

Title Page

The effect of active toe movement (AToM) on calf pump function and deep vein thrombosis in patients with acute foot and ankle trauma treated with cast
– A Prospective Randomised Study

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1. Abstract

Background

Patients with foot and ankle trauma treated with cast are advised to perform toe movements to prevent venous thromboembolism (VTE). Our aim was to determine the effect of active toe movement on asymptomatic deep vein thrombosis (DVT) and venous calf pump function.

Methods

Patients aged 18 to 60 years with acute foot and ankle trauma requiring below knee non weight bearing cast were randomized to intervention (regular active toe movement) or control groups (n=100). Patients had bilateral lower limb venous ultrasound to assess for DVT on discharge from clinic. Patients requiring chemical thromboprophylaxis were excluded.

Results

78 completed the study. 27% sustained asymptomatic DVT, with no statistically significant difference in calf pump function or DVT incidence between groups. All DVT's occurred in the injured lower limb.

Conclusion

Active toe movement is not a viable strategy for thromboprophylaxis in patients with acute foot and ankle trauma treated with cast.

Keywords: Thromboprophylaxis, Venous thrombosis, Deep vein thrombosis

2. Introduction

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5 Thromboprophylaxis is clinically and financially beneficial compared with
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7 treatment of thromboembolic events once they have occurred [1]. In patients
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9 with foot and ankle trauma treated with cast, thromboprophylaxis significantly
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11 reduces venous thromboembolism rate, with thirteen patients requiring
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13 prophylaxis with low molecular weight heparin to prevent one asymptomatic
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15 DVT [2-4]. Considering that chemical thromboprophylaxis for patients with
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17 lower limb cast immobilisation represents 5.3% of the outpatient tariff for
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19 trauma, this represent a significant cost [5]. This also represents a potential
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21 risk, in view that chemical thromboprophylaxis can cause major bleeding [6].
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23 Patients with foot and ankle trauma treated with casts are also advised to
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25 participate in activities of early mobilisation and calf pumping exercises to
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27 reduce their risk of developing DVT [7]. Although we have previously shown
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29 that active toe movement increases venous velocities in the popliteal vein in
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31 healthy volunteers, even with a below knee cast applied, the clinical
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33 importance of these findings requires further investigation [8,9]. Most studies
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35 rule out mechanical thromboprophylaxis in patients with below knee casts for
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37 various reasons [10, 11]. However, considering that venous stasis is thought
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39 to contribute to thrombogenesis, it is possible that regular active toe
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41 movement (AToM) could reduce the development of deep vein thrombosis in
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43 patients with injury and cast treatment [12]. Our primary aim was to determine
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45 the effect of regular active toe movement (AToM) on rates of asymptomatic
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47 DVT in patients with acute foot and ankle trauma treated with cast and define
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1 which venous segments were involved. Our secondary aim was to determine
2 the effect of regular active toe movement on calf pump function.
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11 In this prospective randomized controlled study, adult patients with acute foot
12 or ankle trauma treated with below knee cast [REDACTED]
13 [REDACTED] between 18th February 2014 and 21st January 2015 were recruited.
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17 The local Ethics committee and Research and Development department
18 approved this study. The study was registered on [REDACTED]
19 [REDACTED] Database [REDACTED]
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21 Funding for consumables [REDACTED]. In
22 accordance with NICE guidance and local hospital protocols, all patients were
23 assessed for risk of venous thromboembolism. If patients had any permanent
24 risk factors for VTE they were not eligible for the study and were provided with
25 Low molecular weight heparin (Enoxaparin) thromboprophylaxis 40mg
26 subcutaneous injection once daily and were not eligible for study participation.
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28 Patients currently taking Warfarin or Heparin for any other reason were also
29 excluded.
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48 3.1 Exclusion criteria 49 50 51 52

53 Risk factors for VTE (exclusion criteria) were: Age >60 years, Current
54 hormone therapy (Oral Contraceptive Pill, Hormone Replacement Therapy,
55 Tamoxifen), Personal or first degree relative VTE history, Any recent hospital
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1 admission or major surgery (within 3 months), Pregnancy or immediate
2 postpartum (6 weeks), Any serious medical co-morbidity (including congestive
3 cardiac failure, chronic obstructive pulmonary disease, chronic kidney
4 disease, inflammatory bowel disease), Extensive varicosities, Active cancer,
5 Obesity (BMI over 30 kg/m²), Known thrombophilia, Achilles tendon rupture,
6 Equinus cast. All patients assessed as 'low risk' based on this risk
7 assessment were potentially eligible for the study and were referred to the
8 Chief Investigator for review in the next available fracture clinic. On review in
9 clinic, VTE risk assessment was repeated to confirm patients were 'low risk'
10 and eligible for the study. Patients who were anticipated to be treated in a
11 backslab or cast for less than 1 week were not recruited. Patients with injuries
12 requiring surgery were also not recruited because these patients are provided
13 with Low Molecular Weight Heparin. Patients presenting more than 72 hours
14 after initial injury were excluded.

3.2 Study design and intervention

40 The Chief Investigator recruited all patients. After consenting for participation
41 in this study, patients were allocated to either the intervention (AToM) or
42 control group according to a pre-defined computerized randomization
43 sequence with variable block sizes. Patients were not informed of their
44 randomization allocation group and all assessments of calf pump function and
45 ultrasound for deep vein thrombosis were performed by medical physicists
46 who were blinded to the randomization allocation. Participants who were
47 allocated to the intervention group were provided with an active toe movement

1 protocol to follow, with a compliance diary to complete. Patients allocated to
2 the intervention group were instructed to perform full active toe flexion and
3
4 extension movement exercises at the metatarsophalangeal and
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6 interphalangeal joints as often as possible, with prescriptive advice to perform
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8 these movements at a minimum of 60 movements every 6 hours. Patients
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10 were managed in fracture clinic depending on their injury until discharge.
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12 Patients were shown how to perform these simple exercises and provided
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14 with written advice.
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22 3.3 Outcome measures 23 24 25

26 When the patient no longer required their below knee cast or boot
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28 immobilization as part of their treatment they attended the Medical Physics
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30 department for assessment of calf pump function and bilateral above and
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32 below knee venous Duplex scanning to screen for asymptomatic deep vein
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34 thrombosis. Historically, venography was used to screen for DVT's, however
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36 current clinical practice is to use Duplex ultrasonography. This has previously
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38 been used in other similar studies [13]. Any patient who was discharged from
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40 clinic prior to having Duplex scanning was sent an appointment letter to attend
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42 for Duplex scanning. Senior Medical Physicists who work within the National
43
44 Health Service and perform these scan on patients routinely performed all
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46 scans. If a deep vein thrombosis was present on Ultrasound scanning, the
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48 anatomical location and laterality in relation to the injured limb was recorded.
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50 The patient exited the study at this stage. Patients with positive Doppler scans
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52 for DVT were provided with treatment if the DVT was located in the above
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1 knee veins (Popliteal or more proximal). Patients with DVT in the below knee
2 veins had a repeat Duplex scan a week later to assess for resolution or
3 propagation of the DVT.
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9 In patients who did not sustain deep vein thrombosis, calf pump function was
10 assessed using Doppler ultrasonography according to a standardized
11 protocol. With the patient seated with hips and knees at 90 degrees flexion,
12 baseline popliteal velocity was measured in the popliteal vein after cast
13 removal, using Doppler ultrasound at rest. Each patient then performed 3
14 consecutive active toe dorsiflexion exercises starting with the toe in neutral
15 position, with a rest of 30 seconds between to allow for venous refilling. Peak
16 popliteal velocity was recorded during active toe movement and the mean
17 was calculated. Peak velocity was then recorded during active toe
18 plantarflexion. This method has previously been used to assess calf pump
19 function in healthy volunteers with and without lower limb cast applied [8].
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38 3.4 Statistical analysis 39 40 41 42

43 A power calculation was based on the prediction that asymptomatic DVT
44 would occur in 21.9% of patients with an anticipated intervention effect size of
45 63% reduction [14]. To allow for 5% withdrawal rate after randomization it was
46 planned to randomize 150 patients to each group to achieve 80% power. To
47 ensure randomization worked, baseline characteristics were analysed using t
48 tests for continuous variables and chi square tests for proportions. Shapiro
49 Wilk test was used to test for normality of calf pump function data and
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1 analysis of non parametric results was performed with Mann Whitney U test.
2 A generalization of the Mann Whitney U statistic was also performed to
3 determine the effect size of AToM on calf pump function [15]. All statistical
4 analysis was performed using SPSS for Windows (SPSS, Chicago, Illinois).
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10 Analysis of DVT outcomes between groups was performed using Chi square
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12 test.

13 14 15 16 17 4. Results

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22 During the recruitment, 342 patients between the ages of 18 and 60 years had
23 injuries treated with below knee casts, 242 were excluded prior to
24 randomization. 100 patients entered the study and were randomized to
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27 intervention (AToM) or control groups. 78 patients completed the study
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30 (Figure 1). There were no significant differences between the groups (Table
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32 1). 22 (56%) of the patients randomized to the AToM group returned a fully
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35 completed toe movement activity diary with number of active toe movements
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38 recorded for each day during cast or boot treatment. 13 (59%) of these
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41 patients recorded that they achieved the minimum number of active toe
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44 movements (240) per day (range 16-600). 4 (31%) of these patients sustained
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47 asymptomatic DVT. There were no reported adverse events.
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4.1 Calf pump function

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5 After 100 patients had been recruited, analysis of the calf pump function
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7 between groups was performed to determine whether the intervention had
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9 any statistically significant effect on baseline or peak popliteal velocities. Calf
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11 pump function data was not normally distributed, and was analysed using
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13 Mann-Whitney test. (15,16) The U/nm statistic of 0.572 (95% CI 0.420 –
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15 0.710) for both active toe dorsiflexion and active toe plantarflexion indicated
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17 that patients in the intervention group generally had greater peak velocities
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19 during these movements, however the effects were small (Table 2). The mean
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21 baseline popliteal vein diameter was 7.9mm in both groups. Although baseline
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23 popliteal velocity, peak velocity during active toe dorsiflexion and peak
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25 popliteal velocity, peak velocity during active toe dorsiflexion and peak
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27 velocity during active toe plantarflexion were greater in the AToM group
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29 patients, none of these differences were statistically significant (Table 3).
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4.2 Asymptomatic DVT

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41 In view that AToM did not statistically significantly influence calf pump function
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43 in patients, it was decided by the Chief Investigator with agreement of the
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45 steering committee to request an interim analysis of the effect of the
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47 intervention on asymptomatic deep vein thrombosis. At this stage in the study,
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49 the overall event rate was 33.3% (n=13) in intervention and 20.5% (n=8) in
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51 control. Interim analysis found the confidence interval of the proportions
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53 ranged from 6.9% asymptomatic DVT reduction in the intervention to 31%
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55 increased incidence of asymptomatic DVT in the intervention group [16]. In
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1 view that the anticipated effect size was a 63% asymptomatic DVT reduction
2 in the AToM intervention group, it appeared that the intervention was less
3 effective than expected and the steering committee decided to stop
4 recruitment [17].
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10 11 4.3 Incidence and anatomical location of asymptomatic Deep Vein

12 13 Thrombosis 14 15

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18 Overall, 21 (27%) patients were found to have asymptomatic deep vein
19 thrombosis on ultrasound examination (Table 4). All of these occurred in the
20 lower limb that had been injured and treated in cast. The DVT rate was 13/39
21 (33.3%) in intervention group, 8/39 (20.5%) in control group. These
22 differences were not statistically significant ($p=0.202$). 3 DVT's were above
23 knee and were treated for oral anticoagulants for 3 months. In all patients
24 except 2, the peroneal vein was thrombosed. In 12 patients the DVT was an
25 isolated peroneal DVT. 4 patients had combined peroneal and posterior tibial
26 vein DVT, 1 patient had isolated posterior tibial vein DVT, 2 had popliteal vein
27 DVT which appeared to arise from the peroneal vein, 1 patient had isolated
28 popliteal vein DVT. The mean age of patients who sustained DVT was 36
29 years (range 21 to 53) with a mean BMI of 25kgm^2 (range 19.7 to 30.4). 13
30 were male (65%). There was no statistically significant difference between
31 age or BMI between patients who sustained DVT and those who did not.
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5. Discussion

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5 This is the first study to examine the effects of active toe movement on DVT in
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7 patients with foot and ankle trauma treated with cast. Although we have
8
9 previously shown that active toe movement (AToM) can influence calf pump
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11 function in healthy volunteers with below knee casts applied, we were unable
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13 to find any evidence that this reduces the incidence of DVT [8]. We
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15 anticipated that patients who performed regular active toe movements would
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17 have had improved venous calf pump function parameters, however this
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19 intervention had no significant effect.
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24 The concept that lower limb muscular contraction can influence thrombosis is
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26 not new. In a prospective randomized study performed almost 20 years ago,
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28 38 patients who underwent total hip replacement were randomized to a
29
30 standardized foot and ankle movement protocol and venous plethysmography
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32 was performed 4 days postoperatively [18]. Venous outflow was increased by
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34 22% in the intervention group and it was recommended that regular foot and
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36 ankle exercises should be part of a prophylactic regimen against venous
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38 thrombosis [18]. Although these exercises may have influenced calf pump
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40 function, there was no further study conducted to investigate the effects on
41
42 deep vein thrombosis. Similarly, Kaplan et al (2002) found that electrical
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44 stimulation of the foot or calf muscles increased popliteal and femoral vein
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46 velocities, but failed to investigate the effects on DVT [19]. More recently,
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48 Fuchs et al (2005) conducted a prospective randomized controlled trial of 227
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50 trauma patients with bony or ligamentous trauma to the spine, pelvis including
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52 acetabulum, femur, tibia or ankle [20]. All patients received unfractionated
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heparin, however the intervention group also received mechanical thromboprophylaxis with an ankle continuous passive motion machine (Arthroflow) for 30-minute sessions, three times per day (30 movements per minute, range of motion 20 degree dorsiflexion to 40 degrees plantarflexion). Asymptomatic DVT diagnosed on ultrasound or venogram was significantly reduced in the Arthroflow group, from 25% to 3.6% ($p=0.001$). Whitelaw et al (2001) compared the haemodynamic effects of 6 different mechanical thromboprophylactic devices on calf pump function and found that there was no statistically significant difference in increases in peak velocity between the most effective device (AirCast VenaFlow) and active or passive dorsiflexion [21]. An early prospective randomized controlled trial of 290 patients who underwent total hip replacement, confirmed that not only did AV foot pumps influence popliteal venous velocities, but also reduced asymptomatic DVT to rates comparable to levels achieved with low molecular weight heparin [22]. Since then, intermittent pneumatic compression has been found to reduce symptomatic DVT (from 16.7% in control group, to 7.3% in IPC) and pulmonary embolism (from 2.8% to 1.2%) at meta-analysis level of 70 studies including over 16000 medial and surgical patients [23]. It is also effective in reducing VTE in patients with hip fracture, patients undergoing total knee replacement and following stroke, all of which are considered high risk VTE groups [24, 25, 26].

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Considering that active toe movement influences venous haemodynamics in healthy volunteers to a similar extent to intermittent pneumatic compression foot pump devices, we anticipated that this may also reduce asymptomatic

1 DVT in patients with casts [8, 21]. One of the main reasons why AToM failed
2 to reduce DVT rates may relate to the relative infrequent performance of
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4 exercises by patients. In our AToM study, participants in intervention group
5 performed 60 sets of movements 4 times per day, which equates to 240 sets
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7 in a 24 hour period. In comparison to patients using A-V foot pumps in the
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9 study by Warwick et al (1998) used them for a median of 15 hours in a 24
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11 hour period at a 20 second cycle, equating to approximately 2700
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13 compressions [22]. This is more than 10 times the number of compressions
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15 participants in the AToM study would have performed. To achieve this with
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17 AToM, assuming patients sleep for approximately 8 hours and would be
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19 awake for 16 hours per day, participants would need to perform almost 170
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21 sets of AToM per hour to achieve a similar amount of compression.
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28 Considering that many patients in our study were unable to achieve even the
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30 minimum suggested number of active toe movements (240 in 24 hours) and
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32 that none of them reported performing more than 600 active toe movement
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34 exercises in a 24 hour period it is unlikely that a patient would be able activate
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36 their calf pump as frequently as an AV foot pump. Therefore, although the
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38 effect of active toe movement on popliteal velocities is similar to the effect of
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40 AV foot compression devices, there is a great difference in the number of calf
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42 pump activations performed [21].
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48 Considering that all patients were risk assessed for VTE and all were
49 considered low risk, we were surprised to find that 27% of all patients were
50 found to have an asymptomatic DVT on lower limb ultrasound examination. It
51 appears therefore that current risk assessment tools fail to identify a
52 significant proportion of patients who will develop asymptomatic venous
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1 thrombosis. An important finding is that all of these venous thrombosis
2 occurred in the lower limb that had been injured and treated in cast.
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4 Furthermore, the majority of these events occurred in the peroneal veins
5 (90%). In view of this, interventions to reduce venous stasis in these patients
6 may be more effective if they aim to reduce stasis in the peroneal veins, by
7 stimulation of the musculature in the peroneal compartment of the injured,
8 casted leg. Our intervention focused on active flexion and extension exercises
9 of the great toe, thereby using flexor and extensor hallucis longus to
10 influence calf pump mechanics. These muscles are located in the deep
11 posterior and anterior compartments of the leg, which may be a reason why
12 these exercises did not influence the incidence of peroneal vein thrombosis.
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14 Other potential thromboprophylactic exercises could have included knee
15 flexion and extension to utilize contraction of gastrocnemius, which attaches
16 proximal to the knee joint. However, these muscles are located in the
17 superficial posterior compartment of the leg and may also fail to influence
18 stasis in the peroneal veins. This requires further study. To minimize the
19 potential for venous stasis, minimizing the time duration of rigid cast treatment
20 and using the least immobilizing cast/boot the injury will allow, may also
21 influence venous thrombosis rates.
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48 In view that the patient demographics in each study group were similar, it
49 appears that the randomization sequence used in our study was effective.
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51 This is important, because unknown confounding factors are likely to have
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53 also been similar between groups [27]. We achieved almost 80% follow up,
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58 which is higher than many previous randomized controlled studies of
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1 thromboprophylaxis in a similar patient group [28, 29, 30]. It has previously
2 been acknowledged that co-ordination of studies to reduce the risk of VTE is
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4 challenging due the fact that patients with lower limb casts present and are
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6 treated in several areas within the hospital e.g. Emergency department,
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8 fracture clinic [31]. Although our intervention was relatively simple, this means
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10 our findings have good external validity. It has previously been suggested that
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12 prospective randomized controlled trials are at risk of lacking external validity
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14 due to highly intensive or regimented intervention protocols [32]. Although
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16 only 33% of patients in the intervention group reported achieving the minimum
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18 recommended number of active toe movements, this is an effectiveness study
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20 which assesses how the intervention works in the real world [27]. Although
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22 multiple practitioners performed assessment for DVT, all had a minimum of 5
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24 years experience in the NHS performing these scan as part of their clinical
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26 practice. None of the ultrasound scans for DVT were likely to be false
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28 positives in view that all were still positive on repeat scanning after a week
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30 interval. All assessors of DVT were blinded to the patient randomization
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32 group.
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43 We acknowledge several limitations of our study. Firstly, we were only able to
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45 recruit 100 (26%) patients after screening 380 for eligibility, due to the current
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47 NICE guidelines that recommend chemical thromboprophylaxis for patients
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49 with lower limb trauma treated with cast with additional risk factors. This
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51 meant that none of the patients who underwent surgery could be included (n=
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53 105), with an additional 72 patients being prescribed LMWH for other reasons.
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56 We were also unable to recruit patients over the age of 60 years of age
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(n=97) during the study period because this is also considered to increase VTE risk in patients with lower limb trauma treated with cast [6].

In conclusion, regular active toe movement by patients treated with lower limb cast for acute foot and ankle trauma did not significantly influence calf pump function or reduce the incidence of asymptomatic deep vein thrombosis. All cases of deep vein thrombosis occurred in the lower limb, which had been injured and treated in cast. The majority (90%) of venous thrombosis involved the peroneal veins. Advice to patients to perform regular active toe movement alone appears insufficient to reduce the risk of development of asymptomatic deep vein thrombosis.

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Table 1: Characteristics of participants

Characteristics	AToM (N = 39)	Control (N = 39)
Age (mean)	36.6 (18-60)	36.8 (18-60)
Male sex, n (%)	23 (59)	28 (72)
Bony injury, n (%)	36 (92)	36 (92)
Injuries, n		
Ankle fracture –Weber A	7	8
Ankle fracture – Weber B	15	16
Ankle sprain	3	3
Anterior process of calcaneus fracture	1	0
Cuboid fracture	1	1
Distal fibula avulsion fracture	1	0
Dorsal talonavicular ligament avulsion	3	1
Fifth metatarsal fracture	1	2
Lateral process of talus fracture	1	1
Lisfranc injury	0	1
Medial malleolus fracture	4	5
Navicular fracture	1	1
Posterior malleolus fracture	1	0
Duration of cast or boot, mean +/- SD (days)	42.7 (13.8)	39.6 (17.0)

Table 2: Mann Whitney U statistic analysis of calf pump function parameters

(U/mn)

	U/mn	95% confidence limits	
		Lower	Upper
Baseline popliteal vein diameter - injured/cast leg	0.495	0.349	0.642
Baseline popliteal vein velocity - injured/cast leg	0.533	0.384	0.676
Peak velocity during active toe dorsiflexion (average) - injured/cast leg	0.572	0.420	0.710
Peak velocity during active toe plantarflexion (average) - injured/casted	0.572	0.420	0.710

Table 3: Calf pump function results

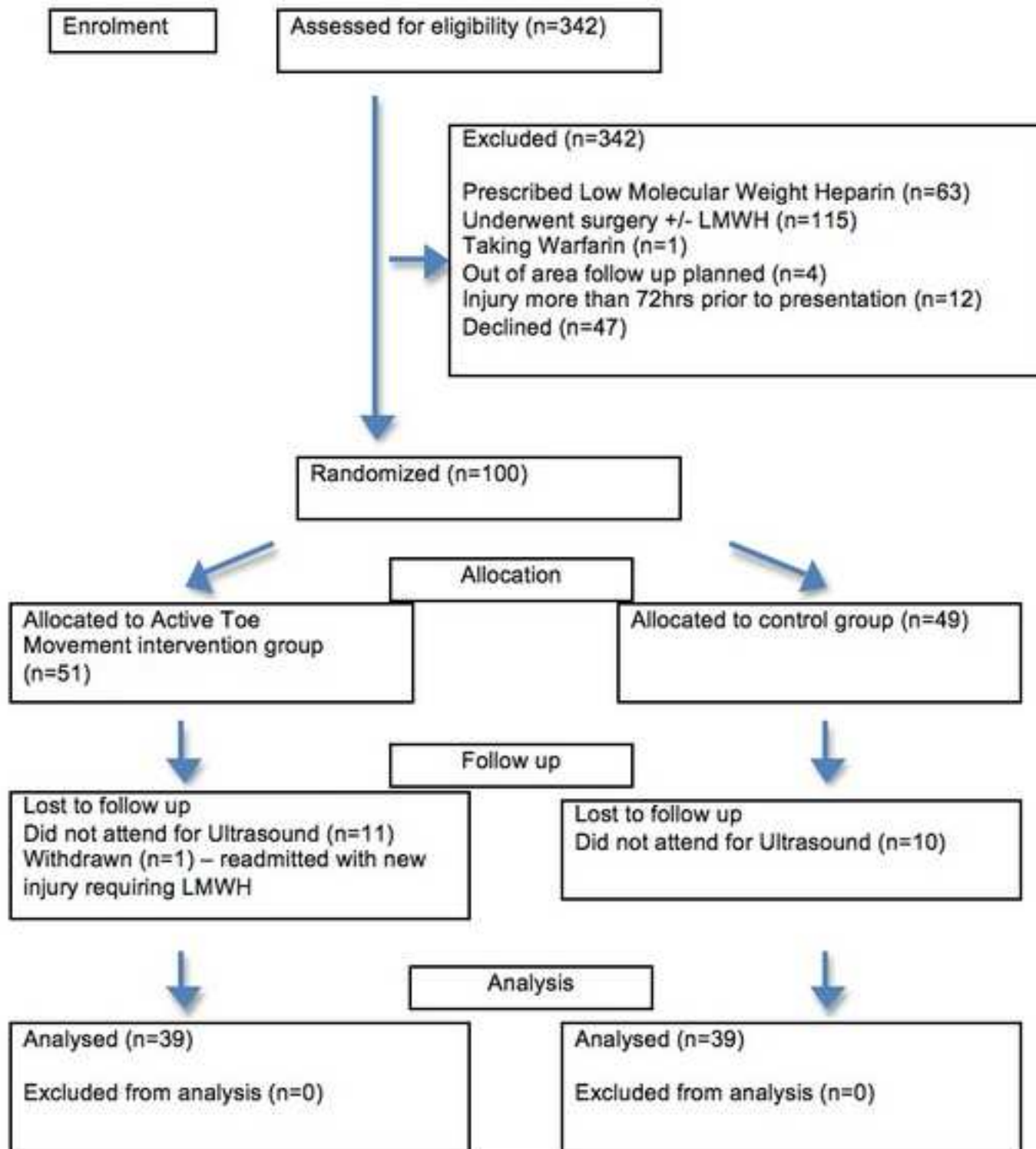
Calf pump function parameter	AToM	Control	p-value
Baseline popliteal vein diameter (mm)	7.9 (1.736)	7.95 (SD 2.084)	0.933
Baseline popliteal vein velocity (cm/s)	7.33 (3.663)	6.8 (2.193)	0.579
Peak popliteal velocity during active toe dorsiflexion (cm/s)	44.04 (30.172)	34.20 (18.878)	0.361
Peak popliteal velocity during active toe plantarflexion (cm/s)	39.04 (23.699)	31.70 (16.398)	0.348

Table 4: Asymptomatic Deep Vein Thrombosis events

	AToM (N=39)	Control (N=39)
Asymptomatic DVT in Popliteal vein or more proximal	1	2
Asymptomatic below knee DVT details:		
Peroneal vein	8	5
Posterior tibial vein	1	0
Peroneal and posterior tibial veins	3	1
Total n (%)	13 (33.3)	8 (20.5)

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Figure 1: Flow diagram of study participants



The effect of active toe movement (AToM) on calf pump function and deep vein thrombosis in patients with acute foot and ankle trauma treated with cast
– A Prospective Randomised Study

Highlights:

There is no current evidence that active toe movement reduces asymptomatic venous thromboembolism in patients with foot and ankle trauma treated with below knee cast

27% (n=21) of patients with acute foot and ankle trauma treated with below knee cast will develop asymptomatic deep vein thrombosis despite being assessed as low risk for thrombosis (above knee DVT incidence of 4% (n=3))

90% (n=19) of asymptomatic deep vein thrombosis events in this patient group involve the peroneal vein

All cases of asymptomatic deep vein thrombosis occur in the lower limb that is treated with below knee cast

The effect of active toe movement (AToM) on calf pump function and deep vein thrombosis in patients with acute foot and ankle trauma treated with cast
– A Prospective Randomised Study

Conflicts of interest statement:

None