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Cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism

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ABSTRACT

Objectives: To determine the likely enrolment rate of eligible participants into a randomised controlled trial (RCT) in which a within-cast intermittent pneumatic compression device using Jet Impulse Technology (IPC/JIT) is 1 of 3 possible interventions in a RCT for the prevention of venous thromboembolism (VTE) in the clinical setting of isolated lower limb cast immobilisation.

Design: A prospective, open-label feasibility study of the IPC/JIT device placed within a lower limb cast.

Setting: Wellington Regional Hospital Fracture Clinic.

Participants: Individuals aged 18–70 who presented with a lower limb injury requiring a minimum of 4 weeks below-knee cast immobilisation.

Intervention: Placement of an IPC/JIT device within lower limb cast.

Outcome measures: The main outcome measure was the proportion of eligible participants who participated in the feasibility study. Secondary outcome measures included adherence to device usage throughout the study, ease of application of the device and adverse events potentially associated with its use.

Results: The proportion of potentially eligible participants for the IPC/JIT device was only 7/142 (5%), 95% CI 2 to 9.9. Devices were used for a mean (range) of 4.1 (1.9 to 10.2) hours per day and none of 7 participants had adequate adherence to the device. 3 of the 7 participants suffered an adverse event, including 1 deep vein thrombosis, 2 dorsal foot ulcer and 1 skin maceration.

Conclusions: A within-cast IPC/JIT device is unlikely to be a feasible randomisation arm for a RCT assessing possible interventions for the reduction of VTE risk in the clinical setting of lower limb injury requiring below knee cast immobilisation for a minimum of 4 weeks.

Trial registration number: ANZCTR 12615000192583.

Strengths and limitations of this study

- This study is generalisable to all adults presenting with acute injury requiring lower limb cast immobilisation.
- Data reflecting intermittent pneumatic compression device usage was downloaded directly from the machines and was not dependent on participant self-reporting.
- Assessment of adverse events and venous thromboembolism rates was limited by low recruitment into the study.

INTRODUCTION

Prolonged cast immobilisation of the lower limb after injury is associated with an increased risk of venous thromboembolism (VTE).[1–7] In a recent analysis of risk factors for VTE in two case–control studies, we found lower limb immobilisation was associated with a 73-fold increased risk of VTE (Braithwaite I, Healy B, Cameron L, *et al*. Lower limb immobilization and VTE risk: combined case-control studies. Submitted to *Postgrad Med J* 2016). Lower limb immobilisation was the most common potentially preventable cause of VTE in the 18–65 year age group, being present in one in seven cases.

A 2014 Cochrane review of low-molecular-weight heparin (LMWH) for prevention of VTE in patients with lower limb immobilisation reported a wide range, between 4.3% and 40%, for the incidence of VTE detected by radiological screening in patients in the control arms of these studies.[1] The risk of VTE was reduced by ~50% by the administration of LMWH. The risk reduction was similar to those with tendon ruptures compared with fractures, and for surgical repairs compared with conservatively treated patients. Widespread use of LMWH could expose a potentially large patient group to the bleeding risks of its use and the American College of Chest Physicians (ACCP), in their Evidence-based Clinical Practice Guidelines on

Prevention of Thrombosis (2012),[8] suggests that the risks and benefits of VTE prophylaxis are fairly evenly balanced and recommend no prophylaxis for cast immobilisation in isolated lower leg injuries distal to the knee. They also suggest that further research in this area is required.

In New Zealand LMWH for the prevention of VTE in the clinical setting of lower limb immobilisation is not funded for outpatients and its use has practical difficulties with patient adherence to a daily subcutaneous injection regime. Some evidence supports the use of low-dose oral aspirin prophylaxis for VTE in a variety of medical and surgical patient groups.[9 10] A single large randomised placebo-controlled trial of low-dose aspirin in hip fracture and elective arthroplasty found one-third reduction in VTE risk with only a small increase in postoperative bleeding.[11] There are no trials of low-dose aspirin in lower limb immobilisation. In an audit in our local institution carried out after the introduction of aspirin 100 mg daily for prophylaxis of VTE, we could identify no change in VTE rates. This suggests that aspirin is not an effective prophylactic measure in this clinical setting.[12] Oral anticoagulants including direct factor Xa inhibitors, such as rivaroxaban and apixaban, reduce the risk of VTE in total hip and knee arthroplasty with a favourable efficacy/risk profile compared with LMWH;[10 13] however, their efficacy and safety profile in lower limb immobilisation is yet to be assessed.

The clinical effectiveness of intermittent pneumatic compression (IPC) systems in the prevention of deep vein thrombosis (DVT) is well established as a non-pharmacological alternative for VTE prevention without the risk of bleeding.[8 14] Intermittent compression can be applied to the thigh, calf or foot, or any combination thereof, of a patient and has been used in surgical and medical settings. IPC achieves an antithrombotic effect through increasing venous blood flow, thus reducing venous stasis, and also through stimulation of endogenous fibrinolysis.[15] Foot pumps, which we have shown increased popliteal vein flow within a lower limb cast (Braithwaite I, Mackintosh S, Buchanan S *et al*. Venous haemodynamics of Jet Impulse Technology within a lower limb fibreglass cast: a randomised controlled trial (RCT) (JIT in-cast trial). Accepted by *JRSM Open* 2015) have proven efficacy in reducing VTE events in total knee replacement surgery,[16] and total hip arthroplasty.[17] Current recommendations for IPC include as adjunctive therapy to pharmaceutical anticoagulation, or in situations in which prophylactic anticoagulation is contra-indicated.[8]

We initially planned to undertake a three-arm, parallel group, (proposed) RCT of low-dose aspirin (100 mg daily), an IPC device plus low-dose aspirin, or rivaroxaban (10 mg daily) alone to prevent VTE secondary to cast immobility for a ruptured Achilles tendon or ankle fracture. However, when developing the details of the proposed RCT it became apparent there were no published trials of IPC devices in the setting of prolonged lower limb cast immobilisation. The potential for its use in this clinical situation was supported by our demonstration that IPC devices increase popliteal vein blood flow within a lower limb cast, (Braithwaite *et al*, submitted to *JRSM Open*, 2015) but this was in a study not exceeding 1-hour.

This current study was a feasibility study of the use of IPC technology in this instance, the VADOplex VenaJet foot pump system marketed in New Zealand as Jet Impulse Technology (IPC/JIT) within lower limb casts. It aimed to estimate recruitment rates for a possible large-scale RCT, the tolerability of IPC/JIT placement under a lower limb cast for a protracted period of time (a minimum of 4 weeks duration, with cast changes of up to 2 weeks apart), adherence to the proposed IPC/JIT in-cast regime, and adverse events potentially associated with its use. We were also interested in the proportion of potential participants who might not be eligible for recruitment to a trial arm that included the use of rivaroxaban based on already using an oral anticoagulant, being at very high risk of VTE, being treated for active upper gastrointestinal ulcer disease, immobility >2 days prior to enrolment, significant liver disease, creatinine clearance <30 mL/min, or concomitant use of HIV protease inhibitors.

PARTICIPANTS AND METHODS

Recruitment for the feasibility study occurred for 6 months, August 2015 to January 2016, with a further 3 months for follow-up of participants. Eligible participants were patients aged between 18 and 70 years presenting to Wellington Hospital Fracture Clinic with ruptured Achilles tendon, stable ankle fracture requiring a non-weight-bearing cast, or, if possible, ankle fracture with operative fixation and then cast immobilisation. Exclusion criteria included patients with a high risk for VTE, active gastric or duodenal ulcer, already using anticoagulation, immobility >2 days before enrolment, significant liver disease (including moderate-to-severe hepatic impairment especially when associated with coagulopathy), renal impairment (estimated creatine clearance <30 mL/min), or concomitant use of HIV protease inhibitors.

Initially recruitment was limited to working hours; however, by the middle of September we identified that many potentially eligible participants presented on weekends, and so ethics approval was obtained at the end of September to extend recruitment over weekends, still within usual business hours of 08:00–17:00. Investigators and orthopaedic nursing staff identified potentially eligible participants, informed them about the open-label trial, and asked them if they would like to participate. Those who declined to participate were given the opportunity to provide a reason for non-participation, and if the reason for not participating was because the treatment was a device rather than a medication, this was documented. A record was kept of potential participants, including those who were treated and discharged

outside of working hours, and of all potential participants approached during the working day. This record was used to identify the proportion of eligible participants likely to be recruited into the proposed RCT.

Potential participants were approached as they arrived in the outpatient department and were given a participant information sheet by the department nursing staff. If they expressed interest in the study, a study investigator was called to explain the study and to answer any queries potential participants had. Participants were advised that they had the ability to withdraw from the study at any time. No study procedures were undertaken until after the participants had signed written informed consent.

Participants who agreed to be enrolled into the feasibility trial had the IPC with Jet Impulse Technology (JIT) placed under their lower limb cast (figure 1) and the usual care of aspirin EC 100 mg daily was also prescribed. They were reviewed fortnightly at the fracture clinic for up to 8 weeks. In-cast pad changes were planned at weeks two and four and possibly six depending on adherence of participants to the device and the treatment plans of the orthopaedic consultant. The IPC/JIT device was preset to inflate to 130 mm Hg once every minute, and participants had only to connect to the pump unit and turn the device on or off as required. To measure adherence with the device, participants were asked to use the IPC/JIT as much as possible while they were seated or immobile during the day and while in bed at night. Good adherence was defined as 60% of the total potential time available, namely 14.4 hours of a potential 24 hours per day. Total time, in hours, of IPC/JIT device usage was collected directly from the device at each clinic visit. To assess ease of application of the device and any adverse events, nursing staff completed a semistructured record regarding the practicalities of device placement and related issues such as skin condition of the lower limb after removal of the cast at each clinic visit. Adverse events and withdrawal reasons (if provided) were documented as they occurred.

The VADOplex VenaJet foot pump system (OPED, Oberlaindern, Germany) is an IPC device that works with Jet Impulse Technology (JIT), to mimic the usual weight-bearing walking process. It comprises a 4.6 kg, 320 mm wide×190 mm high×200 mm deep (including mounting handle), bilateral pump unit, with an in-cast pad that is attached to the pump unit via an air tube (figure 2). The pump mechanism mimics the natural full weight-bearing walking process, rapidly inflating a distal air-cell in the foot cuff to 130 mm Hg, which then settles to 52 mm Hg, followed by a proximal air-cell 0.3 s later, settling to 48 mm Hg. After 6 s of compression at 48–52 mm Hg, both air-cells deflate. This cycle is repeated every minute. The total hours the device has been in use, both with the garment in operation, and without the garment, are indicated on the device readout. These numbers were documented at each visit.

All participants were scheduled for ultrasound examination of the popliteal to femoral vein of the affected limb (accessible above the leg cast) prior to each clinic visit, and again for ultrasound scanning of the entire limb after removal of the cast or moonboot at the end of their orthopaedic treatment period which was expected to be between 6 and 8 weeks. At any time between clinic visits and during the ensuing 6-week follow-up period, if participants experienced signs or symptoms of DVT or pulmonary embolism (PE), they would have an ultrasound scan or CT pulmonary

Figure 1 Jet Impulse Technology (JIT)/intermittent pneumatic compression (IPC) footpad placement under lower limb cast.

Figure 2 Jet Impulse Technology (JIT)/intermittent pneumatic compression (IPC) device.

angiogram (CTPA), respectively, and be treated according to Wellington Hospital protocols. All participants were educated about the symptoms of DVT and PE and advised to seek medical review should these occur. A final follow-up phone call was made 6 weeks after the completion of cast-immobilisation treatment to ensure there had been no VTE event after completing the study.

Sample size and statistical methods

A total of 70 participants in the feasibility trial provided over 95% power to rule out a recruitment rate of ≤50%. It also provided 80% power with an α of 5% to rule out a complication rate of at most 33% if the anticipated complication rate was 10%; and to rule out adherence of ≤60% if the adherence rate was 75%. The main analyses planned were to estimate 95% CI proportions by the exact Clopper-Pearson method and to compare the achieved proportions with those outlined in the sample size calculation.

SAS Version 9.4 was used for the calculation.

RESULTS

The flow of potentially eligible participants is shown in figure 3. Only 7/142 (5%) of potentially eligible participants were enrolled (table 1), with an exact 95% CI of 2% to 9.9%, p value for comparison with a rate of 50% <0.001. There were 58 (41%) potentially eligible participants who were not enrolled for logistics reasons; 39 (27%) were admitted for operative intervention, and due to operation theatre logistics, could not be enrolled and 19 (13%) presented on weekends and evenings before the change in study protocol. There were 77 (54%) potentially eligible participants who were not enrolled due to reasons that were not anticipated at the time of design of the feasibility study, such as a moulded cast preventing the placement of the IPC/JIT, living out of geographical area thus making follow-up of participants impracticable, frailty of potential participants and use of a Plaster of Paris cast, the integrity of which might be impaired by the IPC/JIT device. Six potential participants declined due to the perceived impracticality of using the IPC/JIT device. There were no documented issues with skin integrity at initial device and cast placement. There were no issues with initial device placement by fracture clinic staff. A description of all 142 potential participants is shown in table 2.

Table 1 Flow of potential participants through the feasibility study

Recruitment status, N=142	N (%)
Not enrolled	
Logistic reasons	58 (40.8)
Operative intervention	39 (27.5)
Weekend and evenings	19 (13.4)
Other reasons	60 (42.3)
Moulded cast	31 (21.8)
Out of geographical follow-up area	10 (7.0)
Frailty	10 (7.0)
Plaster of Paris cast—not suitable	9 (6.3)
Owing to exclusion criteria	11 (8.2)
Injury >48 hours prior	8 (5.8)
Weight-bearing cast applied	2 (1.4)
Other VTE risk factor	1 (1)
Declined study	6 (4.2)
Enrolled in study	7 (5.0)
Total	142

VTE, venous thromboembolism.

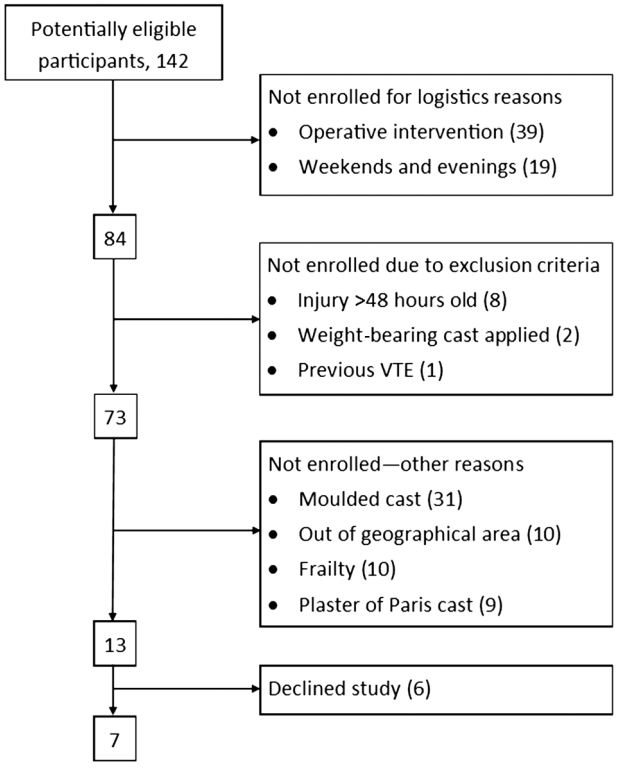

Figure 3 Flow of participants through study. VTE, venous thromboembolism.

Participants enrolled to use the IPC/JIT device

Of the seven participants enrolled in the feasibility study three participants did not complete the minimum 4-week period of IPC/JIT usage; one changed to a weight-bearing cast after 1-week and the device was removed, one withdrew after developing an ulcer on the dorsum of their foot in the initial 2-week period, and one withdrew after 2 weeks due to maceration of the skin. Four participants completed 4 weeks of IPC/JIT device usage. One participant that completed the 4-week intervention had a DVT diagnosed at scheduled 4-week ultrasound scan, and was treated with rivaroxaban. No participants developed symptomatic VTE in the 6-week follow-up period. Excluding the participant who changed to a weight-bearing cast the complication rate was 3/6 (50%) with 95% CI of 11.8 to 88.2; p value for a comparison with 33% of 0.63.

Table 2 Description of potential and enrolled participants in feasibility study

	Not recruited (N=135)	Recruited (N=7)
Continuous variable	Mean (SD)	
Age (years)	43.1 (15.0)	39.4 (7.9)
Categorical variable	N (%)	
Female	75 (56)	3 (43)
Ethnicity		
European	87 (64.4)	2 (28.6)
Maori	19 (14.1)	3 (42.9)
Pacific Islander	11 (8.1)	2 (28.6)
Asian	10 (7.4)	0 (0)
Other	8 (5.9)	0 (0)
Day presenting		
Monday	23 (17.0)	2 (28.6)
Tuesday	19 (14.1)	1 (14.3)
Wednesday	19 (14.1)	1 (14.3)
Thursday	10 (7.4)	1 (14.3)
Friday	22 (16.3)	1 (14.3)
Saturday	27 (20.0)	0 (0)
Sunday	15 (11.1)	1 (14.3)
Injury		
Ankle fracture	64 (47.4)	1 (15)
Achilles tendon	42 (31.1)	6 (85)
Fibula fracture	13 (10.4)	–
Other injury	16 (11.1)	–

Participant adherence to JIT and feedback about the device

The seven participants were issued the IPC/JIT devices and used the device for a total of 148 days. For these participants a total of 608 hours of use were recorded. The mean (range) of daily use was 4.1 hours (1.9–10.2). No participant met the proposed adherence target of an average of 14.4 hours per day in any of the 2-week periods with a 95% CI for adherence of 0 to 41%, p value for comparison with 60%, 0.003. Of the seven participants, six did not use the device at night as it interfered with their sleep. All participants found the pump unit difficult to move around while they were non-weight-bearing and on crutches, and tended to leave the pump unit in a single location where they were likely to spend most of their time. One participant attempted to take the pump unit to and from work, but found that even with a backpack the pump unit was too large and awkward to carry around while on crutches. All participants indicated that they would use an IPC/JIT system again, but that the pump unit would have to be much smaller and lighter to allow ease of use.

Exclusion criteria for rivaroxaban arm of proposed RCT

Of the 142 potentially eligible participants identified in the study, 5 (3.5%) were already prescribed an anticoagulant, 3 (2.1%) had a high risk of VTE (2 had active nephritis and 1 had a history of VTE) and 1 (0.7%) was on treatment for an active gastric ulcer. In all 9/142 (6.3%) would not have been eligible for rivaroxaban treatment, 95% CI 2.9 to 11.7. None of the remaining 133 (91.7%) participants had any of the remaining exclusion criteria: immobility >2 days prior to enrolment, significant liver disease, creatinine clearance <30 mL/min or concomitant use of HIV protease inhibitors.

DISCUSSION

This feasibility study shows that the IPC device using JIT technology is not a feasible randomisation arm in a RCT assessing VTE prevention rates in lower limb immobilisation. Furthermore, it is clearly not a therapeutic option for VTE prophylaxis in this clinical setting, regardless of its potential efficacy.

While our study was of the VADOplex VenaJet foot pump system IPC/JIT device specifically, the findings in this study are broadly generalisable to individuals using IPC foot garments within rigid lower limb casts for prolonged periods in the outpatient community. The size and weight of the pump unit limiting patient mobility, interference with sleep leading to lack of use overnight, and skin-related adverse events are likely to occur with other IPC systems in this clinical setting, thus impacting ongoing patient adherence and denying maximal antithrombotic effect.

It is interesting to compare outpatient usage of the IPC/JIT device when compared with studies of foot IPC use within hospital inpatient settings. In a study of patients after a total joint arthroplasty Pitto and Young[18] reported that while 5% of patients discontinued IPC use between 2 and 6 days after initiation of use, foot pump devices had been used by the remaining 95% of patients for 15.9 hours daily. Charalambous *et al*[19] assessed adherence to foot-pump usage in an inpatient setting after joint arthroplasty, and found that as patients got in and out of bed more frequently, their foot pumps were reapplied less often, and that only 60% of patients used foot pumps at night when confined to bed. In our study, the IPC/JIT device was used for 4 hours/day and six of seven participants did not use the device at night. It is likely that in an unsupervised environment participants may be less likely to use the device, particularly overnight compared with an inpatient group. Adherence might be improved by using a smaller, more portable pump unit that was easier for participants to move around with. Providing more than one of the current devices to each participant to allow placement at strategic locations at home or at work, while possible, is likely to prove too expensive.

It is informative to compare the complications associated with IPC/JIT use in this study with those experienced in other trials. Two of the seven (28.5%) participants suffered complications associated with the JIT device; one had a dorsal foot ulcer and the other one suffered skin maceration. This is higher than skin-related adverse events reposted in previous studies where dorsal ulcers, skin blisters and malleolar sores

have been reported in 0% of 42 patients after hip surgery,[20] 6.7% of patients receiving plantar venous compression after total hip arthroplasty,[21] 4.5% in patients using a plantar compression device after total hip replacement[22] and 7.5% of patients using preoperative plantar compression after ankle fracture.[23] Skin maceration is not uncommon within fibreglass casts, due either to excess sweating or inadvertent wetting of the cast, thus we were uncertain that the IPC/JIT device was the direct cause of the maceration. After this event, we started placing more protective material between the footpad and the skin and no further episodes occurred.

Foot pump devices have been shown to increase lower limb venous flow,[24–26] and a number of early studies have shown that foot pump prophylaxis with or without graduated compression stockings and/or pharmacological prophylaxis significantly reduces the risk of VTE after major orthopaedic surgery compared with; compression stockings alone,[27] or compression stockings and heparin.[21 22] These findings, in conjunction with the high rates of VTE found in the clinical setting of lower limb immobilisation,[1 12 28] raise the question of potential IPC/JIT prophylaxis in this situation, which would eliminate the risk of bleeding that exists with pharmacological prophylaxis. Since the inception of this feasibility study, Domeij-Arverud *et al*[28] have published findings related to the use of an IPC and plastic foot cuff under a Plaster of Paris cast after Achilles tendon repair. They found that 9 of 14 participants randomised to IPC treatment and 6 of 12 who received no intervention developed DVT during the intervention period. IPC malfunction and the need to replace the cast correlated with a higher risk of VTE at 2 weeks resulting in the study being halted, suggesting that IPC prophylaxis in this clinical setting is no better than, and in fact is possibly worse than no prophylaxis. In our study, we enrolled only patients with fibreglass casts, there were no IPC/JIT malfunctions and no unscheduled cast changes were necessary. One in seven participants in our study was found to have a DVT on radiological screening; however, given the small number of participants that used the IPC/JIT in this study, we cannot draw a conclusion about the likely VTE rates with this intervention.

If the randomised IPC/JIT treatment arm was dropped from the proposed RCT, and all the limiting logistics factors of the non-recruited group were suitably addressed for example, full out of hours recruitment; access to the operating theatre postoperatively for device placement, about 130 patients would be eligible in each 6-month period. In this modified RCT, 200 participants would be required in each treatment arm (a total of 400) to ensure 90% power with an α of 5% to detect a 50% relative reduction in VTE events with rivaroxaban compared with the control arm (aspirin), assuming a 20% drop out rate. This suggests that the single Wellington Hospital site would have the potential to fully recruit the proposed RCT within a 2-year period, even if the recruitment rate was 80%.

CONCLUSIONS

The IPC/JIT device placed within a lower limb fibreglass cast is not a feasible randomisation arm for the proposed RCT investigating the rates of VTE in the clinical setting of outpatient temporary lower limb immobilisation due to low recruitment rates, poor adherence to treatment regimens and high rates of adverse events. The characteristics of potential participants suggest that recruitment into the rivaroxaban and aspirin arms of the proposed RCT from a single location is achievable.

Contributors RB, IB, MW, BDR, GK, NW and JC contributed to the study concept and design. IB, BDR, AS and SE were involved in the acquisition of data. RB and IB contributed to the drafting of the manuscript. All authors participated in the critical revision of the manuscript for important intellectual content. IB and MW performed the statistical analysis. All authors provided administrative, technical and material support. IB was responsible for the study supervision.

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Competing interests None declared.

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Data sharing statement Additional data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.5ms8t.

REFERENCES

1. Testroote M, Stigter W, de Visser DC, *et al*. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization (review). *Cochrane Database Syst Rev* 2008;(4):CD006681.
2. Ettema HB, Kollen BJ, Verheyen CCPM, *et al*. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost* 2008;6:1093–8.
3. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;347:726–30.
4. Lapidus LJ, Ponzer S, Elvin A, *et al*. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop* 2007;78:528–35.
5. Lapidus LJ, Rosfors S, Ponzer S, *et al*. Prolonged thromboprophylaxis with dalteparin after surgical treatment of Achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma* 2007;21:52–7.
6. Jørgensen PS, Warming T, Hansen K, *et al*. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. *Thromb Res* 2002;105:477–80.

7. Kock HJ, Schmit-Neuerburg KP, Hanke J, *et al*. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;346:459–61.
8. Falck-Ytter Y, Francis CW, Johanson NA, *et al*. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(Suppl 2):e278S–325S.
9. Collins R, Baigent C, Sandercock P, *et al*. Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. Antiplatelet Trialists' Collaboration. *BMJ* 1994;309:1215–17.
10. Eriksson BI, Kakkar AK, Turpie AG, *et al*. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Jt Surg Br* 2009;91:636–44.
11. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295–302.
12. Braithwaite I, Dunbar L, Eathorne A, *et al*. Venous thromboembolism rates in patients with lower limb immobilization after Achilles tendon injury are unchanged after the introduction of prophylactic aspirin: audit. *J Thromb Haemost* 2016;14:331–5.
13. Lassen MR, Ageno W, Borris LC, *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776–86.
14. Niikura T, Lee SY, Oe K, *et al*. Incidence of venous thromboembolism in fractures around and below the knee with physical prophylaxis. *Orthopedics* 2012;35:e1476–82.
15. Comerota AJ, Chouhan V, Harada RN, *et al*. The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg* 1997;226:306–13; discussion 313–4.
16. Wilson N, Das S, Maurice H, *et al*. Thrombosis prophylaxis in total knee replacement: does a simple mechanical method help? *Br J Surg* 1990;77:1417.
17. Fordyce MJF, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *J Bone Jt Surg Br* 1992;74:45–9.
18. Pitto RP, Young S. Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: efficacy, safety and patient compliance. *Int Orthop* 2008;32:331–6.
19. Charalambous C, Cleanthous S, Tryfonidis M, *et al*. Foot pump prophylaxis for deep venous thrombosis—rate of effective usage following knee and hip arthroplasty. *Int Orthop* 2003;27:208–10.
20. Asano H, Matsubara M, Suzuki K, *et al*. Prevention of pulmonary embolism by a foot sole pump. *J Bone Joint Surg Br* 2001;83:1130–2.
21. Bradley JG, Krugener GH, Jager HJ. The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty. *J Arthroplasty* 1993;8:57–61.
22. Santori FS, Vitullo A, Stopponi M, *et al*. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Jt Surg Br* 1994;76:579–83.
23. Caschman J, Blagg S, Bishay M. The efficacy of the A-V Impulse system in the treatment of posttraumatic swelling following ankle fracture: a prospective randomized controlled study. *J Orthop Trauma* 2004;18:596–601.
24. Charles T, Mackintosh S, Fingleton J, *et al*. Efficacy of micromobile foot compression device in increasing lower limb venous blood flow. *Int J Vasc Med* 2013;2013:948769.
25. Delis KT, Slimani G, Hafez HM, *et al*. Enhancing venous outflow in the lower limb with intermittent pneumatic compression. A comparative haemodynamic analysis on the effect of foot vs. calf vs. foot and calf compression. *Eur J Vasc Endovasc Surg* 2000;19:250–60.
26. Morris RJ, Woodcock JP, Pitto RP, *et al*. Evidence-based compression. *Int Orthop* 2004;239:162–71.
27. Healy B, Beasley R, Weatherall M. Venous thromboembolism following prolonged cast immobilisation for injury to the tendo Achillis. *J Bone Jt Surg Br* 2010;92:646–50.
28. Domeij-Arverud E, Latifi A, Labruto F, *et al*. Can foot compression under a plaster cast prevent deep-vein thrombosis during lower limb immobilisation? *Bone Joint J* 2013;95-B:1227–31.