3.3%	14.73	**.003***
	Yes	6, 66.7%	3, 33.3%	(3.53-61.60)	**(FE)**
FHx of VTE (n, %)					
	No	941, 97.0%	29, 3.0%	24.34	**<.001***
	Yes	8, 57.1%	6, 42.9%	(7.93-74.67)	**(CS)**
FHx of thrombophilia (n, %)					
	No	947, 96.5%	34, 3.5%	13.93	.103
	Yes	2, 66.7%	1, 33.3%	(1.23-157.36)	(FE)
Hormonal contraceptive (n, %)					
	No[†]	148, 99.3%	1, 0.7%	24.67	.088
	Yes	6, 85.7%	1, 14.3%	(1.37-443.61)	(FE)
HRT (n, %)					

No‡	110, 95.7%	5, 4.3%	0.65	1
Yes	6, 100%	0	(0.03-13.01)	(FE)
Current smoker (n, %)				
No	669, 95.6%	31, 4.4%	0.66	.790
Yes	98, 97.0%	3, 3.0%	(0.20-2.20)	(FE)
Unknown	182, 99.5%	1, 0.5%		
BMI (kg/m^2)				
Median (IQR)	26.9 (24.2-30.3)	28.2 (25.3-29.3)	-	.430 (MWU)
SIMD quintile (n, %)				
1 (most deprived)	86, 97.7%	2, 2.3%	-	.851
2	153, 96.2%	6, 3.8%		(CS)
3	155, 97.5%	4, 2.5%		
4	199, 95.7%	9, 4.3%		
5 (least deprived)	356, 96.2%	14, 3.8%		

ATR, Achilles tendon rupture; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CS, chi-squared test; DVT, deep vein thrombosis; FE, Fisher exact test; FHx, family history; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; MWU, Mann-Whitney 'U' test; OR, odds ratio; PE, pulmonary embolism; SIMD, Scottish Index of Multiple Deprivation; VTE, venous thromboembolism

†Denominator = female patients aged 16 to 49 years (n=149)
‡Denominator = female patients aged ≥50 years (n=115)

Table IV: Unadjusted analysis of injury- and management-related risk factors for venous thromboembolism within 90 days of Achilles tendon rupture (n=984)

	No VTE (n=949)	VTE (n=35)	OR (95% CI)	p-value (test)
Mechanism of injury (n, %)				
Sport	519, 97.2%	15, 2.8%	-	.145
Dance	104, 98.1%	2, 1.9%		(CS)
Low-energy incident	286, 94.4%	17, 5.6%		
Direct trauma	29, 96.7%	1, 3.3%		
Unknown	11, 100.0%	0		
Side of injury (n, %)				
Left	522, 95.6%	24, 4.4%	-	.274
Right	423, 97.5%	11, 2.5%		(CS)
Bilateral	4, 100.0%	0		
Other injuries (n, %)				
None	924, 96.6%	33, 3.4%	2.24	.249
≥1	25, 92.6%	2, 7.4%	(0.51-9.86)	(FE)
Injury to presentation (days)				
Median	1	0	-	.380
(IQR)	(0-2)	(0-2)		(MWU)
Management (n, %)				
Operative	44, 97.8%	1, 2.2%	1.65	1
Non-operative	905, 96.4%	34, 3.6%	(0.22-12.36)	(FE)
Non-operative management (n, %)				
Equinus cast	484, 95.5%	23, 4.5%	0.55	.104
Aircast boot	421, 97.5%	11, 2.5%	(0.27-1.14)	(CS)
Non-WB period (days)				
Median	52	58	-	.160
(IQR)	(9-70)	(28-72)		(MWU)

CI, confidence interval; CS, chi-squared test; FE, Fisher exact test; LMWH, low molecular weight heparin; MWU, Mann-Whitney 'U' test; OR, odds ratio; VTE, venous thromboembolism; WB, weight bearing

Table V: Unadjusted analysis of the relationship between anticoagulation/thromboprophylaxis and venous thromboembolism within 90 days of Achilles tendon rupture (n=984)

		No VTE (n=949)	**VTE (n=35)**	**OR (95% CI)**	**p-value (test)**
Any pre-injury anticoagulation (n, %)					
	No	874, 97.0%	27, 3.0%	3.50	**.002***
	Yes	74, 90.2%	8, 9.8%	(1.54-7.99)	**(CS)**
Pre-injury anticoagulation [for previous VTE] (n, %)					
	No	945, 96.8%	31, 3.2%	30.48	**<.001***
	Yes	4, 50.0%	4, 50.0%	(7.29-127.55)	**(FE)**
Pre-injury anticoagulation [other indication] (n, %)					
	No	879, 96.6%	31, 3.4%	1.62	.327
	Yes	70, 94.6%	4, 5.4%	(0.56-4.72)	(FE)
Any post-injury anticoagulation (n, %)					
	No	842, 97.0%	26, 3.0%	2.72	**.009***
	Yes	107, 92.2%	9, 7.8%	(1.24-5.97)	**(CS)**
Post-injury VTE prophylaxis (n, %)					
	No	911, 96.9%	29, 3.1%	4.96	**<.001***
	Yes	38, 86.4%	6, 13.6%	(1.94-12.66)	**(CS)**
New post-injury VTE prophylaxis (n, %)					
	No	915, 96.5%	33, 3.5%	1.63	.370
	Yes	34, 94.4%	2, 5.6%	(0.38-7.08)	(FE)

CI, confidence interval; CS, chi-squared test; FE, Fisher exact test; OR, odds ratio; VTE, venous thromboembolism

Table VI: Independent predictors of venous thromboembolism (VTE) following an Achilles tendon rupture (n=984); p<0.001, Nagelkerke R^2=0.146

Predictors in the model			**95% CI**		
		OR	**Lower**	**Upper**	**p-value**
Age at injury					
	<50 yrs	Ref			
	≥50 yrs	2.300	1.101	4.806	**.027***
Personal VTE risk factors					
	No	Ref			
	Yes	6.129	1.583	23.740	**.009**
Family history of VTE					
	No	Ref			
	Yes	20.898	5.611	77.827	**<.001***
Initial non-WB period					
	<2 wks	Ref			
	≥2 wks	3.218	1.147	9.028	**.026**
Constant		.007			**<.001**

B, regression coefficient; CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism; WB, weight-bearing ***significant at the p<0.05 level**

NB. 'Personal VTE risk factors' comprised patients with a personal history of thrombophilia, those with personal history of VTE, or both

Table VII: Personal and family history of venous thromboembolism (VTE) as predictors of VTE within 90 days of Achilles tendon rupture (n=984)

	Prevalence	**Sn**	**Sp**	**PPV**	**NPV**
Age ≥50 years (1)	42.5% (418/984)	57.1% (20/35)	58.1% (551/949)	4.8% (20/418)	97.3% (551/566)
Personal VTE risk factors (2)	1.7% (17/984)	14.3% (5/35)	98.7% (937/949)	29.4% (5/17)	96.9% (937/967)
Family history of VTE (3)	1.4% (14/984)	17.1% (6/35)	99.2% (941/949)	42.9% (6/14)	97.0% (941/970)
Any positive	43.9% (432/984)	68.6% (24/35)	57.0% (541/949)	5.6% (24/432)	98.0% (541/552)
(1) and (2)	1.0% (10/984)	8.6% (3/35)	99.3% (942/949)	30.0% (3/10)	96.7% (942/974)
(1) and (3)	0.4% (4/984)	5.7% (2/35)	99.8% (947/949)	50.0% (2/4)	96.6% (947/980)
(2) and (3)	0.4% (4/984)	8.6% (3/35)	99.9% (948/949)	75.0% (3/4)	96.7% (948/980)
All positive	0.1% (1/984)	2.9% (1/35)	100% (949/949)	100% (1/1)	96.5% (949/983)

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

FIGURES

Figure 1: Time from Achilles tendon rupture to diagnosis of venous thromboembolism (VTE) (n=36)

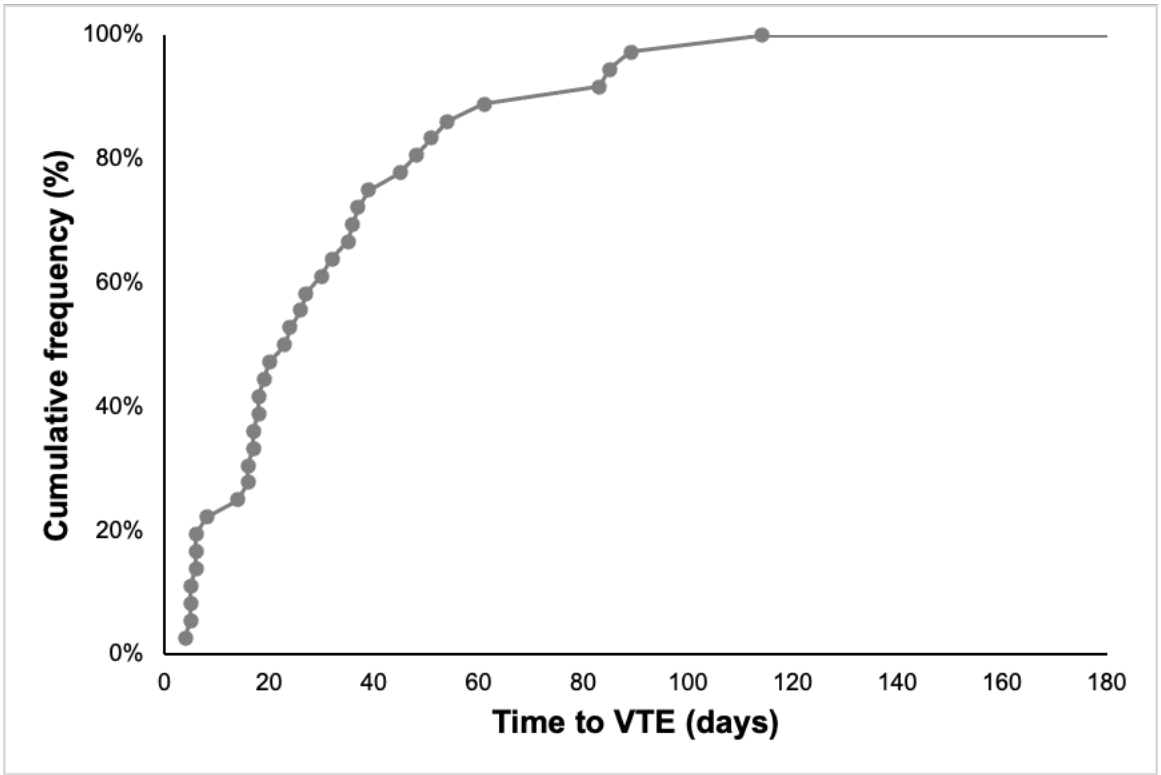

Figure 2: Clinical risk assessment tool for venous thromboembolism (VTE) following Achilles tendon rupture, and observed rate of VTE in the study cohort (n=984)