

Title: Alternative physical treatments for deep venous thrombosis prophylaxis in surgical patients: a systematic review.

Authors: Juan Enrique Berner MD^{1,2}, Luke Geoghegan MBBS^{3,5}, Ioannis Kyriazidis MD², Jagdeep Nanchahal PhD⁴, Abhilash Jain PhD^{3,5}

Affiliations:

1. Kellogg College, University of Oxford. Oxford, United Kingdom.
2. Queen Victoria Hospital. East Grinstead, United Kingdom
3. Imperial College NHS Trust. London, United Kingdom
4. The Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedic, Rheumatology and Musculoskeletal Sciences, University of Oxford. Oxford, United Kingdom.
5. Nuffield Department of Orthopaedic, Rheumatology and Musculoskeletal Sciences, University of Oxford. Oxford, United Kingdom

Corresponding author:

Mr Juan Enrique Berner MD MSc MRCS

Address: Kellogg College, University of Oxford. Oxford, United Kingdom. OX2 6PN.

Telephone: +447427074300

E-mail: juan.berner@nhs.net

Luke Geoghegan - luke.geoghegan13@imperial.ac.uk

Ioannis Kyriazidis - jkyriazidis@gmail.com

Jagdeep Nanchahal - jagdeep.nanchahal@kennedy.ox.ac.uk

Abhilash Jain - abhilash.jain@kennedy.ox.ac.uk

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Introduction

Prolonged intra- and post-operative immobilisation results in deep venous stasis due to inactivity of the calf muscle pump, leading to increased risk of deep venous thrombosis (DVT)[1]. Surgical trauma and systemic inflammatory responses predispose to endothelial injury and hypercoagulability respectively[2], following the principles of Virchow's triad.

Venous thromboembolism (VTE) represents a significant clinical and socioeconomic burden, contributing to at least 100,000 deaths per year[3]. Even for survivors, VTE adversely affects quality of life with chronic sequelae such as post-thrombotic syndrome and chronic thrombotic pulmonary hypertension, with an estimated direct healthcare cost of \$5-10 billion per annum[4]. Preventive interventions aimed at reducing the incidence of DVT in high-risk patients have demonstrated to be cost-effective[5], and consequently have become an important aspect of inpatient care[6].

Current standard peri-operative DVT prophylaxis includes early mobilisation[7], chemoprophylaxis with low-molecular weight heparin (LMWH)[8], graduated compression stockings[9] and intermittent pneumatic compression devices[10]. These interventions are cost-effective in reducing DVT rates and are standard practice as part of national guidance[6]. However, standard prophylaxis is unsuitable for some patients. For example, early mobilisation may be contraindicated in critical patients and those who suffer from polytrauma, LMWH is unsuitable in coagulopathic patients due to the risk of intracranial haemorrhage and graduated compression stockings may be poorly tolerated in those with peripheral arterial disease. Similarly, intermittent pneumatic compression devices cannot always be used in patients who have recently undergone lower limb reconstruction.

Several alternative physical treatments that recruit or replace the calf muscle pump function have been proposed, including bandaging, massage therapy, physical activity and electrostimulation of calf muscles. A recent Cochrane systematic review evaluated neuromuscular electrostimulation of calf muscles for DVT prevention and found it to be inferior to low-molecular weight heparin, but showed a reduction in DVT rates when compared to no intervention. The authors concluded that the quality of evidence to support these conclusion was low, with a high-risk of bias[11]. However, this review did not appraise other forms of alternative physical treatments for perioperative DVT prophylaxis. Despite the very limited evidence, electrostimulation devices have been licensed for DVT prophylaxis in high risk patients in whom standard prophylactic strategies are contraindicated[12].

The aim of this systematic review is to identify reported alternative active and passive physical treatments for the prophylaxis of deep venous thrombosis in trauma and surgical patients, and appraise their clinical utility.

Materials and Methods

The PRISMA statement was used as a guideline for the planning, conduction and reporting of this systematic literature review[13]. Before performing any searches, clear inclusion and exclusion criteria were defined, focusing on studies on physical modalities to reduce the risk of DVT in surgical patients (Table 1). A protocol for this systematic review was registered with PROSPERO (CRD42019133684).

In order to include all forms of physical treatments in the literature, a combination of free search terms were used, including: “exercise therapy”, “physical therapy modalities”, “isometric contraction”, “electric stimulation therapy” and “muscle stretching”. These were combined with the terms “venous thrombosis” and “venous thromboembolism”, along with “lower extremity and “lower limb”. This search strategy was used to scrutinise MEDLINE and EMBASE, without any filters. A senior librarian with expertise in systematic reviews aided in the design of the definitive search strategy that was conducted on the 27th of July 2019, including all studies published prior to that date. Eligibility was not limited by language (Appendix 1).

Retrieved publications were managed using EndNote X8 (Clarivate Analytics, Pennsylvania, USA) software. Duplicate entries were identified and discarded. Two authors (JB and IK) independently screened the titles and abstracts first for eligible articles. Eligible studies then underwent full-text review to ascertain compliance with the predefined inclusion and exclusion criteria. The senior author (AJ) was nominated to resolve any arising disputes.

The complete articles were independently scrutinised by two authors (JB and LG). A pre-established data collection proforma was used to collect demographic, treatment characteristics and outcome data. The risk of bias for each individual study was assessed either by using the Cochrane risk of bias tool for randomised controlled trials (RoB2)[14] or the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[15], depending on study design. A final assessment of the quality of evidence was reported for each study using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework[16].

Results

The systematic search strategy retrieved a total of 272 articles, of which 159 were acquired from EMBASE and 113 from MEDLINE. A PRISMA flow-chart illustrating the study selection process can be found in Figure 1. After removal of 93 duplicate entries, a list of 179 articles was obtained, of which ten met inclusion criteria.

These 10 studies, published between 1988 and 2019, included 7 randomised controlled trials (RCT) and 3 non-randomised cohort studies. Seven studies were conducted on orthopaedic patient cohorts, with the remaining three on neurosurgical, general surgery and trauma surgery patients.

A total of 1,136 patients were reported in the publications, with a median age of 58 years (range 18-79 years). Five studies evaluated the use of calf muscle electrostimulation therapy for reducing DVT incidence in surgical patients, with two of these involving post-operative stimulation only[17,18], one study utilising this modality intra-operatively only[19] and two studies using this modality throughout the peri-operative period[20,21]. Each of the remaining five studies looked at different interventions. The first described post-operative use of a modified Robert Jones bandage[22], the second a regime of active toe movements for lower limb trauma treated with casting[23], another blood flow restriction exercises after surgery[24], the fourth manual calf massage and passive range of motion exercises post-operatively[25], finally one reported the use of a portable calf compression device post-operatively[26]. Preoperative VTE risk-assessment was not consistently reported in these articles.

Even for studies looking at similar physical modalities, the treatment protocols were variable. Four out of the 10 eligible articles reported use of standard prophylaxis therapy, including LMWH and graduated compression stockings, in both control and treatment groups. Eight studies used duplex ultrasound scanning to diagnose DVT. There was one study that relied on clinical diagnosis only and a second study utilised phethysmography followed by venogram to confirm the presence of DVT. Despite that the exact timing was inconsistent, all the included articles except one reported the incidence of DVT within two weeks after surgery or trauma. A summary of the main findings for each article can be found in Table 2. Four studies reported a statistically significant reduction of DVT rates between their control and intervention arms: two using electrostimulation, one by means of calf muscle massage and passive ankle movements and the last one utilising a portable intermittent pneumatic compression device.

Interestingly, all the studies that reported a significant reduction in DVT rates included the administration of LMWH post-operatively in both the treatment and control groups. Of the six articles that failed to show a beneficial effect of the studied physical treatment, in all except one, LMWH was not given as an adjunct.

GRADE assessments were Moderate and Low for all of the studies included in our review. A detailed risk of bias assessment for the eligible randomised controlled trials included in this review can be found in Figure 2. Due to the heterogeneity in study designs, it was not possible to meta-analyse the data obtained in this systematic review.

Discussion

Deep venous thrombosis prophylaxis is standard care for all patients admitted with traumatic injuries or undergoing surgery. The use of prophylactic LMWH, along with physical interventions such as early mobilisation, graduated compression stockings and intermittent pneumatic compression, have proven efficacy in reducing DVT and associated complications [27]. However, these prophylactic strategies can be contraindicated in specific groups of high risk patients. Early mobilisation may not be possible for patients unable to transfer to a chair, or weightbear as a result of their condition. Although LMWH has a more predictable effect than unfractionated heparin, it can still lead to an increased risk of surgical site bleeding[28] and is contraindicated in patients at high risk of bleeding[29]. Similarly, graduated compression stockings cannot always be used following recent surgery to the lower extremity, limiting their applicability following foot and ankle surgery and lower limb reconstruction.

This review demonstrates that a variety of alternative, non-pharmacological, physical treatments exist for the prophylactic management of DVT. Physiological studies have demonstrated that electrostimulation of calf muscles is able to optimise venous return[30,31] and this was the most commonly studied intervention included in this review. Izumi et al[21] and Lobastov et al[18] both investigated the use of calf muscle electrostimulation devices, demonstrating statistically significant reduction in DVT rates when compared to control groups. Prevot also reported similar findings, although his study did not test the statistical significance. All these three studies contained methodological flaws that put their results at risk of bias. Therefore, we consider that these should be appraised with care, especially considering that the other two electrostimulation studies by Goyal et al[19] and Velmahos et al[17] did not demonstrate any benefits (GRADE: Low).

Postoperative manual calf massage[25] and automated intermittent pneumatic compression delivered with a portable device[26] also demonstrated significant reduction in DVT rates. It has been proposed that these interventions act by replacing the action of calf muscles, obtaining a similar haemodynamic effect by external compression. Both these studies were assessed as having a more robust methodological design with a lesser risk of bias (GRADE: Moderate). Overall, the four studies that reported significant benefits also had some methodological flaws in terms of risk of bias. The RCTs conducted by Sobieraj-Teague[26] et al and Izumi et al[21] were considered to have “some concerns” in their risk of bias analysis, while the cohort studies by Lobastov et al[18] and Imai et al[25] were rated as “fair”.

All alternative physical treatments identified in the present review facilitate central venous return via displacement of blood from both superficial and deep venous systems. This establishes a proximal-distal pressure gradient across the lower extremity, which reduces both venous stasis and venous hydrostatic pressure[32]. The use of the modified Robert Jones bandage[22], active toe movements[23] and lower extremity exercises under tourniquet control[24] failed to demonstrate a significant DVT risk reduction. This may be in part explained by inherent heterogeneity in the study interventions, although it can also be considered that these interventions failed to adequately facilitate central venous return.

There are limited data on which to make any recommendations in relation to the use of these alternatives to standard DVT prophylaxis in surgical patients. Electrostimulation to activate calf muscles could have a beneficial role, but it is not possible to ascertain this based on studies published to date due to their high risk of bias. Other options, such as intensive massage or miniaturised pneumatic

compression devices have shown promising results so far; however, better designed randomised controlled trials, with clear and reproducible prophylaxis protocols implemented in well-defined representative patient cohorts are required to demonstrate efficacy.

Our main finding was that, in the reviewed studies, alternative physical treatments were only of benefit when used in conjunction with LMWH. However, there is insufficient good-quality evidence to determine if they work well in the absence of anticoagulants. This contradicts the conclusion reached by Hajibandeh et al in their 2017 Cochrane Review[11]. This could be explained due to differences in search strategies and inclusion criteria, as our systematic review was broader and not limited to electrostimulation only. Physical modalities may act synergistically with LMWH by addressing different components of Virchow's triad - while LMWH reduces the hypercoagulability state associated with surgery and trauma, physical treatments may improve venous return and reduce stasis. There was not a clear association between the timing of administration of physical modalities and efficacy.

The benefits of early mobilisation and graduated compression stockings for surgical and trauma patients is well established for preventing DVT[6,7]. However, for patients who have a contraindication for these modalities, the evidence base for using alternative physical treatments as a prophylactic measure is limited. Evidence from individual studies suggests a role for electrostimulation devices, intermittent pneumatic compression and manual calf massage in reducing the incidence of DVT when used in conjunction with post-operative LMWH. Hence, the current available evidence is insufficient to support the use of these modalities for patients with contraindications for standard therapy, such as higher risk of bleeding. There is no evidence to support the role of physical modalities alone for DVT prophylaxis.

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Conflicts of interest

All the authors deny any conflicts of interest.

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References

1. Saleh J, El-Othmani MM, Saleh KJ. Deep Vein Thrombosis and Pulmonary Embolism Considerations in Orthopedic Surgery. *Orthop Clin North Am* [Internet]. 2017 Apr [cited 2019 Jun 25];48(2):127–35. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28336037>
2. Johansson PI, Sørensen A, Perner A, Welling K, Wanscher M, Larsen CF, Ostrowski SR. Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. *Crit Care* [Internet]. 2011 [cited 2019 Jul 31];15(6):R272. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22087841>
3. The Lancet Haematology. Thromboembolism: an under appreciated cause of death. *Lancet Haematol* [Internet]. 2015 Oct [cited 2019 Jul 3];2(10):e393. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26686033>
4. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. *Thromb Res* [Internet]. 2016 Jan [cited 2019 Jul 3];137:3–10. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0049384815302097>
5. Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA, ENDORSE Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* (London, England) [Internet]. 2008 Feb 2 [cited 2019 Jul 31];371(9610):387–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18242412>
6. National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism [Internet]. NICE

guideline [NG89]. NICE; 2018 [cited 2019 Jul 31]. Available from:

<https://www.nice.org.uk/guidance/ng89>

7. Hillegass E, Puthoff M, Frese E, Thigpen M, Sobush D, Auten B. The Role of Physical Therapists in the Management of Individuals at Risk for or Diagnosed with Venous Thromboembolism-An Evidence-Based Clinical Practice Guideline. Am Phys Ther Assoc. 2016;
8. Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. Cochrane Database Syst Rev [Internet]. 2017 Aug 6 [cited 2019 Jun 25];8:CD006681. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28780771>
9. Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev [Internet]. 2018 Nov 3 [cited 2019 Jun 25];11:CD001484. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30390397>
10. Pavon JM, Adam SS, Razouki ZA, McDuffie JR, Lachiewicz PF, Kosinski AS, Beadles CA, Ortel TL, Nagi A, Williams JW. Effectiveness of Intermittent Pneumatic Compression Devices for Venous Thromboembolism Prophylaxis in High-Risk Surgical Patients: A Systematic Review. J Arthroplasty [Internet]. 2016 Feb [cited 2019 Jun 25];31(2):524–32. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26525487>
11. Hajibandeh S, Hajibandeh S, Antoniou GA, Scurr JR, Torella F. Neuromuscular electrical stimulation for the prevention of venous thromboembolism. Cochrane Database Syst Rev [Internet]. 2017 Nov 21 [cited 2019 Jun 30];11:CD011764. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29161465>
12. National Institute for Health and Care Excellence (NICE). Recommendations: The geko device for reducing the risk of venous thromboembolism [Internet]. 2014. NICE; [cited 2019 Jun 30]. Available

from: <https://www.nice.org.uk/guidance/mtg19/chapter/1-Recommendations>

13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med [Internet]. 2009 Jul 21 [cited 2017 Dec 31];6(7):e1000097. Available from: <http://dx.plos.org/10.1371/journal.pmed.1000097>
14. Higgins J, Sterne J, Savovic J, Page M, Hrobjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials. Cochrane Database Syst Rev. 2016;(10 (Suppl 1)).
15. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [Internet]. National Institutes of Health. [cited 2019 Jun 30]. Available from: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ [Internet]. 2008 Apr 26 [cited 2019 Jun 30];336(7650):924–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18436948>
17. Velmahos GC, Petrone P, Chan LS, Hanks SE, Brown C V., Demetriades D. Electrostimulation for the prevention of deep venous thrombosis in patients with major trauma: A prospective randomized study. Surgery. 2005;137(5):493–8.
18. Lobastov K, Ryzhkin V, Vorontsova A, Schastlivtsev I, Barinov V, Laberko L, Rodoman G. Electrical calf muscle stimulation in patients with post-thrombotic syndrome and residual venous obstruction after anticoagulation therapy. Int Angiol [Internet]. 2018;37(5):400–10. Available from: <https://www.minervamedica.it/en/getpdf/ZLCaAN5ZRRei8QD1S36C%252BqcQb%252BBuaUPY8dsqXTu8bmTEz6H%252FCKZxKuEy6QrXgzkmq8oQQedbpyPuNYZPI7UGYQ%253D%253D/R34Y2018N05A0400.pdf>
19. Goyal A, Arora S, Batra S, Sharma R, Mittal MK, Sharma VK. Role of calf muscle stimulation in the

prevention of DVT in Indian patients undergoing surgeries for fractures around the hip. Indian J Orthop [Internet]. 2012;46(5):542–7. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem1&NEWS=N&AN=23162147>

20. Prevot JM, Mollard JM, Baulande M. [Prevention of deep venous thrombosis by physical methods. Use of an external electrical stimulator. Initial results in surgery of the hip]. Phlebologie [Internet]. 1988;41(4):815–7. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=3875112>

21. Izumi M, Ikeuchi M, Aso K, Sugimura N, Kamimoto Y, Mitani T, Ueta T, Sato T, Yokoyama M, Sugiura T, Tani T. Less deep vein thrombosis due to transcutaneous fibular nerve stimulation in total knee arthroplasty: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc [Internet]. 2015;23(11):3317–23. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med11&NEWS=N&AN=24957913>

22. Pornrattanamaneewong C, Ruangsomboon P, Narkbunnam R, Chareancholvanich K. The Modified Robert Jones Bandage Does Not Improve Performance or Functional Outcome after Total Knee Arthroplasty : A Randomized Controlled Trial. J Med Assoc Thail. 2019;102(6):355–60.

23. Hickey BA, Cleves A, Alikhan R, Pugh N, Nokes L, Perera A. 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 randomized study. Foot Ankle Surg [Internet]. 2017;23(3):183–8. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=28865588>

24. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood flow restriction training after knee arthroscopy: A randomized controlled pilot study. Clin J Sport Med. 2017;27(3):245–52.

25. Imai N, Ito T, Suda K, Miyasaka D, Endo N. Manual calf massage and passive ankle motion reduce the incidence of deep vein thromboembolism after total hip arthroplasty. *J Orthop Sci* [Internet]. 2017;22(4):726–30. Available from: <https://doi.org/10.1016/j.jos.2018.01.016>
26. Sobieraj-Teague M, Hirsh J, Yip G, Gastaldo F, Stokes T, Sloane D, O'Donnell MJ, Eikelboom JW. Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients. *J Thromb Haemost*. 2012;10(2):229–35.
27. Robinson R, Wirt TC, Barbosa C, Amidi A, Chen S, Joseph RM, Fleischer AE. Routine Use of Low-Molecular-Weight Heparin For Deep Venous Thrombosis Prophylaxis After Foot and Ankle Surgery: A Cost-Effectiveness Analysis. *J Foot Ankle Surg* [Internet]. 2018 May [cited 2019 Jul 3];57(3):543–51. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1067251617306956>
28. Suen K, Westh RN, Churilov L, Hardidge AJ. Low-Molecular-Weight Heparin and the Relative Risk of Surgical Site Bleeding Complications: Results of a Systematic Review and Meta-Analysis of Randomized Controlled Trials of Venous Thromboprophylaxis in Patients After Total Joint Arthroplasty. *J Arthroplasty* [Internet]. 2017 Sep [cited 2019 Jul 3];32(9):2911-2919.e6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28522244>
29. Rein N, Biedermann JS, Meer FJM, Cannegieter SC, Wiersma N, Vermaas HW, Reitsma PH, Kruip MJHA, Lijfering WM. Major bleeding risks of different low-molecular-weight heparin agents: a cohort study in 12 934 patients treated for acute venous thrombosis. *J Thromb Haemost* [Internet]. 2017 Jul 30 [cited 2019 Sep 4];15(7):1386–91. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28440008>
30. Ojima M, Takegawa R, Hirose T, Ohnishi M, Shiozaki T, Shimazu T. Hemodynamic effects of electrical muscle stimulation in the prophylaxis of deep vein thrombosis for intensive care unit patients: a randomized trial. *J intensive care* [Internet]. 2017;5:9. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem2&NEWS=N&AN=28101364>

31. Broderick BJ, Breathnach O, Condon F, Masterson E, ÓLaighin G. Haemodynamic performance of neuromuscular electrical stimulation (NMES) during recovery from total hip arthroplasty. *J Orthop Surg Res* [Internet]. 2013;8(1):3. Available from:

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med9&NEWS=N&AN=23497524>

32. Recek C. Calf Pump Activity Influencing Venous Hemodynamics in the Lower Extremity. *Int J Angiol* [Internet]. 2013 Feb 6 [cited 2019 Jul 25];22(01):023–30. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/24436580>

Figure 1: PRISMA flow-diagram depicting article screening process.

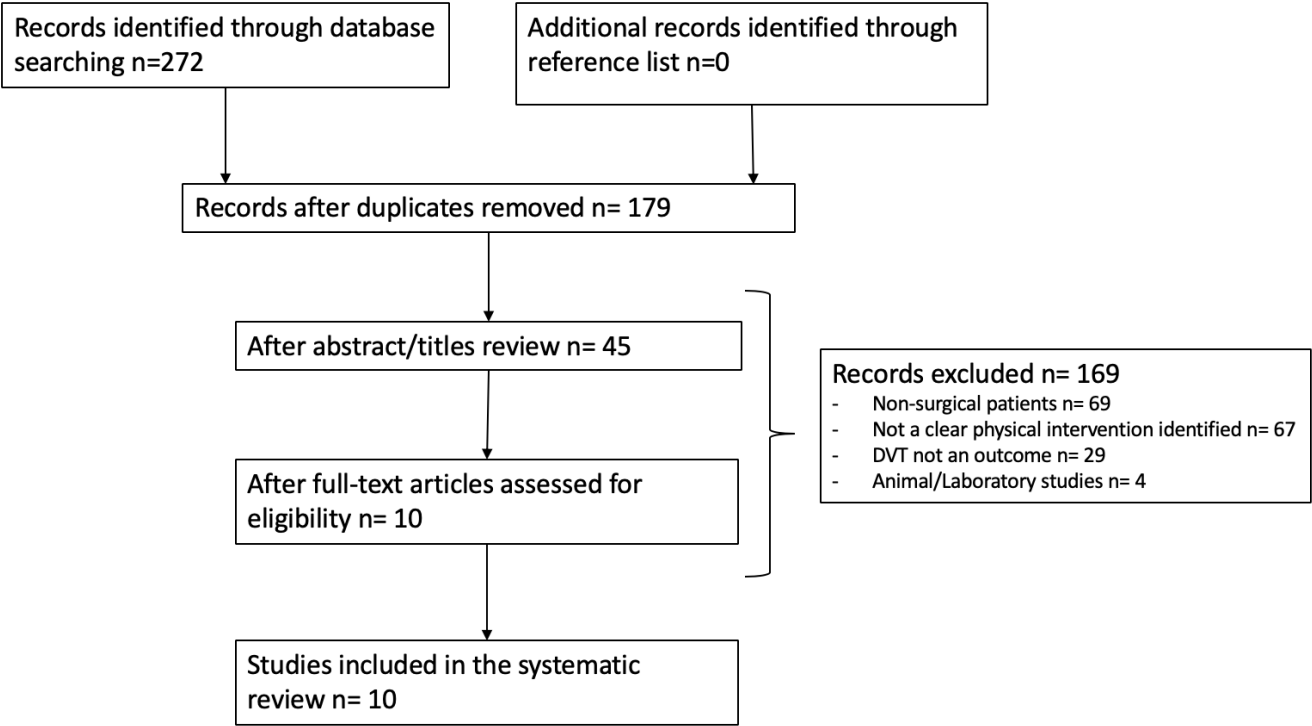


Figure 2: Cochrane risk-of-bias tool for randomised trials (RoB 2) assessment for included studies.

	Risk of bias arising from randomisation	Risk of bias due to deviations from intended interventions	Missing outcome data	Risk of bias in measurement of outcome	Risk of bias in selection of the reported result	Overall risk of bias
Pornrattanamaneeewong 2019 ²¹	+	+	+	-	?	-
Hickey 2017 ²²	+	+	+	+	+	+
Tennent 2017 ²³	+	+	+	+	+	+
Izumi 2015 ²⁰	+	+	+	?	+	?
Goyal 2012 ¹⁸	-	+	+	+	+	-
Sobieraj-Teague 2012 ²⁵	+	+	+	?	?	?
Velmahos 2005 ¹⁶	?	+	?	+	+	?

Key

- Low risk of bias
- High risk of bias
- Some concerns

Table 1: Inclusion and exclusion criteria for systematic review

Inclusion	Exclusion
Studies on surgical and trauma patients	Animal or pre-clinical studies in healthy individuals
DVT rates recorded as an outcome	Studies focusing only on standard prophylaxis modalities, such as: early mobilisation and graduate compression stockings
A defined physical therapy was used for DVT prophylaxis	

Table 2: Summary of findings on studies included in systematic review along with their quality of evidence assessment.

Reference	Lead author specialty	Study type	Number of patients		Surgery type / Trauma	Mean age	Intervention treatment	Control treatment	Standard prophylaxis	DVT diagnostic modality	DVT incidence		Quality of evidence	GRADE certainty rating
			Intervention	Control							Intervention	Control		
Pornrattanamanee Wong et al., 2019 ²²	T&O	RCT	35	35	Primary total knee arthroplasty	70	Post-operative Robert-Jones bandage	Non compressive dressing	None	Clinical	0%	0%	High risk of bias	Low
Hickey et al., 2017 ²³	T&O	RCT	39	39	Foot and ankle fractures	37	Post-trauma active toe movement	No additional therapy	None	Duplex USS	33%	20.5%	Low risk of bias	Moderate
Tennent et al., 2017 ²⁴	T&O	RCT	10	7	Knee arthroscopic procedures	37	Post-operative Blood flow restriction	Exercise without blood flow restriction	None	Duplex USS	0%	0%	Low risk of bias	Moderate
Imai et al., 2017 ²⁵	T&O	Cohort	138	126	Primary hip arthroplasty	62	Post-operative calf massage and passive ankle motion	No additional therapy	Post-operative GCS and LMWH for 10 days	Duplex USS	0.79%*	6.25%*	Fair	Moderate
Izumi et al., 2015 ²¹	T&O	RCT	45	45	Primary total knee arthroplasty	76	Intra and post-operative transcutaneous fibular nerve stimulation	No additional therapy	GCS and post-operative fondaparinux	Duplex USS and D-dimer	11%*	31%*	Some concerns	Low
Lobastov et al., 2014 ¹⁸	General surgery	Cohort	40	40	Intra-abdominal and neurosurgical operations	65	Post-operative electrostimulation	No additional therapy	LMWH post-operatively	Duplex USS	2.5%*	25%*	Fair	Low
Goyal et al., 2012 ¹⁹	T&O	RCT	100	100	Hip trauma operations	54	Intra-operative Electrostimulation	No additional therapy	None	Duplex USS	2%	6%	High risk of bias	Low
Sobieraj-Teague et al., 2012 ²⁶	Neurosurgery	RCT	75	75	Cranial and spinal operations	62	Post-operative intermittent compression device	No additional therapy	LMWH and GCS at discretion of neurosurgeon	Duplex USS	3%*	14%*	Some concerns	Moderate
Velmahos et al., 2005 ¹⁷	Trauma surgery	RCT	21	16	Major trauma (ISS > 9)	39	Post-trauma electrostimulation	No additional therapy	GCS and LMWH post-operatively when no longer contraindicated	Duplex USS and venography	27%	28.5%	Some concerns	Low
Prevot et al., 1988 ²⁰	T&O	Cohort	75	75	Hip trauma operations	N/R	Peri-operative electrostimulation	No additional therapy	Physiotherapy and calcium supplement	Plethysmography and venography	4%	20%	Poor	Low

DVT- Deep venous thrombosis; GRADE- Grading of Recommendations, Assessment, Development and Evaluations; RCT- Randomised controlled trial; T&O- Trauma and Orthopaedics; ISS- Injury Severity Score; USS- Ultrasound scan; *statistically significant (p-value<0.05)

Appendix 1: Systematic search strategy used.

# ▲	Searches
1	exp ELECTRIC STIMULATION THERAPY/
2	exp ISOMETRIC CONTRACTION/
3	PHYSICAL THERAPY MODALITIES/
4	EXERCISE THERAPY/
5	"electrostimulat*".ab,ti.
6	"electric stimulation* ".ab,ti.
7	(muscle* and stimulat*).ab,ti.
8	(muscle* and contract*).ab,ti.
9	(isometric and contract*).ab,ti.
10	(isometric and muscle*).ab,ti.
11	(isometric and calf).ab,ti.
12	(Voluntary and contract*).ab,ti.
13	(voluntary and exercis*).ab,ti.
14	(movement* or motion* or massag*).ab,ti.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp LOWER EXTREMITY/
17	exp LEG/
18	exp FOOT/
19	exp ANKLE/
20	("lower extremit*" or "lower limb*" or leg or legs or calf or calves or foot or feet or toe or toes or ankle*).ab,ti.
21	16 or 17 or 18 or 19 or 20
22	exp MUSCLE STRETCHING EXERCISES/
23	exp MUSCLE,SKELETAL/
24	(muscle* or muscular).ab,ti.
25	22 or 23 or 24
26	VENOUS THROMBOEMBOLISM/
27	VENOUS THROMBOSIS/
28	("venous thrombo*" or VTE).ab,ti.
29	("deep vein thrombo*" or DVT).ab,ti.
30	26 or 27 or 28 or 29
31	15 and 21 and 25 and 30