Journal Pre-proof

Meta-Analysis and Systematic Review of Randomized Controlled Trials Assessing the Role of Thromboprophylaxis post-Vascular Surgery

Tarek Haykal, MD, Yazan Zayed, MD, Josiane Kerbage, MD, Smit Deliwala, MD, Chandler A. Long, MD, Thomas L. Ortel, MD, PhD

PII: S2213-333X(21)00429-7

DOI: https://doi.org/10.1016/j.jvsv.2021.08.019

Reference: JVSV 1319

To appear in: *Journal of Vascular Surgery: Venous and Lymphatic Disorders*

Received Date: 11 February 2021

Accepted Date: 27 August 2021

Please cite this article as: T. Haykal, Y. Zayed, J. Kerbage, S. Deliwala, C.A. Long, T.L. Ortel, Meta-Analysis and Systematic Review of Randomized Controlled Trials Assessing the Role of Thromboprophylaxis post-Vascular Surgery, *Journal of Vascular Surgery: Venous and Lymphatic Disorders* (2021), doi: https://doi.org/10.1016/j.jvsv.2021.08.019.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2021 Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.

Journal Pre-proof

Meta-Analysis and Systematic Review of Randomized Controlled Trials Assessing the Role of Thromboprophylaxis post-Vascular Surgery

R1WC: 277/2498

Tarek Haykal[1], MD; Yazan Zayed[2], MD; Josiane Kerbage[3], MD; Smit Deliwala[4-5], MD; Chandler A. Long, MD[6]; Thomas L. Ortel[1, 7], MD, PhD

1-Duke University, Division of Hematology, Department of Medicine, Durham, North Carolina, USA

2-University of Florida, Department of Pulmonary, Critical Care, and Sleep Medicine, Gainesville, Florida, USA.

3-Lebanese University, Department of Anesthesiology, Beirut, Lebanon

4- Hurley Medical Center, Department of Internal Medicine, Flint, Michigan, USA.

5- Michigan State University, College of Human Medicine, East Lansing, Michigan, USA.

6- Duke University, Division of Vascular and Endovascular Surgery, Department of Surgery, Durham, North Carolina, USA

7- Duke University, Department of Pathology, Durham, North Carolina, USA

<u>Corresponding authors:</u>

Tarek Haykal, MD

Thomas L. Ortel, MD, PhD

Journal Pre-proof

Journal Pre-proof

Division of Hematology
Department of Medicine
Duke University Medical Center
Box 3939
Durham, NC 27710, USA
Phone: (919) 684-6899
Fax: (919) 681-6174
Email: tarek.haykal@duke.edu

Division of Hematology
Departments of Medicine and Pathology
Duke University Medical Center
Box 3422
Durham, NC 27710, USA
Phone: (919) 684-5350
Fax: (919) 681-1177
Email: thomas.ortel@duke.edu

Journal Pre-proof

Abstract

Background: Venous thromboembolism (VTE) is a well-known complication associated with surgical procedures. The implementation of thromboprophylaxis in this population has become a vital aspect of peri-operative care to decrease VTE-associated morbidity and mortality risk. However, data assessing the role of thromboprophylaxis for patients undergoing vascular surgery is sparse.

Objective: Assessing the role of thromboprophylaxis by low molecular weight heparin (LMWH) or unfractionated heparin (UFH) in vascular surgery.

Methods: We searched MEDLINE, Embase, and the Cochrane Collaboration Central Register of Controlled Trials from inception until December 2020, for randomized controlled trials (RCTs) assessing the role of thromboprophylaxis in vascular surgery.

Results: Eight RCTs met inclusion criteria, including 3,130 patients, with a mean age of 55.35 years and 45% were females. Compared to placebo, anticoagulant use was associated with a reduction of deep venous thrombosis (DVT) (RR 0.34; 95% CI: 0.11-1.05; P=0.06: I^2=68%) and pulmonary embolism (PE) (RR 0.17; 95% CI: 0.02-1.22; P=0.08; I^2=41%), but this trend did not reach statistical significance. There was no difference for bleeding outcomes between anticoagulants and placebo (RR 0.90; 95% CI: 0.05-15.01; P=0.94; I^2=76%). There was no significant difference in outcomes when LMWH was compared directly to UFH. In a sensitivity analysis, anticoagulant use was associated with a significant reduction of DVT or PE in patients undergoing venous surgeries, but was not associated with a significant reduction of DVT or PE in patients undergoing arterial surgeries, although this analysis was limited by the small number of studies in each group.

Journal Pre-proof

Conclusion: Among patients undergoing vascular surgery, thromboprophylaxis with anticoagulants, showed a trend toward reduced incidence of VTE when compared to placebo, though not statistically significant. Bleeding outcomes were comparable between both treatment groups.

Keywords: Heparin; Low-Molecular-Weight Heparin; Vascular surgery; Venous Thromboembolism; Thromboprophylaxis

Journal Pre-proof

Introduction

Venous thromboembolism (VTE) is associated with a high mortality and morbidity burden amongst hospitalized patients. [1] Many factors have been implicated, including immobility, cancer, surgery, older age, and obesity. [2-4] Surgery poses a significant risk for VTE, and as many as 40% of patients who undergo surgery without appropriate thromboprophylaxis can develop a VTE . [5]. Over the past twenty years, many measures have been implemented to reduce VTE incidence and its associated morbidity and mortality. [6] These measures include improved operative and anesthetic techniques, early ambulation, and standardization of postoperative mechanical and pharmaceutical thromboprophylaxis. However, VTE still occurs in 10% of surgical patients despite peri-operative care progress, necessitating more effective measures. [7,8]

Despite unclear guidelines and concern for bleeding in procedures such as treatment of varicose veins or interventions that require grafting, most vascular surgery patients do receive some form of anticoagulation in the peri-operative period. However, practice patterns vary, and a standardized assessment for the best modality to reduce VTE risk remains essential.

Recent consensus statements have emphasized the importance of thromboprophylaxis following major surgery (defined as surgery duration >30 minutes), and LMWH and UFH have long been the standard of care for preventing VTE in these patients. [9] Unfortunately, there are few dedicated guidelines for VTE prophylaxis post-vascular surgery specifically, and vascular surgery is frequently included with general surgery or major surgery and treated as such. [9]

One study demonstrated that the VTE risk for vascular surgery patients was significantly higher than the risk for general and trauma surgery patients, emphasizing the need for useful, practical tools and treatments to prevent VTE complications in this patient population. [10]

Journal Pre-proof

Given the limited available evidence and current guideline recommendations, we conducted a systematic review and meta-analysis comparing the benefits and harms of thromboprophylaxis with anticoagulants in patients undergoing vascular surgery.

Methods

Search Strategies and Criteria

The study was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015. [11] We performed a comprehensive search of the literature using MEDLINE® (via PubMed®), Embase®, Web of Science, and the Cochrane Collaboration Central Registry of Controlled Trials for peer-reviewed publications assessing the role of thromboprophylaxis post-vascular surgery from inception to December 2020. Our search strategy used the National Library of Medicine medical subject headings (MeSH) keyword nomenclature and text words for thromboprophylaxis using anticoagulants and the condition of interest. Our final search terms included: (Anticoagulant OR anticoagulation) AND (LMWH OR "low molecular weight heparin" OR Enoxaparin OR Dalteparin OR Nardoparin OR Bemiparin OR Parnaparin OR Reviparin) AND (Warfarin OR Coumadin OR Heparin OR “unfractionated Heparin” OR UFH) AND (VTE OR PE OR DVT OR "deep vein thrombosis" OR "pulmonary embolism" OR "venous thromboembolism" OR thromboprophylaxis OR prophylaxis) AND (“vascular surgery” OR “vascular procedure” OR ”arterial surgery” OR “venous surgery” OR “amputation”). We limited the search to studies involving human subjects 18 years of age and older and published in peer-reviewed journals. Full-text articles identified by either reviewer as potentially relevant were retrieved for further review. Two reviewers, using prespecified

Journal Pre-proof

eligibility criteria, examined each article separately and independently. Disagreements on inclusion or exclusion were resolved by discussion or by a third reviewer.

Inclusion and Exclusion Criteria

Study inclusion criteria were: 1) Randomized controlled trials (RCTs); 2) Studies that used anticoagulants as a comparator in one of the study arms; 3) Studies primarily studying vascular surgical patients or included within subgroup analyses from other RCTs studying the same subject; 4) Studies that reported our outcomes of interest (DVT, PE, or Bleeding); 5) All studies on VTE prophylaxis and not treatment. Study exclusion criteria were: 1) Previous meta-analyses, commentaries, retrospective studies, case-control studies, case reports/series, prospective non-randomized studies; 2) Studies not including anticoagulants in either study arms, 3) Studies including non-vascular surgery patients, 4) Studies that had used either experimental drugs or procedures for thromboprophylaxis that are not available on the market.

Data collection and abstraction

For included studies, data describing the study population (data extracted from the included trials for patients who underwent a vascular surgery or procedure and had an anticoagulant as thromboprophylaxis in either of the trial's arm, as mentioned in the inclusion criteria), interventions, and outcomes, were abstracted independently and separately by two reviewers. A third reviewer resolved discrepancies.

Outcomes

The primary outcome was DVT, defined as composite events of DVT of the lower limbs (symptomatic or incidental). The secondary outcomes were PE and all bleeding. All bleeding was defined as any form of bleeding as perceived in the trial studies (major or minor).

Journal Pre-proof

Quality assessment:

The quality of the included studies was assessed based on the Jadad scoring system.[12] Each of the included studies was assessed for risk of bias for random sequence generation, allocation concealment, blinding of participants and healthcare personnel, blinding of outcome assessment, and other biases. The RCT that scores 2 or less on the Jadad scoring system is considered of low quality, whereas a score of 3 or 4 is considered moderate and 5 is of excellent quality. Two reviewers performed quality assessments independently, and a third reviewer resolved any discrepancies.

Meta-analysis and methodology

We calculated summary risk ratios (RRs) and 95% confidence intervals (CIs) using the Mantel-Haenszel method for dichotomous data. We used the random-effects model to account for heterogeneity between studies. Heterogeneity among the studies was examined using Cochrane's Q statistic and I^2 statistic test. The I^2 describes the percentage of variation across studies due to heterogeneity rather than to chance. [13] Heterogeneity was categorized as low, moderate, or high based on I^2 values of 25, 50, and 75 percent, respectively. Publication bias was assessed by visual inspection of the funnel plot. Sensitivity analysis was performed by removing trials sequentially. The analysis was performed using Review Manager (RevMan) v5.3 (The Cochrane Collaboration, Oxford, UK).

Results

Study Selection and Trial Characteristics

Journal Pre-proof

After applying eligibility criteria, 8 RCTs were retained for data abstraction. **Figure 1** illustrates the study selection process.

Characteristics of RCTs

We identified 8 RCTs, including 3,130 patients with a mean age of 55.35 years, and 45% were females. The mean follow-up period was 37 days after surgery. **Table 1** outlines the characteristics of the included trials, and **Table 2** includes baseline clinical and demographic characteristics of the patient population**.**

All studies had at least a form of an anticoagulant (UFH or LMWH) for thromboprophylaxis in vascular surgery in one of their comparative arms; 3 RCTs compared UFH to LMWH [14-16], and Wang at al. had a third arm of no thromboprophylaxis [16]. Three RCTs compared UFH to either no thromboprophylaxis or no anticoagulants [17-19], while two trials compared LMWH to no thromboprophylaxis or anticoagulation [20,21]. Three RCTs studied varicose vein surgeries [16,20,21], while another looked at amputations exclusively [15], and four included various types of arterial and aortic surgeries for various indications such as repair, revascularization amongst others [14,17-19]. Most trials extended thromboprophylaxis until the patient became ambulatory or until hospital discharge following surgery. Treatment duration ranged from 3-4 days to almost ten days, while follow-up ranged from the end of the treatment period to six months after surgery. Additionally, all trials reported the diagnosis of PE based on the development of symptoms, which was subsequently confirmed radiologically. In contrast, all patients underwent assessment for DVT at the end of the treatment period, or sooner based on the development of symptoms. Most of the included studies were single-blinded studies that used subcutaneous placebo injections.

Journal Pre-proof

Quality assessment of the included studies was based on author judgments, and objective measures such as the Jadad scoring are detailed in **Supplemental Table 1.** Most of the included studies are of moderate quality, except few studies of low to moderate quality.

Primary Outcome

In patients undergoing vascular surgery, the use of anticoagulants (UFH or LMWH) for thromboprophylaxis was associated with a trend toward reduction of total DVT events compared with placebo, though it did not reach statistical significance (RR 0.34; 95% CI: 0.11-1.05; P=0.06; I^2=68%) **(Figure 2A)**. Sensitivity analysis, performed by removing each trial sequentially, demonstrated consistent results. The funnel plot for the primary efficacy outcome was asymmetric, suggesting a likelihood of a publication bias among studies (**Supplemental Figure 1**). There was no significant difference in DVT incidence when LMWH was compared directly to UFH (RR 1.18; 95% CI: 0.53-2.61, P=0.32; I^2=11%) (**Supplemental Figure 2**).

Secondary Outcomes

Similar to DVT, there was a trend toward reduction in PE events with the use of UFH or LMWH for thromboprophylaxis when compared to placebo, although the difference was not statistically significant between the two groups (RR 0.17; 95% CI: 0.02-1.22; P=0.08; I^2=41%) **(Figure 2B)**. Comparing LMWH directly to UFH, the difference was not statistically estimable for PE occurrence, given the absence of events reported in the trials **(Supplemental Figure 2).**

There was no significant difference between the groups receiving anticoagulants or placebo in bleeding (RR 0.90; 95% CI: 0.05-15.01; P=0.94; I^2=76%) **(Supplemental Figure 3).** There was also no difference in the bleeding outcome when comparing UFH with LMWH **(Supplemental**

Journal Pre-proof

Figure 2). Sensitivity analysis, performed by removing each trial sequentially, demonstrated consistent results for all secondary outcomes.

We also performed a sensitivity analysis based on the type of surgery (venous vs arterial). In venous surgeries, when anticoagulation with UFH or LMWH was compared to placebo, there was a significant reduction in the incidence of DVT (RR 0.15; 95% CI: 0.04-0.49; P=0.002; I^2=61%) and PE (RR 0.04; 95% CI: 0.01-0.31; P=0.002; I^2=0%) (**Figure 3**). In arterial surgeries, however, when anticoagulation was compared to placebo, there was no significant difference on the incidence of DVT (RR 0.99; 95% CI: 0.33-3.00; P=0.98; I^2=0%) or PE (RR 0.90; 95% CI: 0.10-8.44; P=0.93; I^2=0%) (**Figure 3**). There was no difference in the risk for bleeding in patients undergoing venous surgeries with UFH or LMWH compared to placebo (**Supplemental Figure 4**). Bleeding events were not reported in patients with arterial surgeries in either the group receiving UFH or LMWH or the group receiving placebo (**Supplemental Figure 4**).

Discussion

Studies investigating the frequency of VTE in vascular surgery are limited, but suggest that the incidence is not insignificant. Reilly *et al.* performed a retrospective analysis of 100 patients undergoing aortic reconstruction without any VTE prophylaxis and found that 13% of patients developed postoperative DVT and 1% developed nonfatal PE.[22] Olin et al. reviewed 50 patients who underwent aortic reconstruction; none received VTE prophylaxis, and 18% developed postoperative DVT. [23] It has also been well proven that vascular surgery patients have a higher risk for VTE than general surgery patients. [10,24] In contrast, when Espinosa *et al.* analyzed 133 patients undergoing endovascular aneurysm repair, all patients in this study received VTE

Journal Pre-proof

prophylaxis while hospitalized and only one developed PE, demonstrating decreased occurrences of VTE when adequate thromboprophylaxis is administered. [25]

Patients undergoing any major surgery are at an increased risk for VTE. In addition, a host of clinical factors can contribute to the risk of VTE in this population, including older age, obesity, previous VTE, and family history of VTE.[26,27] In the absence of appropriate thromboprophylaxis, the incidence of radiologically-confirmed DVT is unclear for patients who undergo vascular surgery, but as many as 40% of patients who undergo major surgery can have a VTE complication without appropriate thromboprophylaxis, though the risk of VTE varied significantly depending on the type of surgery. [5] Patients at highest risk for post-operative VTE can be identified by using risk stratification scores, and this approach should be used in future studies investigating thromboprophylaxis in patients undergoing vascular surgery.

International and national multi-task forces have prepared guidelines that differ considerably. The NICE and European guidelines strongly endorse intermittent pneumatic compression for low-risk vascular surgeries, while for higher-risk surgeries with low risk of bleeding, the recommendation for thromboprophylaxis is backed by a low level of evidence. [28,29] Most recently, the American Society of Hematology guidelines (ASH) for 2019 recommended anticoagulants with LMWH or UFH for thromboprophylaxis after most vascular surgeries. [9]

Our pooled analysis comprising of RCTs with more than 3,000 vascular surgery patients, thromboprophylaxis with either LMWH or UFH was associated with a trend toward reducing major VTE (DVT and PE occurrence), compared to placebo, but this difference did not achieve statistical significance. Bleeding risk was the same between both groups, including differences between various anticoagulants in DVT, PE, or bleeding events. In our meta-analysis that included only RCTs representing patients with different types of vascular surgeries, we found a

Journal Pre-proof

trend toward reducing VTE for thromboprophylaxis with anticoagulants without reaching statistical significance. The limited sample sizes of included studies may have impacted the outcome of these results. Most importantly, we found that the use of anticoagulants was safe with no additional risk of bleeding in vascular surgeries. Based on our subgroup analysis, we found prophylactic anticoagulation was associated with significant reduction of the DVTs and PE in venous but not arterial surgeries. This finding should be interpreted with caution, however, as it was predominantly driven by the effect of a single study which included a large patient population with varicose vein surgeries and showed significant reduction of VTE events when LMWH and UFH were compared to placebo.

Previous meta-analyses evaluating the role of thromboprophylaxis with anticoagulants are also quite limited. A recent study by Toth *et al.* did show similar results to our study by demonstrating a lower incidence of VTE incidence among vascular surgery patients who received an anticoagulant as thromboprophylaxis; however, this analysis included only 2 RCTs in addition to 2 prospective studies and 1 retrospective study. [30]

Based on the available data, anticoagulants are likely safe and effective for thromboprophylaxis in vascular surgery.

Our study has several limitations. First, some of the included studies did not report on outcomes for extended follow-up periods and only reported outcomes for treatment duration. Second, we could not perform subgroup analyses based on age, sex, and other baseline characteristics due to large data reporting variances among studies dating back to 1980. Third, most of the trials studied various vascular surgery modalities amongst a diverse subset of patient populations with unique study designs and treatment arms, causing a high degree of heterogeneity. Fourth, most of the included studies are of moderate quality, except few studies of low to moderate quality,

Journal Pre-proof

Journal Pre-proof

likely affecting the quality of the evidence. Fifth, we combined studies that were conducted many years apart (1981 vs. 2015), over which significant advancements in therapeutic and diagnostic modalities have evolved. Sixth, some studies were larger in size than others, hence potential added bias.

Conclusion

For patients undergoing vascular surgery, evidence from the included studies suggests that thromboprophylaxis with anticoagulants (LMWH or UFH) is likely effective at preventing VTE when compared with placebo, with no difference in bleeding outcomes between different treatment groups. There was also no difference in outcomes between the different anticoagulants used (LMWH or UFH). However, this finding lacked statistical significance, primarily due to underpowered studies and a lack of robust data to better prove the thromboprophylaxis benefit with anticoagulants in this patient population. In the future, there is a need for larger randomized prospective trials that are better designed and powered to detect any benefit.

Conflicts of Interest:

The authors have no conflict of interest to declare.

Financial Disclosures:

No financial disclosures to declare.

Journal Pre-proof

References

1. Sartori M, Gabrielli F, Favaretto E, Filippini M, Migliaccio L, Cosmi B. Proximal and isolated distal deep vein thrombosis and Wells score accuracy in hospitalized patients. Intern Emerg Med. 2019;14(6):941-7.

2. Prandoni P, Samama MM. Risk stratification and venous thromboprophylaxis in hospitalized medical and cancer patients. Br J Haematol. 2008;141(5):587-97.

3. Muntz JE, Michota FA. Prevention and management of venous thromboembolism in the surgical patient: options by surgery type and individual patient risk factors. Am J Surg. 2010;199(1 Suppl):S11-20.

4. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-e77S.

5. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381s-453s.

6. Shapiro R, Vogel JD, Kiran RP. Risk of postoperative venous thromboembolism after laparoscopic and open colorectal surgery: an additional benefit of the minimally invasive approach? Dis Colon Rectum. 2011;54(12):1496-502.

7. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients

Journal Pre-proof

undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Annals of surgery. 2001;233(3):438-44.

8. Qadan M, Tyson M, McCafferty MH, Hohmann SF, Polk HC, Jr. Venous thromboembolism in elective operations: balancing the choices. Surgery. 2008;144(4):654-60, discussion 60-1.

9. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3(23):3898-944.

10. Mommertz G, Sigala F, Glowka TR, Sigalas P, Langer S, Koeppel T, et al. Differences of venous thromboembolic risks in vascular general and trauma surgery patients. J Cardiovasc Surg (Torino). 2007;48(6):727-33.

11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

12. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

Journal Pre-proof

Journal Pre-proof

14. Farkas JC, Chapuis C, Combe S, Silsiguen M, Marzelle J, Laurian C, et al. A randomised controlled trial of a low-molecular-weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing vascular surgery. Eur J Vasc Surg. 1993;7(5):554-60.

15. Lastória S, Rollo HA, Yoshida WB, Giannini M, Moura R, Maffei FH. Prophylaxis of deep-vein thrombosis after lower extremity amputation: comparison of low molecular weight heparin with unfractionated heparin. Acta Cir Bras. 2006;21(3):184-6.

16. Wang H, Sun Z, Jiang W, Zhang Y, Li X, Wu Y. Postoperative prophylaxis of venous thromboembolism (VTE) in patients undergoing high ligation and stripping of the great saphenous vein (GSV). Vasc Med. 2015;20(2):117-21.

17. Spebar MJ, Collins GJ, Jr., Rich NM, Kang IY, Clagett GP, Salander JM. Perioperative heparin prophylaxis of deep venous thrombosis in patients with peripheral vascular disease. Am J Surg. 1981;142(6):649-50.

18. Urbanyi B, Spillner G, Schleinzer P, Freidank H, Schlosser V. Prophylaxis Against Thromboembolism in Vascular Surgery: (A Randomised Clinical Trial). Vascular Surgery. 1982;16(4):253-9.

19. Killewich LA, Aswad MA, Sandager GP, Lilly MP, Flinn WR. A randomized, prospective trial of deep venous thrombosis prophylaxis in aortic surgery. Arch Surg. 1997;132(5):499-504.

20. San Norberto Garcia EM, Merino B, Taylor JH, Vizcaino I, Vaquero C. Low-molecular-weight heparin for prevention of venous thromboembolism after varicose vein surgery in moderate-risk patients: a randomized, controlled trial. Ann Vasc Surg. 2013;27(7):940-6.

Journal Pre-proof

21. Warot M, Synowiec T, Wencel-Warot A, Daroszewski P, Bojar I, Micker M, et al. Can deep vein thrombosis be predicted after varicose vein operation in women in rural areas? Ann Agric Environ Med. 2014;21(3):601-5.

22. Reilly MK, McCabe CJ, Abbott WM, Brewster DC, Moncure AC, Reidy NC, et al. Deep venous thrombophlebitis following aortoiliac reconstructive surgery. Arch Surg. 1982;117(9):1210-1.

23. Olin JW, Graor RA, O'Hara P, Young JR. The incidence of deep venous thrombosis in patients undergoing abdominal aortic aneurysm resection. J Vasc Surg. 1993;18(6):1037-41.

24. Aziz F, Patel M, Ortenzi G, Reed AB. Incidence of Postoperative Deep Venous Thrombosis Is Higher among Cardiac and Vascular Surgery Patients as Compared with General Surgery Patients. Ann Vasc Surg. 2015;29(4):661-9.

25. Espinosa G, Marchiori E, Silva LF, de Araújo AP, Riguetti C, Baquero RA. Initial results of endovascular repair of abdominal aortic aneurysms with a self-expanding stent-graft. J Vasc Interv Radiol. 2002;13(11):1115-23.

26. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, 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(2 Suppl):e278S-e325S.

27. Zoller B, Svensson PJ, Sundquist J, Sundquist K, Pirouzifard M. Postoperative Joint Replacement Complications in Swedish Patients With a Family History of Venous Thromboembolism. JAMA Netw Open. 2018;1(5):e181924.

Journal Pre-proof

Journal Pre-proof

28. Afshari A, Ageno W, Ahmed A, Duranteau J, Faraoni D, Kozek-Langenecker S, et al. European Guidelines on perioperative venous thromboembolism prophylaxis: Executive summary. Eur J Anaesthesiol. 2018;35(2):77-83.

29. National Institute for Health and Clinical Excellence. NICE Clinical guideline 46. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism London2019 [Available from: http://www.nice.org.uk/ Guidance/NG89/Guidance/pdf/English.

30. Toth S, Flohr TR, Schubart J, Knehans A, Castello MC, Aziz F. A meta-analysis and systematic review of venous thromboembolism prophylaxis in patients undergoing vascular surgery procedures. J Vasc Surg Venous Lymphat Disord. 2020;8(5):869-81 e2.

Journal Pre-proof

Table 1 - Characteristics of studies included

Studies	Country	Total patients/ Subgroups	Study design	Inclusion criteria	Exclusion criteria	Dose/Duration of therapy	VTE diagnosis - DVT/PE	Follow-up period	Primary outcomes	Secondary outcomes	Type of surgery
Spebar 1981	United States (1979 – 1980)	**43 Pts** - UF heparin group: 24 Pts - No thromboprophylaxis group: 19 Pts	Prospective RCT	Patients scheduled to undergo elective peripheral vascular surgical procedures	- Allergic to iodine or contrast medium - Expected to be heparinized or receive Coumadin postoperatively	UF heparin 5000U SC 2 hours preoperatively continued every 12 hours postoperatively while undergoing serial leg scans	- A scan was considered positive if the reading was 20 percent greater than the surrounding ipsilateral or contralateral mirror-image samples, and further evaluated using the Grass Instruments phleborheograph - Iodine-125 fibrinogen scans for DVT diagnosis	Daily until isotopes no longer present in sufficient quantities to be detected reliably or until the patient discharged.	DVT	PE, bleeding	Aortic reconstruction, CA reconstruction, lumbar sympathectomy, leg revascularization, pseudoaneurysm repair, repair of arteriovenous fistula.
Urbanyi 1982	Germany	**130 Pts** - Low-dose heparin: 43 Pts -Heparin+ DHE: 41 Pts - Dextran-60: 46 Pts	Prospective RCT	Patients undergoing vascular procedures above the inguinal ligament and at least 30 minutes in duration	- Pregnancy and children - With-holding antithrombotics five days prior	- UF heparin 5000U SC once pre-op followed by TID until discharge - Heparin 5000U and 0.5 mg DHE SC pre-op followed by BID until discharge.	The 125-I-fibrinogen scan was used to detect thrombus formation. The test was considered positive if a difference of 20% or more was found between two neighboring points on the same leg, between corresponding points on the contralateral leg or the same point on two separate measurements with persistence over two days. In case of positive scan, venography and pulmonary scintigraphy was obtained to correlate the scan findings with a radiological confirmation of thrombosis and	Daily for seven days	DVT	PE, bleeding, mortality	CA endarterectomy, carotid aneurysm resection, axillo-femoral bypass, coarctation of aorta, aorto-subclavian/renal bypass, thoracic outlet syndrome, aortoiliac femoral bifurcation/prosthesis, thoracic sympathectomy, PDA

Journal Pre-proof

Journal Pre-proof

							to determine or rule out pulmonary embolism.				
Farkas 1993	France (1989 – 1991(	**233 Pts** - Enoxaparin: 122 Pts -UF heparin: 111 Pts	Prospective, comparative RCT	- Above 18 years - Elective abdominal aortic surgery or lower limb revascularisation and admitted inpatient admission	Pregnancy, hypersensitivity to heparin, previous HIT, nonelective intervention; renal dysfunction (creatinine >350 txmol/1); hepatic failure (albumin <30 g/l; prothrombin time ratio under 50%); pre-existing coagulation disorders; active peptic ulcer; non-tissue cardiac valve; pre-existing cerebral infarction within four months before the study; concomitant treatment with antithrombotics within five days; and normovolemic hemodilution.	- Enoxaparin 20 mg SC pre-op and 40 mg SC post-op - UF heparin 5000U SC pre-op and 7500U post-op for ten days	- Duplex-scanning if there was clinical evidence of DVT confirmed by venography based on the presence of a homogeneous, hypoechogenic intraluminal filling or flow defect producing a dilatation of major veins below the thrombosis and a partially or non-compressible vein. - If positive, ascending venography was performed, as previously described, 18 within 48h. If venography was positive, the patient was considered to have a PDVT. - Any suspected pulmonary embolism had to be confirmed by angiography.	One month	Proximal DVT	Postoperative arterial graft patiency	- Abdominal aortic surgery - lower limb revascularisation
Killewich 1997	United States (1994 – 1996)	**98 Pts** -UF heparin: 50 Pts -No Thromboprophylaxis: 48 Pts	Prospective RCT	Patients undergoing elective aortic reconstruction	Prior history of a DVT, long-term anticoagulation, malignancy, or consent refusal.	- UF heparin 5000U SC BID and calf-length IMC device intra and post-op for seven days or full ambulatory	Venous duplex ultrasound scanning was performed preoperatively on all patients to document no venous abnormalities. Scanning was performed on both legs from the confluence of the tibial veins. Subsequent surveillance was performed in all cases on postoperative days 1, 3, 7, and	Seven days	DVT	PE	Aneurysmal surgery (supra and infrarenal)

Journal Pre-proof

						status achieved. - All received intraoperative UF heparin at 70U/Kg before cross-clamping	weekly if the patient remained immobilized.				
Lastória 2006	Brazil (1995 – 1996)	**75 Pts** -Enoxaparin: 41 Pts -UF heparin: 34 Pts	Prospective RCT	- Above 18 years - Elective or emergency lower-limb amputation for critical-limb ischemia - Signed consent	Previous VTE, refusal to participate, and contraindication to anticoagulants	UF heparin 5000U SC TID or enoxaparin 40 mg daily during hospitalization. Started 12 hours before surgery or, in emergency cases, postoperatively.	Evaluation of DVT was performed by daily clinical examination and duplex scanning before and 5 to 8 days after surgery. Diagnostic criteria were abnormal venous flow and evidence of intraluminal thrombi confirmed with compressive ultrasonography. When inconclusive, the duplex scanning was repeated before discharge.	Eight days	DVT	bleeding	Major lower extremity amputation
Garcia 2013	Spain (Jan 2010 – March 2010	**262 Pts** - LMWH: 130 - No LMWH: 132	Prospective RCT	- Above 18 years - Elective VVS	- Active bleeding or a high risk of bleeding, contraindication to bemiparin or need for bemiparin dose adjustment, including severe renal impairment. - Patients with renal insufficiency or those > 80 years of age were not included - Need for anticoagulant therapy (4 patients); significant liver	Bemiparin 2500/3500 IU subcutaneously once daily, six hours after wound closure for ten days post-op	Presence of signs and symptoms consistent with DVT and confirmation by diagnostic procedures, including compression ultrasonography. DVT was defined as any clot occurring in the iliac, femoral, popliteal, or calf location. A single certified vascular surgeon performed color-flow duplex venous ultrasound examinations of all enrolled patients' lower extremities. Clinical DVT was defined, in line with Wells criteria, as an increase in calf circumference of >3 cm.	Six months	DVT	- Superficial venous thrombosis, postoperative bleeding complications, and D-dimer at 1,3 and 6 months.	Varicose vein surgery

Journal Pre-proof

					disease (2 patients); pregnancy or breastfeeding; concomitant use of human immunodeficiency virus (HIV) protease inhibitors; or use of fibrinolytic therapy.					- The main safety outcome was the inicidence of major bleeding events after the first intake and at 6 months.	
Warot 2014	Poland	**93 pts** - Enoxaparin A: 45 Pts - No Enoxaparin B: 48 Pts	Prospective RCT	1. Insufficiency of the great saphenous vein (III or IV degree) and varices of lower limb; 2. lack of acute or chronic DVT in colour Doppler imaging; 3. Baseline D-dimer value normal;	1. Chronic treatment with an anticoagulant drug; 2. Chronic treatment with venoactive drugs 3. Insufficiency of GSV (I or II degree); 4. Insufficiency of SSV; 5. recurrent varices after surgery; 6. patient with active cancer; 7. Lymphatic oedema; 8. Women who are pregnant or breast feeding; 9. Presence of 2 or	- A: Enoxaparin 40 mg before, SC same day and after surgery only for 7 days -B: Enoxaparin 40 mg before, 40mg SC on the same day and the day after surgery	Doppler ultrasonography examination was performed with a LOGIQ P5/A5 device, for both LE on the days of post-op follow-up	At the 7th and 28th day post-op	Estimate the influence of LMWH	Sensitivity and specificity of clinical examination and D-dimer value in the diagnosis of postoperative DVT in women.	Varicose vein surgery

Journal Pre-proof

				4. Presence of 1 – 2 insufficient perforating veins 5. Female over 18 years 6. Good general condition of the patient	more DVT risk factors, excluding varicose veins; 10. presence of skin infection; 11. history of DVT, haemorrhagic diathesis, HIT 12. ankle-brachial index (ABI) < 0.8.						
Wang 2015	China (2002 – 2012)	**2196 Pts** - No thromboprophylaxis (A): 542 Pts - UF heparin: 531 Pts (B) - Enoxaparin (C & D): 1123 Pts	Prospective RCT	Isolated varicose veins of the lower extremity requiring conventional surgery (high ligation and stripping of the GSV, and removal of superficial varicosities).	Prior varicose vein procedure, prior VTE; leg trauma within 2 years; congenital venous malformations; autoimmune diseases; stenosis or occlusion of the inferior vena cava; anticoagulant, antiplatelet, or hormonal therapy; cancers; or nephrotic syndrome.	UF heparin 125 U/kg SC TID daily in group B, Enoxaparin 6000 IU SC daily in group C, or enoxaparin 4000 IU twice daily until 3 days post-op	Ultrasound DVT screening was performed for all the patients at weeks 1, 2, and 4 after surgery. Patients found to have a DVT also underwent a computed tomography pulmonary angiography scan for PE detection	30 days post-op	VTE (DVT and PE) and bleeding within the first 30 days postoperatively.	NR	Varicose vein conventional surgery (high ligation and stripping of the GSV, and removal of superficial varicosities).

Abbreviations: BID = twice daily, CA = carotid artery, DHE = Heparin-dihydergotamine, HIT = heparin induced thrombocytopenia, IMC = intermittent mechanical compression, PDA = patent ductus arteriosus, PE = pulmonary embolism, pre-op = before operation, post-op = after operation, Pts = patients, RCT = randomized control trial, SC = subcutaneous, TID = thrice daily, U = units, UF = unfractionated, VTE = venous thromboembolism, VVS = varicose vein surgery

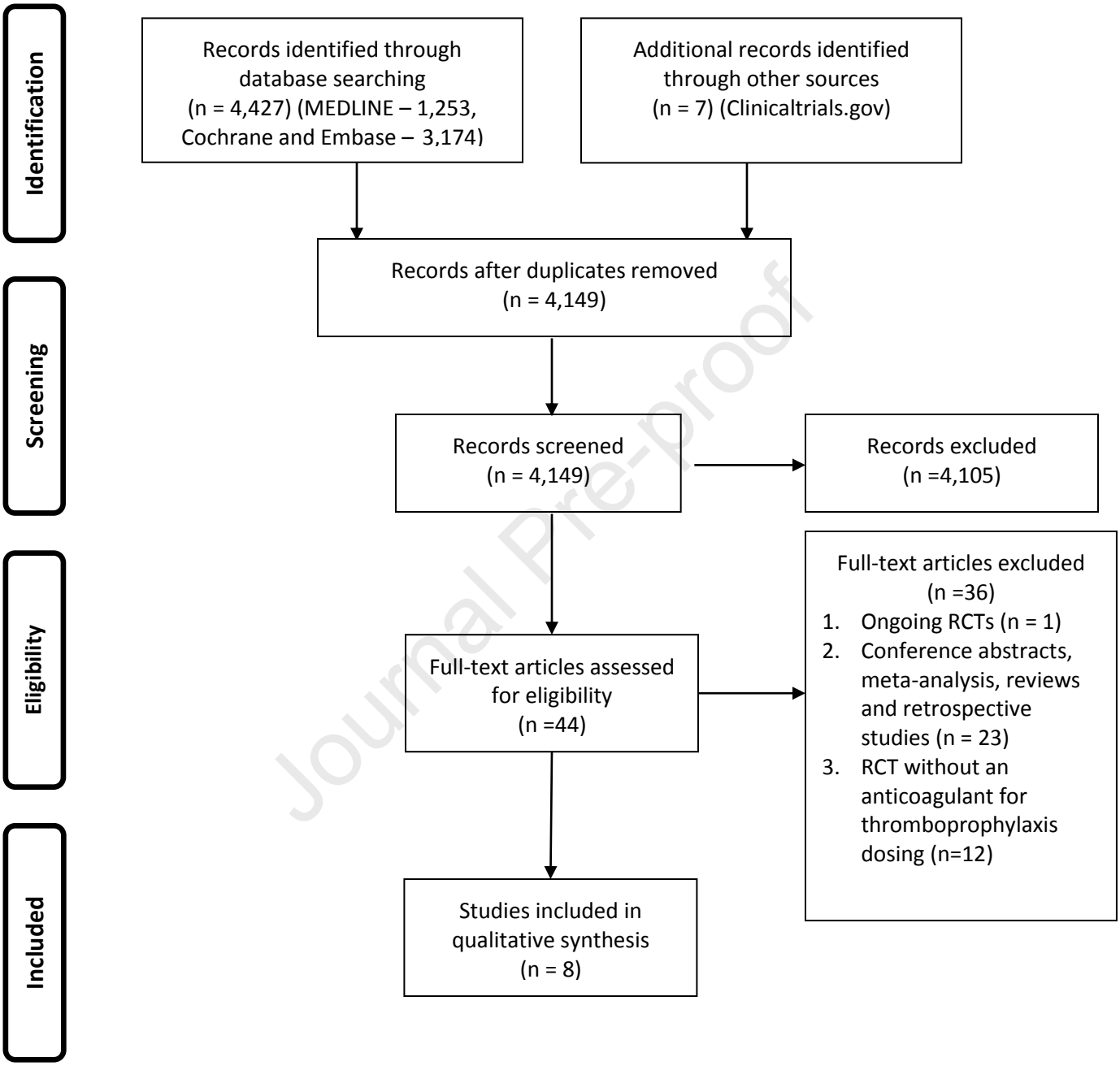
Journal Pre-proof

Table 2 – Patient characteristics within included studies

Studies	**Age in years (mean ± standard deviation) or mean (IQR)**	**Female sex – n (%)**	**BMI n (mean ± standard deviation) Kg/m^2**	**Previous VTE - n (%)**	**Duration of surgery in hours – mean ± standard deviation**
Spebar 1981	NR	NR	NR	NR	NR
Urbanyi 1982	NR	NR	NR	NR	Minimum of 0.5 hours
Farkas 1993	- Enoxaparin: 65 ± 11 - UF heparin: 64 ± 11	- Enoxaparin: 25 (20.5%) - UF heparin: 18 (16.21%)	- Enoxaparin: 24.1 - UF heparin: 24.5	- Enoxaparin: 5% - UF heparin: 9%	- Enoxaparin: 4.8 hrs - UF heparin: 4.8 hrs
Killewich 1997	64 (44-83)	29 (28.57%)	NR	4 patients were initially excluded due to a DVT history	- UF heparin: 5.2 ±0.3 - No Thromboprophylaxis: 5.6 ± 0.2
Lastória 2006	29 - 89	16 Pts (21.33%)	NR	Excluded from the study	NR
Garcia 2013	- LMWH: 56 ± 6.4 - No LMWH: 58 ± 7.1	- LMWH: 86 (66.15%) - No LMWH: 76 (57.57%)	Obesity – LMWH 50.8%, No LMWH 43.9%	- LMWH: 2 (1.5%) - No LMWH: 2 (1.5%)	NR
Warot 2014	- Enoxaparin A: 51.82 ± 9.23 - No Enoxaparin B: 50.50 ± 13.17)	93 Pts (100%)	- Enoxaparin A: 24.66 ± 1.85 - Enoxaparin B: 24.47 ± 2.05	Excluded from the study	NR
Wang 2015	- No thromboprophylaxis (A): 49.95 ± 10.62 - UF heparin (B): 47.84 ± 11.46 - Enoxaparin (C & D): 46.39 ± 10.39	NR	NR	NR	- No thromboprophylaxis (A): 1.12 ±0.33 - UF heparin (B): 1.07 ± 0.57 - Enoxaparin (C & D): 1.09 ± 0.51

Abbreviations: BMI = body mass index, hrs = hours, IQR = inter-quartile range, LMWH = low molecular weight heparin, NR = not reported, UF = unfractionated, VTE = venous thromboembolism

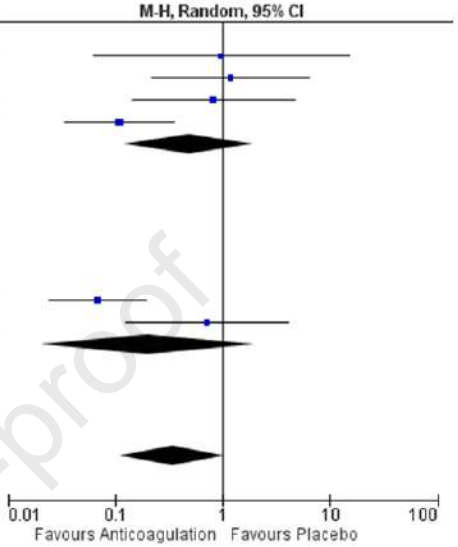
Journal Pre-proof



Journal Pre-proof

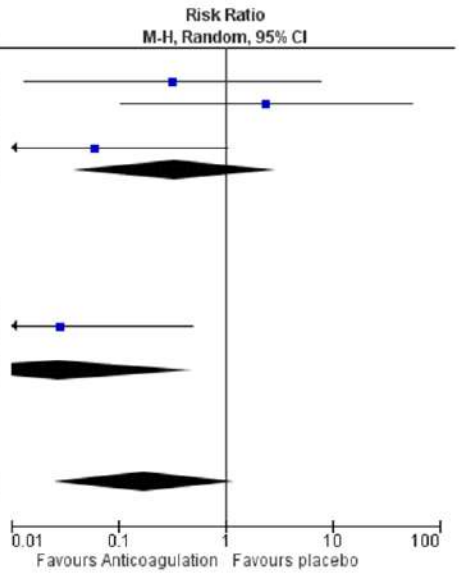
A.

Study or Subgroup	UFH or LMWH Events	UFH or LMWH Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Unfractionated heparin (UFH) versus Placebo						
Killewich 1997	1	50	1	48	10.2%	0.96 [0.06, 14.92]
Spebar 1981	3	24	2	19	16.4%	1.19 [0.22, 6.40]
Urbanyi 1982	3	84	2	46	15.9%	0.82 [0.14, 4.74]
Wang 2015	3	531	28	542	20.2%	0.11 [0.03, 0.36]
Subtotal (95% CI)		**689**		**655**	**62.7%**	**0.48 [0.12, 1.94]**
Total events	10		33			
Heterogeneity: Tau² = 1.18; Chi² = 7.68, df = 3 (P = 0.05); I² = 61%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.1.2 Low molecular weight heparin (LMWH) versus placebo						
Garcia 2013	0	130	0	132		Not estimable
Wang 2015	4	1123	28	542	21.3%	0.07 [0.02, 0.20]
Warot 2014	2	45	3	48	16.0%	0.71 [0.12, 4.06]
Subtotal (95% CI)		**1298**		**722**	**37.3%**	**0.20 [0.02, 1.96]**
Total events	6		31			
Heterogeneity: Tau² = 2.21; Chi² = 5.13, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**1987**		**1377**	**100.0%**	**0.34 [0.11, 1.05]**
Total events	16		64			
Heterogeneity: Tau² = 1.26; Chi² = 15.42, df = 5 (P = 0.009); I² = 68%						
Test for overall effect: Z = 1.88 (P = 0.06)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



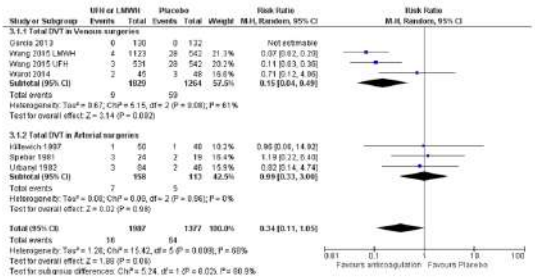
B.

Study or Subgroup	UFH or LMWH Events	UFH or LMWH Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Unfractionated heparin (UFH) versus Placebo						
Killewich 1997	0	50	1	48	23.3%	0.32 [0.01, 7.67]
Spebar 1981	1	24	0	19	23.6%	2.40 [0.10, 55.79]
Urbanyi 1982	0	84	0	46		Not estimable
Wang 2015	0	531	8	542	26.5%	0.06 [0.00, 1.04]
Subtotal (95% CI)		**689**		**655**	**73.5%**	**0.33 [0.04, 2.94]**
Total events	1		9			
Heterogeneity: Tau² = 1.29; Chi² = 3.06, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.2.2 Low molecular weight heparin (LMWH) versus placebo						
Garcia 2013	0	130	0	132		Not estimable
Wang 2015	0	1123	8	542	26.5%	0.03 [0.00, 0.49]
Warot 2014	0	0	0	0		Not estimable
Subtotal (95% CI)		**1253**		**674**	**26.5%**	**0.03 [0.00, 0.49]**
Total events	0		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.45 (P = 0.01)						
Total (95% CI)		**1942**		**1329**	**100.0%**	**0.17 [0.02, 1.22]**
Total events	1		17			
Heterogeneity: Tau² = 1.60; Chi² = 5.05, df = 3 (P = 0.17); I² = 41%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 1.80, df = 1 (P = 0.18), I² = 44.5%						

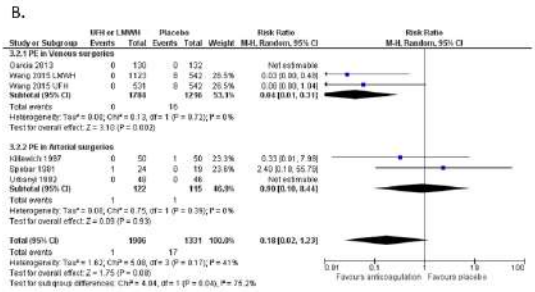


Journal Pre-proof

A.



B.



Journal Pre-proof

Journal of
Vascular Surgery
Publications

Journal Pre-proof

iThenticate
Professional Plagiarism Prevention
Learn more and pre-check your work

Application for Publication

Manuscript Title: Thromboprophylaxis post-Vascular Surgery: A Meta-Analysis and Systematic Review of Randomized Controlled Trials

AUTHORITY OF THE CORRESPONDING AUTHOR. The authors designate Thomas L. Ortel as the corresponding author and give this person the authority to submit this form, the manuscript text, figures, tables, and all other accompanying files to the Journal of Vascular Surgery Publications. The authors also authorize the corresponding author to communicate with the Editorial Office and the Publisher regarding the submission, peer-review, revision, and publication of this manuscript on behalf of the authors.

CORRESPONDING AUTHOR RESPONSIBILITY. The corresponding author confirms that they and the co-authors have read and agreed to follow the policies of the Journal of Vascular Surgery Publications. The corresponding author also confirms that they and the co-authors have approved the manuscript files, disclosed all relevant conflicts of interest, and verified their contributions and conflicts on this form prior to submission. The corresponding author is responsible for serving these same functions for the revision and resubmission of this work.

NOTE: Please include the names of the corresponding author and the **post-publication corresponding author** on the title page of the manuscript.

Originality of Research. Please select **one** option.

☒ **COMPLETELY ORIGINAL.** The authors certify that this manuscript is original, has been written by the stated authors, has not been published previously, and is not under consideration for publication by another journal.

☐ **FOLLOW UP.** This work is a follow up from a previously published study. It contains a patient cohort that has been reported previously.

Please provide a link to the original publication, cite the original study in the manuscript, and list the increase in the number of patients and follow up time below.

Link: _____

% Increase in Patient number: ____%____ **Increase in follow up time:** ____years____

☐ **OTHER**. Parts of the work or patient data included in this manuscript have been previously published. The authors have disclosed this information explicitly in the manuscript. In addition, the authors have received approval to submit previously published data from the Editor-in-Chief. **If you select this option, detailed description of the previously published information below:**

Journal Pre-proof

Journal Pre-proof

Authorship Responsibility and Contributions to Authorship. The authors must use the contributions table to indicate their involvement in the creation of this manuscript. It is important that a box is checked in each authorship category, otherwise the person will not qualify for authorship and the manuscript will be returned to the authors for correction.

The boxes for "Approval" and Accountability" must be checked for ALL authors. If an author declines to approve or be accountable for the work, they may not be included as authors.

CRITERIA REQUIRED FOR AUTHORSHIP. Authors must have contributed in all four categories.

1	**Research**	including study design and conception; data collection; or data analysis and interpretation
2	**Manuscript Development**	including writing the manuscript or providing critical revisions that are important for the intellectual content
3	**Approval**	of the final version of the manuscript files submitted to the Journal
4	**Accountability**	Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

CONTRIBUTIONS TABLE.

List 2 initials for each author (example: AS, BP). In the case of two authors with the same initials, please use their middle initial to differentiate between them (example: JEB, JTB).		**Authors Must have contributed in All 4 Categories**							**Other (Optional)**	
		1 Research (Select one or more)			**2 Manuscript Development (Select one or both)**		**3 Approval (Select)**	**4 Accountability (Select)**		
Author Last Name	**Initials**	Conception and Design	Analysis and Interpretation	Data Collection	Writing the Manuscript	Critical Revision	Approval of the Manuscript	Agreement to be Accountable	Statistical Analysis	Obtaining Funding
Haykal	TH	X	X	X	X		X	X		
Zayed	YZ		X	X		X	X	X	X	
Kerbage	JK		X	X		X	X	X		
Deliwala	SD		X	X		X	X	X		
Long	CAL		X			X	X	X		
Ortel	TLO	X	X			X	X	X		

You may add more rows if needed.

Overall responsibility. **Thomas L. Ortel** assumes overall responsibility and guarantees the scientific integrity

Journal Pre-proof

of the work as a whole.

Optional Authorship Designations:

☐ **SHARED FIRST AUTHORSHIP:** Check this box if two authors participated equally and should share "first authorship". List these as first and second authors.

SHARED SENIOR AUTHORSHIP: If two authors participated equally and should share "senior authorship" enter their initials here: _____

Conflict of Interest Disclosure

EACH author must disclose all relevant financial and nonfinancial potential conflicts of interest with respect to this manuscript. Potential conflicts of interest include, but are not limited to:

1. A financial contribution to the author or the authors' institution from a company or organization that might benefit (or lose) financially from the results, conclusions or discussion presented in the manuscript
   Examples include: Royalties, Patents (or patents pending), fees for consulting, fees for speaking when organized by a corporate sponsored speakers' bureau, funds for a member of the author's staff or family

2. Ownership of stocks, shares or options in a company or organization that might benefit (or lose) financially from the results, conclusion or discussion presented in the paper/letter

3. A commercial interest in the form of a relationship with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients

4. Other potential conflicts include:
   a. an academic association or antagonism with someone whose interest might be affected by the paper
   b. membership in a special interest group whose interests might be affected by the paper
   c. other strong convictions that might have affected what was written

List conflicts of interest for EACH author below. If there are no conflicts of interest, please state "The authors have no competing interests" in the space below.

The authors have no competing interests

Journal Pre-proof

Journal Pre-proof

Role of Sponsors

Each author must disclose the name and involvement of all entities that provided financial support for this work. Please list the funding (grant, scholarships, donated devices, etc.) and describe the involvement of each sponsor in the:

1. Study design; collection, analysis, and interpretation of data;
2. Manuscript writing
3. The decision to submit the manuscript for publication
4. Any other involvement in the creation of the manuscript (Artwork, critical revision, etc.)

There are no financial sponsors for this work.

Journal Pre-proof

Off Label Drugs and Devices

The authors must make a meaningful disclosure regarding their discussions of off label or unapproved drugs or devices.

☐ This study does include off label drugs and/or devices.

The specific names of the products discussed are: Click or tap here to enter text.

☒ This study does not include off label drugs and/or devices.

The corresponding author confirms that they and the co-authors believe that this form and all accompanying files describe truthful facts. The corresponding author also certifies that they and each co-author have participated to a sufficient degree to take public responsibility for this manuscript, that their contributions and relevant conflicts of interest are accurately and completely reported on this form.

Signed Thomas L. Ortel, MD, PhD

*Date 7/13/2021

***(Please update for revised manuscripts and certify all statements in this manuscript are true.**

Journal Pre-proof

Supplemental Table 1 -- Jadad scoring of included studies.

Studies	Jadad score
Spebar 1981	3
Urbanyi 1982	3
Farkas 1993	2
Killewich 1997	2
Lastória 2006	3
Garcia 2013	3
Warot 2014	2
Wang 2015	2

Journal Pre-proof

Journal Pre-proof

Figure Legends

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2: Forest plots comparing thromboprophylaxis with placebo. In panel A, the primary outcomes of total DVT when comparing unfractionated heparin, low molecular weight heparin, or all combined, to placebo is shown. In panel B, the secondary outcomes of total PE when comparing unfractionated heparin, low molecular weight heparin, or all combined, to placebo is shown.

Figure 3: Forest plot of subgroup analyses (arterial vs venous surgeries) for DVT outcomes (panel A) and for PE outcomes (panel B)

Supplemental Figure 1: Funnel plot for the primary outcome (total DVT).

Supplemental Figure 2: Forest plot of subgroup analysis (LMWH vs. UFH) for all reported outcomes.

Supplemental Figure 3: Forest plot of bleeding.

Supplemental Figure 4: Forest plot of subgroup analysis (arterial vs. venous surgeries) for bleeding outcomes.

Table Legends

Table 1: Details of randomized clinical trials.

Table 2: Patients demographics.

Journal Pre-proof

Journal Pre-proof

Supplemental Table 1: Jadad scoring for quality assessment of all included trials

Journal Pre-proof