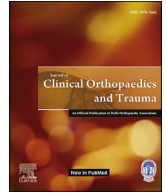




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## Thromboprophylaxis across orthopaedic surgery: Bibliometric analysis of the most cited articles

Anil Sedani <sup>a,\*</sup>, Ramakanth Yakkanti <sup>b</sup>, Paul Allegra <sup>b</sup>, Lavi Mattingly <sup>a</sup>, Amiethab Aiyer <sup>b</sup><sup>a</sup> University of Miami Miller School of Medicine, 1600, NW 10th Ave #1140, Miami, FL, USA<sup>b</sup> University of Miami Miller School of Medicine, Department of Orthopaedics, 1600, NW 10th Ave, Miami, FL, USA

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## ABSTRACT

**Purpose:** One of the most common adverse events after orthopaedic surgery, with a potential for subsequent serious morbidity and mortality is venous thromboembolism (VTE). Bibliometric analysis has been performed regarding many topics and across orthopaedics. As DVT prophylaxis is a major component of both orthopaedic surgery considerations and research, a bibliometric analysis in this area would prove beneficial in not only in understanding the research done in the field thus far, but would also direct future research efforts.

**Methods:** The Web of Science (WoS) database from the Institute of Scientific Information (ISI) was used to compile articles for bibliometric analysis using Boolean search: ((Orthopaedic\* OR Orthopaedic\*) AND (thromboprophylaxis OR Thromboembolism OR Deep vein thrombosis OR thrombus OR embolism OR anticoagulation OR Embolus OR prophylaxis)).

**Results:** The Top 100 cited articles included in the final list generated a total of 21,099 citations. The highest cited article was *Prevention of venous thromboembolism* by Geerts et al. published in Chest, which had a total of 2802 on WoS, and a calculated citation density of 215.54 of citations/years since publication. Comparing the overall citation against the year of publication there was a slight positive trend favoring more recent publications (R-value: 0.142; adjusted R-squared: 0.01; p = 0.16). Analysis of an articles Level of Evidence (LOE), 17 were grade with a level of I.

**Conclusions:** Orthopaedic thromboprophylaxis is an ever-changing field that is at the forefront of orthopaedic literature. The significant trend favoring high quality research within orthopaedic thromboprophylaxis demonstrates the importance of this topic and there was a need for a guide to best understand the evolution of DVT prophylaxis.

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## 1. Introduction

One of the most common adverse events after orthopaedic surgery, with a potential for subsequent serious morbidity and mortality is venous thromboembolism (VTE).<sup>1</sup> The incidence of deep venous thrombosis (DVT) has been reported to be as high as 60% in major orthopaedic surgery, with mortality of 6% associated with DVT and 12% with pulmonary embolism (PE).<sup>2</sup> The economic cost to the health system has been estimated to be more than twice as high for patients with VTE than without, for various orthopaedic surgery procedures,<sup>3–5</sup> with costs increasing over time.<sup>6</sup>

There are many different prophylactic anticoagulation regimens

available for treatment of VTE.<sup>2,7</sup> Similarly, various professional societies and countries have different guidelines for prevention of DVT in orthopaedics.<sup>8</sup> The American College of Chest Physicians (ACCP) published guidelines in 2012 for antithrombotic therapy for patients undergoing various orthopaedic procedures.<sup>9</sup> A recent comparison of guidelines highlights the ACCP recommendations to still be the most thorough and appropriate.<sup>2</sup>

Treatment and prevention of VTE in orthopaedic surgery is one of the most heavily studied topics in orthopaedic surgery, and is ever evolving. A search of “orthopaedic/orthopaedic” and “deep vein thrombosis prophylaxis” yields over 40,000 results on Web of Science. Given the volume and complexity of this landscape, it is difficult to thoroughly evaluate and interpret the large body of literature surrounding VTE in orthopaedic surgery. One type of analysis of scientific literature is a bibliometric analysis, which can be useful in stratifying literature based on its impact on a field. It

\* Corresponding author.

E-mail address: [axs2038@med.miami.edu](mailto:axs2038@med.miami.edu) (A. Sedani).

was first defined as a term in 1969, and became a Medical Subject Heading (MeSH) in 1990.<sup>10</sup> The use of bibliometric analyses has grown substantially in orthopaedic surgery, especially over the past 20 years.<sup>10</sup>

A bibliometric analysis provides understanding of how literature regarding a topic changes over time, and allows us to evaluate the most influential articles to inform decision-making. The parameters examined are the number of publications by year, author, country, type of study design, and overall number of citations. Analyzing citation patterns with bibliometrics can reveal how a specific field has been influenced by past publications, the growth patterns of certain publications, which papers have had the greatest impact. A bibliometric analysis can also identify gaps in the publication pool in specific areas. Bibliometric analysis has been performed regarding many topics and across all sub-specialties of orthopaedics and medicine,<sup>11–14</sup> however, to our knowledge there has not yet been an analysis of the body of literature of DVT prophylaxis in orthopaedic surgery. As DVT prophylaxis is a major component of both orthopaedic surgery considerations and research, a bibliometric analysis in this area may prove beneficial in not only in understanding the research done in the field thus far, but may also help direct future research efforts.

The primary aim of this study is to identify the top cited publications and utilize bibliometric analysis to objectively analyze the most influential articles regarding thromboembolism in orthopaedic surgery. This information could aid surgeons, educators and researchers in understanding the important historic and current literature regarding DVT in orthopaedic surgery.

## 2. Methods

The Web of Science (WoS) database from the Institute of Scientific Information (ISI) was used to compile articles for bibliometric analysis using Boolean search. The Boolean terms which generated the most number of articles for the top 100 list were: ((Orthopaedic\* OR Orthopaedic\*) AND (thromboprophylaxis OR Thromboembolism OR Deep vein thrombosis OR thrombus OR embolism OR anticoagulation OR Embolus OR prophylaxis)) Initial query was conducted in June 2020 and was reviewed independently by two of the authors (AS and RY). Boolean search terms were conducted using both Topic Search (TS) and Title Search (TI) parameters and results were then aggregated on WoS to create a Combined list. Peer-reviewed research articles, meta-analyses, systematic reviews, case reviews, literature reviews, and panel opinions were included in analysis. Notes, errata, editorial comments, or letters to the editor were excluded. Each abstract of articles on the Combined list was used to screen relevant articles to be included in a Secondary Combined List. Articles of the Secondary List were further screened based on analysis of each full text to determine its relevance to orthopaedic surgery and DVT thromboprophylaxis to create a final list for analysis (Fig. 1).

Initial search query was not limited by language, country of publication, institution affiliation, date range, or journal. Articles were then only included if they were peer-reviewed articles, systematic reviews, or editorials. Search results were then sorted by number of citations and the most prolific articles were selected for analysis. There were no additional exclusion criterion.

From the final compiled lists of most cited articles the following data was extracted: date of publication, total citation count, overall citation rate (overall number of citations/years since publication), current citation rate (citations since 2013/years since publication), lead author, country of publication, level of evidence (LOE), topic category. LOE was determined using the Canadian Task Force on Preventative Health's evidence based medicine guidelines<sup>15</sup> and unanimously decided by two authors (AS and LM). Articles were

then put in to categories based on clinical focus and are the following; Epidemiologic, Comparison, Aspirin, Asymptomatic DVT, Direct Thrombin Inhibitor, LMWH, Mechanical, Novel Xa Inhibitors, Panel Opinion, Unfractionated Heparin and Warfarin. Comparison classification included all papers which compared two different thromboprophylaxis regiment. Mechanical included all forms of mechanical based thromboprophylaxis, including but not limited to Inferior Vena Cava Filters (IVCs), Sequential Compression Device (SCDs), or Pneumatic Boots.

### 2.1. Statistics

All analysis was conducted using Microsoft Excel v. 16.16.7 and IBM SPSS v. 26. Shapiro-Wilk test was conducted to test for normality and all normalized data is expressed with medians and standard deviations. Kruskal-Wallis tests were used to assess differences of nonparametric values. One way ANOVA were used to compare normally distributed data, additional post-hoc analysis was conducted to accurately compare significance between groups. Kendall tau tests were used to determine correlations over time. A p value of 0.05 was used to determine significance.

### 2.2. VOS viewer

Terms were analyzed using Visualization of Similarities (VOS) software version 1.6.15 as it is a recognized and widely used analysis tool especially in bibliometric analyses. Terms with a minimum of 3 connections were used and the top 60% of terms were included in the keyword web.

## 3. Results

The Top 100 cited articles included in the final overall orthopaedic list generated a total of 21,099 citations (Tables 1 and 2). The most commonly cited keywords of articles included in VOS Viewer analysis include, "deep vein thrombosis", "low molecular-weight heparin", and "prevention" (Fig. 2A).

The highest cited article was *Prevention of venous thromboembolism* by Geerts et al.,<sup>16</sup> published in Chest, which had a total of 2802 on WoS, and a calculated citation density of 215.54 of citations/years since publication (Fig. 2B). The second highest cited article was *Reduction In Fatal Pulmonary-Embolism And Venous Thrombosis By Perioperative Administration Of Subcutaneous Heparin - Overview Of Results Of Randomized Trials In General, Orthopaedic, And Urologic Surgery* by Collins et al.<sup>17</sup> with a total of 1122 citations and a citation density of 34.0 was published in the New England Journal of Medicine (NEJM) (Fig. 2B).

When comparing the overall citation against the year of publication there was a slight positive trend favoring more recent publications (R-value: 0.142; adjusted R-squared: 0.01; p = 0.16). The current citation rate demonstrated a slightly more positive trend in favor of recent articles (R-value: 0.276; adjusted R-squared: 0.07; p = 0.005) (Fig. 3).

Bengt Eriksson was the most prolific author whose articles made it to the final list accounting for 16% of the top 100 and 3688 citations in total (230.5 citations/article). Alexander Turpie was the second most prolific author included in the final list with a total of 11 publications (11%) with 1626 citations in total (147.82 citations/article).

The journal with the most number of publications in the top 100 was The Journal of Thrombosis and Haemostasis (21%) which had an impact factor of 4.662. Followed by the Journal of Bone and Joint Surgery with 11% of publications, and with an impact of 4.31. Lastly, the Archives of Internal Medicine (JAMA) and CHEST each accounting for 7% of the total analyzed articles, with an impact factor

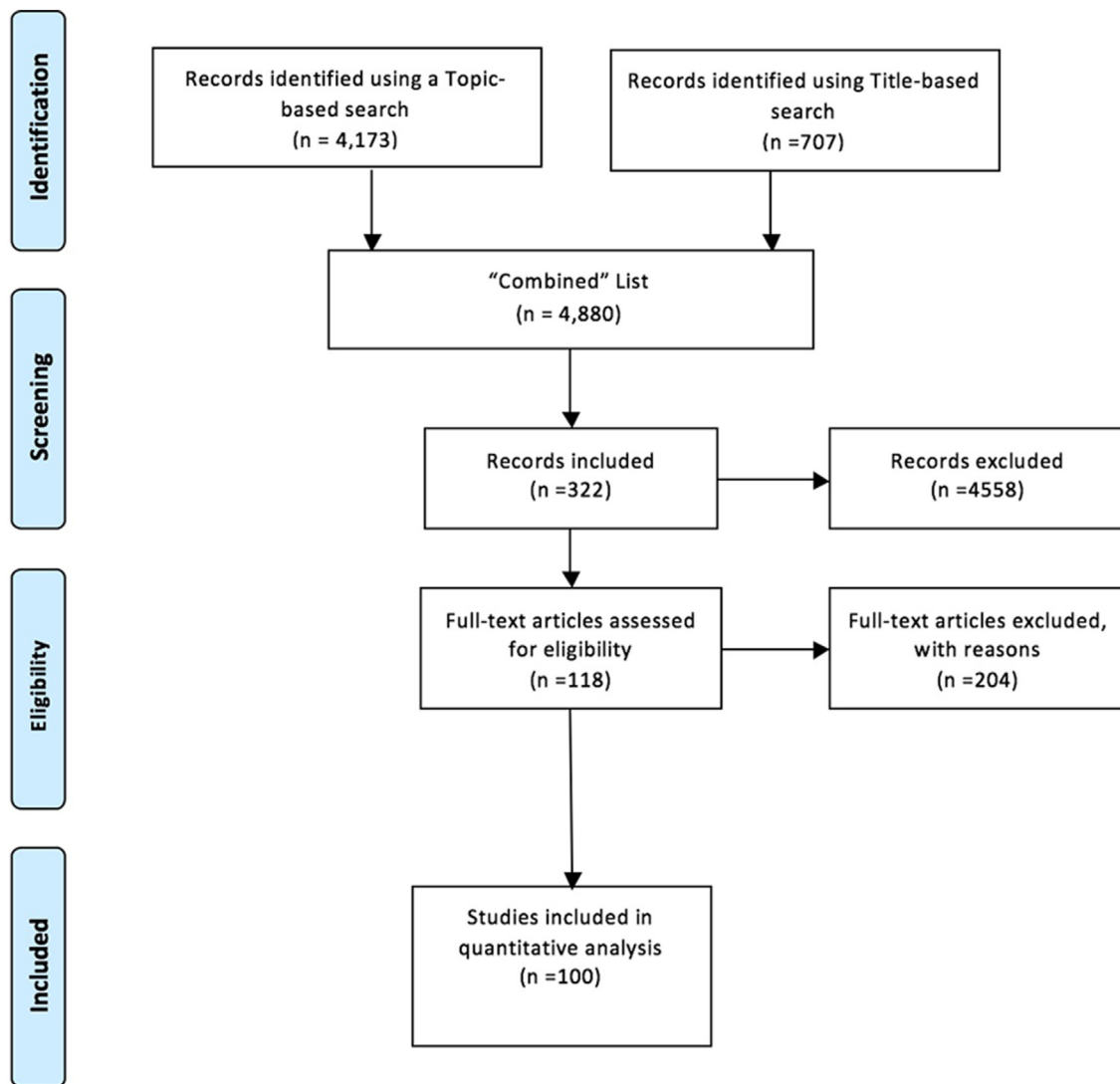


Fig. 1. PRISMA-style flow diagram of inclusion and exclusion criterion.

of 20.77 and 9.67, respectively (Fig. 4A).

The included publications had a date range of 1976–2014, with a majority of publications published in the decade of 2000–2009 (54%) followed by the decade of 1990–1999 (30%). Only 4% of articles included in analysis were published between the years 1976–1989. The most recent decade from 2010 to 2019 only accounted for 14% of articles (Fig. 4C).

Articles included in the final list were assigned a LOE determined by the study design and strength of analysis. Based on the Oxford Centre determination<sup>37</sup> of LOE, 11 articles were graded with a level of V, 17 articles were graded with a level of IV, 27 were graded with a level of III, 26 were graded with a level of II, and lastly 17 were grade with a level of I (Fig. 4B). Initial one-way ANOVA determined a statistically significant difference of number citations amongst the 5 LOEs ( $p = 0.002$ ). Follow-up post-hoc analysis determined there was only a statistically significant difference in number of citations of those articles graded LOE of level I against all other LOE grades (Grade I vs II  $p = 0.04$ ; Grade I vs III  $p = 0.008$ ; Grade I vs IV  $p = 0.2$ ; Grade I vs V  $p = 0.01$ ).

Final analysis of the Top 100 list focused on the articles' topic categories. We found that 25% ( $n = 25$ ) of articles focused on Epidemiology, followed by articles focused on comparing two

different thromboprophylaxis regimens (23%;  $n = 23$ ). Lastly, 18% ( $n = 18$ ) of articles included in analysis were panel opinions (Fig. 4D).

#### 4. Discussion

Our study's aggregation and further analysis aims to provide a toolkit for orthopaedic surgeons to navigate the topic of venous thromboembolism, DVT thromboprophylaxis across orthopaedic surgery. This study's focus on citation number provides an accurate and objective measure of a publication's impact within the orthopaedic literature. Our study's use of the VOS Viewer provides a visual mapping of keywords and journals of the most prolific publications on DVTs. This was included in part to provide readers a quick overview of the most relevant topics included in the literature, as well as providing a list of the most influential journals on the topic of DVTs. Studies included in analysis were highly cited for a multitude of factors like clinical significance, study quality, and importance of the work in orthopaedics.

Primary analysis of the top 5 most cited articles highlights many of the most influential trends in orthopaedic thromboprophylaxis. Of the top five, two are the ACCP thromboprophylaxis

**Table 1**

Top 100 most cited articles on venous thromboembolism and thromboprophylaxis across orthopaedic surgery: Articles 1-50.

No.	Article Title	Authors	Source Title	Publication Date	Total Citations
1	Prevention Of Venous Thromboembolism	Geerts, William H. Et Al.	Chest	Jun 2008	2802
2	Reduction In Fatal Pulmonary-Embolism And Venous Thrombosis By Perioperative Administration Of Subcutaneous Heparin - Overview Of Results Of Randomized Trials In General, Orthopaedic, And Urologic Surgery	Collins, R Et Al.	New England Journal Of Medicine	May-88	1122
3	Rivaroxaban Versus Enoxaparin For Thromboprophylaxis After Knee Arthroplasty	Eriksson, Bengt Et Al.	New England Journal Of Medicine	Jun-08	957
4	Prevention Of Vte In Orthopaedic Surgery Patients Antithrombotic Therapy And Prevention Of Thrombosis, 9 Th Ed: American College Of Chest Physicians Evidence-Based Clinical Practice Guidelines	Falck-Ytter, Yngve Et Al.	Chest	Feb 2012	909
5	A Prospective-Study Of Venous Thromboembolism After Major Trauma	Geerts, Wh Et Al.	New England Journal Of Medicine	Dec-94	868
6	Oral Dabigatran Etexilate Vs. Subcutaneous Enoxaparin For The Prevention Of Venous Thromboembolism After Total Knee Replacement: The Re-Model Randomized Trial	Eriksson, B. I. Et Al.	Journal Of Thrombosis And Haemostasis	Nov 2007	712
7	Prevention Of Pulmonary Embolism And Deep Vein Thrombosis With Low Dose Aspirin: Pulmonary Embolism Prevention (Pep) Trial	O'Brien, J Et Al.	Lancet	Apr-00	690
8	Low-Molecular-Weight Heparin Versus Standard Heparin In General And Orthopaedic-Surgery - A Metaanalysis	Nurmohamed, Mt Et Al.	Lancet	Jul-92	552
9	Fondaparinux Vs Enoxaparin For The Prevention Of Venous Thromboembolism In Major Orthopaedic Surgery - A Meta-Analysis Of 4 Randomized Double-Blind Studies	Turpie, Ag Etal.	Archives Of Internal Medicine	Sep-02	546
10	A Comparison Of Low-Dose Heparin With Low-Molecular-Weight Heparin As Prophylaxis Against Venous Thromboembolism After Major Trauma	Geerts, Wh Et Al.	New England Journal Of Medicine	Sep-96	524
11	Low-Molecular-Weight Heparin (Enoxaparin) As Prophylaxis Against Venous Thromboembolism After Total Hip Replacement	Bergqvist, D Et Al.	New England Journal Of Medicine	Sep-96	389
12	Regular Review - Risk Of And Prophylaxis For Venous Thromboembolism In Hospital Patients	Lowe, Gdo Et Al.	Bmj-British Medical Journal	Sep 5, 1992	379
13	Extended-Duration Prophylaxis Against Venous Thromboembolism After Total Hip Or Knee Replacement: A Metaanalysis Of The Randomized Trials	Eikelboom, Jw Et Al.	Lancet	Jul-01	376
14	Low-Molecular-Weight Heparin In Prevention Of Perioperative Thrombosis	Leizorovicz, A Et Al.	Bmj-British Medical Journal	Oct-92	330
15	A New Oral Direct Thrombin Inhibitor, Dabigatran Etexilate, Compared With Enoxaparin For Prevention Of Thromboembolic Events Following Total Hip Or Knee Replacement: The Bistro Ii Randomized Trial	Eriksson, Bi Et Al.	Journal Of Thrombosis And Haemostasis	Jan 2005	314
16	Accuracy Of Ultrasound For The Diagnosis Of Deep Venous Thrombosis In Asymptomatic Patients After Orthopaedic-Surgery - A Metaanalysis	Wells, Ps Et Al.	Annals Of Internal Medicine	Jan 1, 1995	285
17	Incidence Of Venous Thromboembolism Verified By Necropsy Over 30 Years	Lindblad, B Et Al.	British Medical Journal	Mar 23, 1991	282
18	Duration Of Prophylaxis Against Venous Thromboembolism With Fondaparinux After Hip Fracture Surgery - A Multicenter, Randomized, Placebo-Controlled, Double-Blind Study	Eriksson, Bi Et Al.	Archives Of Internal Medicine	Jun 9, 2003	277
19	Prolonged Thromboprophylaxis Following Hip Replacement Surgery - Results Of A Double-Blind, Prospective, Randomized, Placebo-Controlled Study With Dalteparin (Fragmin(R))	Dahl, Oe Et Al.	Thrombosis And Haemostasis	Jan 1997	264
20	A Meta-Analysis Of Thromboembolic Prophylaxis Following Elective Total Hip Arthroplasty	Freedman, Kb Et Al.	Journal Of Bone And Joint Surgery-American Volume	Jul 2000	242
21	Differences In Mortality After Fracture Of Hip - The East-Anglian Audit	Todd, Cj Et Al.	British Medical Journal	Apr 8, 1995	238
22	Bay 59-7939: An Oral, Direct Factor Xa Inhibitor For The Prevention Of Venous Thromboembolism In Patients After Total Knee Replacement. A Phase Ii Dose-Ranging Study	Turpie, Agg Et Al.	Journal Of Thrombosis And Haemostasis	Nov 2005	237
23	Subcutaneous Low-Molecular-Weight Heparin Compared With Continuous Intravenous Unfractionated Heparin In The Treatment Of Proximal Deep-Vein Thrombosis	Simonneau, G Et Al.	Archives Of Internal Medicine	Jul-93	229
24	Direct Thrombin Inhibitor Melagatran Followed By Oral Ximelagatran In Comparison With Enoxaparin For Prevention Of Venous Thromboembolism After Total Hip Or Knee Replacement - The Methro Iii Study	Eriksson, Bi Et Al.	Thrombosis And Haemostasis	Feb 2003	219
25	Prevention Of Deep-Vein Thrombosis After Hip-Replacement - Randomized Comparison Between Unfractionated Heparin And Low-Molecular-Weight Heparin	Leyvraz, Pf Et Al.	British Medical Journal	Sep-91	215
26	Frequency Of Myocardial Infarction, Pulmonary Embolism, Deep Venous Thrombosis, And Death Following Primary Hip Or Knee Arthroplasty	Mantilla, Cb Et Al.	Anesthesiology	May 2002	209
27	Death And Thromboembolic Disease After Total Hip-Replacement - A Series Of 1162 Cases With No Routine Chemical Prophylaxis	Warwick, D Et Al.	Journal Of Bone And Joint Surgery-British Volume	Jan 1995	207
28	Efficacy And Safety Of The Oral Direct Factor Xa Inhibitor Apixaban For Symptomatic Deep Vein Thrombosis. The Botticelli Dvt Dose-Ranging Study	Buller, H. Et Al.	Journal Of Thrombosis And Haemostasis	Aug 2008	197
29	A Metaanalysis Of Methods To Prevent Venous Thromboembolism Following Total Hip-Replacement	Imperiale, Tf Et Al.	Jama-Journal Of The American Medical Association	Jun 8, 1994	197
30	Population Pharmacokinetics And Pharmacodynamics Of Rivaroxaban - An Oral, Direct Factor Xa Inhibitor In Patients Undergoing Major Orthopaedic Surgery	Mueck, Wolfgang Et Al.	Clinical Pharmacokinetics	2008	190
31	A Cost-Effectiveness Analysis Of Prophylaxis Against Deep-Vein Thrombosis In Major Orthopaedic-Surgery	Oster, G Et Al.	Jama-Journal Of The American Medical Association	Jan 9, 1987	181
32	Prevention Of Deep-Vein Thrombosis After Total Hip Replacement: Direct Thrombin Inhibition With Recombinant Hirudin, Cgp 39,393	Eriksson, Bi Et Al.	Lancet	Mar 9, 1996	172
33	Outcomes For Older Patients With Hip Fractures: The Impact Of Orthopaedic And Geriatric Medicine Cocare	Fisher, Aa Et Al.	Journal Of Orthopaedic Trauma	Mar 2006	168

Table 1 (continued)

No.	Article Title	Authors	Source Title	Publication Date	Total Citations
34	Insufficient Duration Of Venous Thromboembolism Prophylaxis After Total Hip Or Knee Replacement When Compared With The Time Course Of Thromboembolic Events - Findings From The Global Orthopaedic Registry	Warwick, D. Et Al.	Journal Of Bone And Joint Surgery-British Volume	Jun 2007	167
35	The Direct Thrombin Inhibitor Melagatran Followed By Oral Ximelagatran Compared With Enoxaparin For The Prevention Of Venous Thromboembolism After Total Hip Or Knee Replacement: The Express Study	Eriksson, Bi Et Al.	Journal Of Thrombosis And Haemostasis	Dec 2003	165
36	Preoperative Or Postoperative Start Of Prophylaxis For Venous Thromboembolism With Low-Molecular-Weight Heparin In Elective Hip Surgery?	Strebel, N Et Al.	Archives Of Internal Medicine	Jul-02	147
37	Prophylaxis Of Postoperative Thromboembolism With Low-Molecular-Weight Heparins	Jorgensen, Ln Et Al.	British Journal Of Surgery	Jun 1993	147
38	Prevention Of Venous Thromboembolism In Orthopaedic Patients	Salzman, Ew Et Al.	Journal Of Bone And Joint Surgery-American Volume	1976	144
39	Efficacy And Cost Of Low-Molecular-Weight Heparin Compared With Standard Heparin For The Prevention Of Deep-Vein Thrombosis After Total Hip-Arthroplasty	Anderson, Dr Et Al.	Annals Of Internal Medicine	Jan 2008	137
40	Efficacy And Safety Of Dabigatran Etexilate For The Prevention Of Venous Thromboembolism Following Total Hip Or Knee Arthroplasty A Meta-Analysis	Wolowacz, Sorrel E. Et Al.	Thrombosis And Haemostasis	Dec-93	135
41	American Association Of Orthopaedic Surgeons And American College Of Chest Physicians Guidelines For Venous Thromboembolism Prevention In Hip And Knee Arthroplasty Differ What Are The Implications For Clinicians And Patients?	Eikelboom, Jw Et Al.	Chest	Feb 2009	134
42	Oral Rivaroxaban For The Prevention Of Symptomatic Venous Thromboembolism After Elective Hip And Knee Replacement	Eriksson, B. I. Et Al.	Journal Of Bone And Joint Surgery-British Volume	May 2009	130
43	Comparison Of The Use Of A Foot Pump With The Use Of Low-Molecular-Weight Heparin For The Prevention Of Deep-Vein Thrombosis After Total Hip Replacement - A Prospective, Randomized Trial	Warwick, D Et Al.	Journal Of Bone And Joint Surgery-American Volume	Aug 1998	129
44	Hospitals' Compliance With Prophylaxis Guidelines For Venous Thromboembolism	Yu, Hsing-Ting Et Al.	American Journal Of Health-System Pharmacy	Jan-07	128
45	Deep-Vein Thrombosis Rates After Major Orthopaedic Surgery In Asia. An Epidemiological Study Based On Postoperative Screening With Centrally Adjudicated Bilateral Venography	Piovella, F Et Al.	Journal Of Thrombosis And Haemostasis	Dec 2005	128
46	Incidence Of Venographically Proved Deep Vein Thrombosis After Knee Arthroscopy	Demers, C Et Al.	Archives Of Internal Medicine	Jan-98	122
47	Coagulation Parameters In Patients Receiving Dabigatran Etexilate Or Rivaroxaban: Two Observational Studies In Patients Undergoing Total Hip Or Total Knee Replacement	Freyburger, G Et Al.	Thrombosis Research	May 2011	118
48	Prevention Of Venous Thromboembolism - Adherence To The 1995 American College Of Chest Physicians Consensus Guidelines For Surgical Patients	Stratton, Ma Et Al.	Archives Of Internal Medicine	Feb-00	118
49	Rd Heparin Compared With Warfarin For Prevention Of Venous Thromboembolic Disease Following Total Hip Or Knee Arthroplasty	Friedman, Rj Et Al.	Journal Of Bone And Joint Surgery-American Volume	Aug 1994	117
50	A Dose-Ranging Study Of The Oral Direct Thrombin Inhibitor, Ximelagatran, And Its Subcutaneous Form, Melagatran, Compared With Dalteparin In The Prophylaxis Of Thromboembolism After Hip Or Knee Replacement: Methro I	Eriksson, Bi Et Al.	Thrombosis And Haemostasis	Feb 2002	116

guidelines with the 8th edition being the most cited,<sup>16</sup> and 9th edition as the fourth most cited<sup>9</sup>; both of which are highly influential and will be discussed in greater detail later in the discussion. One explanation for the number of citations of the ACCP guidelines is the broad, multidisciplinary recommendations brought forth by the ACCP. Interestingly, similar AAOS guidelines tallied a total of 84 citations and was 66th overall on our list.<sup>18</sup>

The second most cited article in our analysis, *Reduction In Fatal Pulmonary-Embolism And Venous Thrombosis By Perioperative Administration Of Subcutaneous Heparin - Overview Of Results Of Randomized Trials In General, Orthopaedic, And Urologic Surgery*<sup>17</sup> captures some of the earliest high quality findings in orthopaedic thromboprophylaxis. Published in the NEJM in 1988, Rory Collins et al. found inconclusive evidence in a metaanalysis of RCT for the use of subcutaneous heparin in orthopaedic surgery. The authors recognized the smaller sample sizes of the orthopaedic RCTs which may have accounted for the non-significance. Some of the earliest articles included in analysis focused on whether surgeons of the 1970's and 1980's used any thromboprophylaxis or if there was even a cost-benefit of thromboprophylaxis with subcutaneous unfractionated heparin in the post-operative setting due to production costs of heparin vs cheaper agents like warfarin or mechanical prevention.<sup>19–22</sup>

The third most cited article, *Rivaroxaban versus enoxaparin for thromboprophylaxis after knee arthroplasty (2008)*,<sup>23</sup> highlights both the role of novel factor Xa inhibitors and the driving force of Arthroplasty in DVT literature. Novel anticoagulants, Factor Xa and

direct thrombin inhibitors, have been a source of interest in orthopaedics due to the limited risk profile and ease of dosing. Eriksson BI, Borris LC, Friedman RJ et al. are some of the earliest investigators studying the use of these novel anticoagulants in orthopaedics, and demonstrated that "Rivaroxaban reduced the absolute risk of the composite of deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause by 9.2%." Furthermore, investigators found a decrease in risk of major venous thromboembolism by 1.6% against enoxaparin in a RCT of 2459 patients undergoing hip arthroplasty. More recent studies have replicated similar results,<sup>24–31</sup> as a result novel anticoagulants have been recognized as a viable alternative in both the most recent ACCP and AAOS guidelines.<sup>9,18</sup>

The 5th most cited article in analysis, *A Prospective-Study Of Venous Thromboembolism After Major Trauma (1994)*<sup>32</sup>, was a non-interventional study which followed 716 patients in the trauma unit using serial impedance plethysmography and lower-extremity venography. Geerts et al. found that 69% of those with a lower-extremity orthopaedic injury had a radiographically confirmed DVT. Additionally, investigators found a significant increase in risk of DVT after femur or tibia fracture (Odds Ratio: 4.82; 95th CI: 2.79–8.33). This article was a call for a standardization of a safe thromboprophylaxis regiment in orthopaedic trauma.

Further analysis showed an increasing trend in the number of articles published on DVT prophylaxis starting in the early 1990's and ultimately peaking by 2009, with numbers tapering off in the most recent decade. Prior to any formal guidelines, there was a

**Table 2**

Top 100 most cited articles on venous thromboembolism and thromboprophylaxis across orthopaedic surgery: Articles 51-100.

No.	Article Title	Authors	Source Title	Publication Date	Total Citations
51	Dabigatran, Rivaroxaban, Or Apixaban Versus Enoxaparin For Thromboprophylaxis After Total Hip Or Knee Replacement: Systematic Review, Meta-Analysis, And Indirect Treatment Comparisons	Gomez-Outes, A Et Al.	Bmj-British Medical Journal	Jun-12	115
52	Antithrombotic Therapy Practices In Us Hospitals In An Era Of Practice Guidelines	Tapson, Vf Et Al.	Archives Of Internal Medicine	Jul-05	113
53	Intermittent Pneumatic Compression And Deep Vein Thrombosis Prevention - A Meta-Analysis In Postoperative Patients	Urbankova, J Et Al.	Thrombosis And Haemostasis	Dec 2005	108
54	Deep Venous Thrombosis After Posterior Spinal Surgery	Oda, T Et Al.	Spine	Nov-00	108
55	Late Occurring Clinical Deep Vein Thrombosis In Joint-Operated Patients	Dahl, Oe Et Al.	Acta Orthopaedica Scandinavica	Feb 2000	108
56	Epidemiology Of Venous Thromboembolism In Asian Patients Undergoing Major Orthopaedic Surgery Without Thromboprophylaxis. The Smart Study	Leizorovicz, A Et Al.	Journal Of Thrombosis And Haemostasis	Jan 2005	107
57	Temporal Trends In Prevention Of Venous Thromboembolism Following Primary Total Hip Or Knee Arthroplasty 1996–2001 - Findings From The Hip And Knee Registry	Anderson, Fa Et Al.	Chest	Dec 2003	107
58	Effectiveness Of Pneumatic Leg Compression Devices For The Prevention Of Thromboembolic Disease In Orthopaedic Trauma Patients - A Prospective, Randomized Study Of Compression Alone Versus No Prophylaxis	Fisher, Cg Et Al.	Journal Of Orthopaedic Trauma	Feb 1995	105
59	Subcutaneous Low-Molecular Weight Heparin Or Oral Anticoagulants For The Prevention Of Deep-Vein Thrombosis In Elective Hip And Knee Replacement?	Hamulyak, K Et Al.	Thrombosis And Haemostasis	Dec 1995	103
60	Efficacy And Safety Of Enoxaparin To Prevent Deep Venous Thrombosis After Hip- Replacement Surgery	Spiro, Te Et Al.	Annals Of Internal Medicine	Jul-94	103
61	Mortality And Fatal Pulmonary Embolism After Primary Total Hip Replacement - Results From A Regional Hip Register	Fender, D Et Al.	Journal Of Bone And Joint Surgery-British Volume	Nov 1997	101
62	Aspirin Versus Low-Molecular-Weight Heparin For Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty A Randomized Trial	Anderson, Dr Et Al.	Annals Of Internal Medicine	Jun-13	98
63	Prevention Of Venous Thromboembolism After Knee Arthroscopy With Low-Molecular Weight Heparin (Reviparin): Results Of A Randomized Controlled Trial	Wirth, T Et Al.	Arthroscopy	Apr 2001	96
64	Prevention Of Venous Thromboembolism In Orthopaedic Surgery With Vitamin K Antagonists: A Meta-Analysis	Mismetti, P Et Al.	Journal Of Thrombosis And Haemostasis	Jul 2004	87
65	Controversies In Timing Of The First Dose Of Anticoagulant Prophylaxis Against Venous Thromboembolism After Major Orthopaedic Surgery	Raskob, Ge; Hirsh, J	Chest	Dec 2003	85
66	American Academy Of Orthopaedic Surgeons Clinical Practice Guideline On Prevention Of Symptomatic Pulmonary Embolism In Patients Undergoing Total Hip Or Knee Arthroplasty	Johanson, Na Et Al.	Journal Of Bone And Joint Surgery-American Volume	Jul 2009	84
67	Identifying Orthopaedic Patients At High Risk For Venous Thromboembolism Despite Thromboprophylaxis	Schiff, Rl Et Al.	Chest	Nov 2005	77
68	Orthopaedic Surgeons And Thromboprophylaxis	Laverick, Md Et Al.	British Medical Journal	Sep-91	77
69	Ultrasound Screening For Asymptomatic Deep Vein Thrombosis After Major Orthopaedic Surgery: The Venus Study	Schellong, Sm Et Al.	Journal Of Thrombosis And Haemostasis	Jul 2007	75
70	Efficacy And Safety Of Low Molecular Weight Heparin, Unfractionated Heparin And Warfarin For Thrombo-Embolism Prophylaxis In Orthopaedic Surgery: A Meta-Analysis Of Randomized Clinical Trials	Palmer, Aj Et Al.	Haemostasis	Mar–Apr 1997	73
71	Oral Anticoagulants In Development - Focus On Thromboprophylaxis In Patients Undergoing Orthopaedic Surgery	Eriksson, B Et Al.	Drugs	2006	70
72	Prevention Of Venous Thromboembolism - A Survey Of Methods Used By Orthopaedic And General Surgeons	Morris, Gk	Lancet	1980	70
73	Prophylaxis For Thromboembolic Disease - Recommendations From The American College Of Chest Physicians - Are They Appropriate For Orthopaedic Surgery?	Callaghan, Jj Et Al.	Journal Of Arthroplasty	Apr 2005	63
74	Rivaroxaban For Thromboprophylaxis After Orthopaedic Surgery: Pooled Analysis Of Two Studies	Fisher, Wd Et Al.	Thrombosis And Haemostasis	Jun 2007	59
75	Superiority Of Fondaparinux Over Enoxaparin In Preventing Venous Thromboembolism In Major Orthopaedic Surgery Using Different Efficacy End Points	Turpie, Agg Et Al.	Chest	Aug 2004	59
76	Risks And Benefits Of Prophylaxis Against Venous Thromboembolism In Orthopaedic Surgery	Gillespie, W Et Al.	Journal Of Bone And Joint Surgery-British Volume	May 2000	59
77	Preadmission Hyperglycemia Is An Independent Risk Factor For In-Hospital Symptomatic Pulmonary Embolism After Major Orthopaedic Surgery	Mraovic, B Et Al.	Journal Of Arthroplasty	Jan 2010	51
78	The Cost-Effectiveness Of Fondaparinux Compared With Enoxaparin As Prophylaxis Against Thromboembolism Following Major Orthopaedic Surgery	Gordoio, A Et Al.	Journal Of Thrombosis And Haemostasis	Oct 2003	50
79	Efficacy And Safety Of Fondaparinux In Major Orthopaedic Surgery According To The Timing Of Its First Administration	Turpie, A Et Al.	Thrombosis And Haemostasis	Aug 2003	50
80	Cost Of Venous Thromboembolism Following Major Orthopaedic Surgery In Hospitalized Patients	Ollendorf, Da Et Al.	American Journal Of Health-System Pharmacy	Sep 15, 2002	50
81	Venous Thromboembolism Prophylaxis After Major Orthopaedic Surgery: A Pooled Analysis Of Randomized Controlled Trials	Brown, Greg A.	Journal Of Arthroplasty	Sep 2009	49
82	A Non-Interventional Comparison Of Rivaroxaban With Standard Of Care For Thromboprophylaxis After Major Orthopaedic Surgery In 17,701 Patients With Propensity Score Adjustment	Turpie, Agg Et Al.	Thrombosis And Haemostasis	Jan 2014	48
83	Flexibility In Administration Of Fondaparinux For Prevention Of Symptomatic Venous Thromboembolism In Orthopaedic Surgery	Colwell, Cw Et Al.	Journal Of Arthroplasty	Jan 2006	47
84	Economic Consequences Of Venous Thromboembolism Following Major Orthopaedic Surgery	Oster, G Et Al.	Annals Of Pharmacotherapy	Mar 2004	45
85	Comparing Consensus Guidelines On Thromboprophylaxis In Orthopaedic Surgery	Struijk-Mulder, Mc Et Al.	Journal Of Thrombosis And Haemostasis	Apr 2010	44
86		Stewart, Dw Et Al.	Annals Of Pharmacotherapy	Jan 2013	43

Table 2 (continued)

No.	Article Title	Authors	Source Title	Publication Date	Total Citations
87	Aspirin For The Prophylaxis Of Venous Thromboembolic Events In Orthopaedic Surgery Patients: A Comparison Of The Aaos And Accp Guidelines With Review Of The Evidence Symptomatic Venous Thromboembolism And Mortality In Orthopaedic Surgery - An Observational Study Of 45,968 Consecutive Procedures	Lapidus, Lj Et Al.	Bmc Musculoskeletal Disorders	Jun 4, 2013	42
88	Venous Thromboembolism Following Major Orthopaedic Surgery: Review Of Epidemiology And Economics	Edelsberg, J Et Al.	American Journal Of Health-System Pharmacy	Nov 1, 2001	42
89	Measurement Of Dabigatran And Rivaroxaban In Primary Prevention Of Venous Thromboembolism In 106 Patients, Who Have Undergone Major Orthopaedic Surgery: An Observational Study	Samama, Mm Et Al	Journal Of Thrombosis And Thrombolysis	Feb 2013	41
90	Systematic Review And Meta-Analysis On The Rate Of Postoperative Venous Thromboembolism In Orthopaedic Surgery In Asian Patients Without Thromboprophylaxis	Kanchanabat, B Et Al.	British Journal Of Surgery	Oct 2011	41
91	Deep Venous Thrombosis After Orthopaedic Surgery In Adult Cancer Patients	Lin, Pp Et Al.	Journal Of Surgical Oncology	May 1998	41
92	The Safety And Efficacy Of Extended Thromboprophylaxis With Fondaparinux After Major Orthopaedic Surgery Of The Lower Limb With Or Without A Neuraxial Or Deep Peripheral Nerve Catheter: The Expert Study	Singelyn, Fj Et Al.	Anesthesia And Analgesia	Dec 2007	40
93	Deep Venous Thrombosis Prophylaxis For Total Joint Arthroplasty: American Academy Of Orthopaedic Surgeons Guidelines	Parvizi, J Et Al.	Journal Of Arthroplasty	Oct 2008	39
94	Orthopaedic Thromboprophylaxis	Warwick, D.; Dahl, O. E.; Fisher, W. D.	Journal Of Bone And Joint Surgery-British Volume	Feb 2008	39
95	Post Discharge Clinically Overt Venous Thromboembolism In Orthopaedic Surgery Patients With Negative Venography An Overview Analysis	Ricotta, S	Thrombosis And Haemostasis	Dec 1996	38
96	Impaired Fibrinolysis And Postoperative Thromboembolism In Orthopaedic Patients	Eriksson, Bi	Thrombosis Research	Apr 1991	38
97	The Risk Of Venous Thromboembolism In The Orthopaedic Patient: Epidemiological And Physiological Data	Paiement, Gd	Orthopaedics	Feb 1997	37
98	Assessing The Safety Profiles Of New Anticoagulants For Major Orthopaedic Surgery Thromboprophylaxis	Hull, Rd Et Al	Clinical And Applied Thrombosis-Hemostasis	Aug-09	36
99	Incidence And Risk Factors For Development Of Venous Thromboembolism In Indian Patients Undergoing Major Orthopaedic Surgery: Results Of A Prospective Study	Bagaria, V	Postgraduate Medical Journal	Feb 2006	36
100	Aspirin Versus Anticoagulation For Prevention Of Venous Thromboembolism Major Lower Extremity Orthopaedic Surgery: A Systematic Review And Meta-Analysis	Drescher, Fs Et Al.	Journal Of Hospital Medicine	Sep 2014	35

wide array of DVT prophylactic protocols across hospital networks, using combinations of Warfarin, Aspirin, Unfractionated Heparin, and LMWH. Our analysis captured many of these initial studies and metanalyses highlighting the debate.<sup>17,19,33–38</sup>

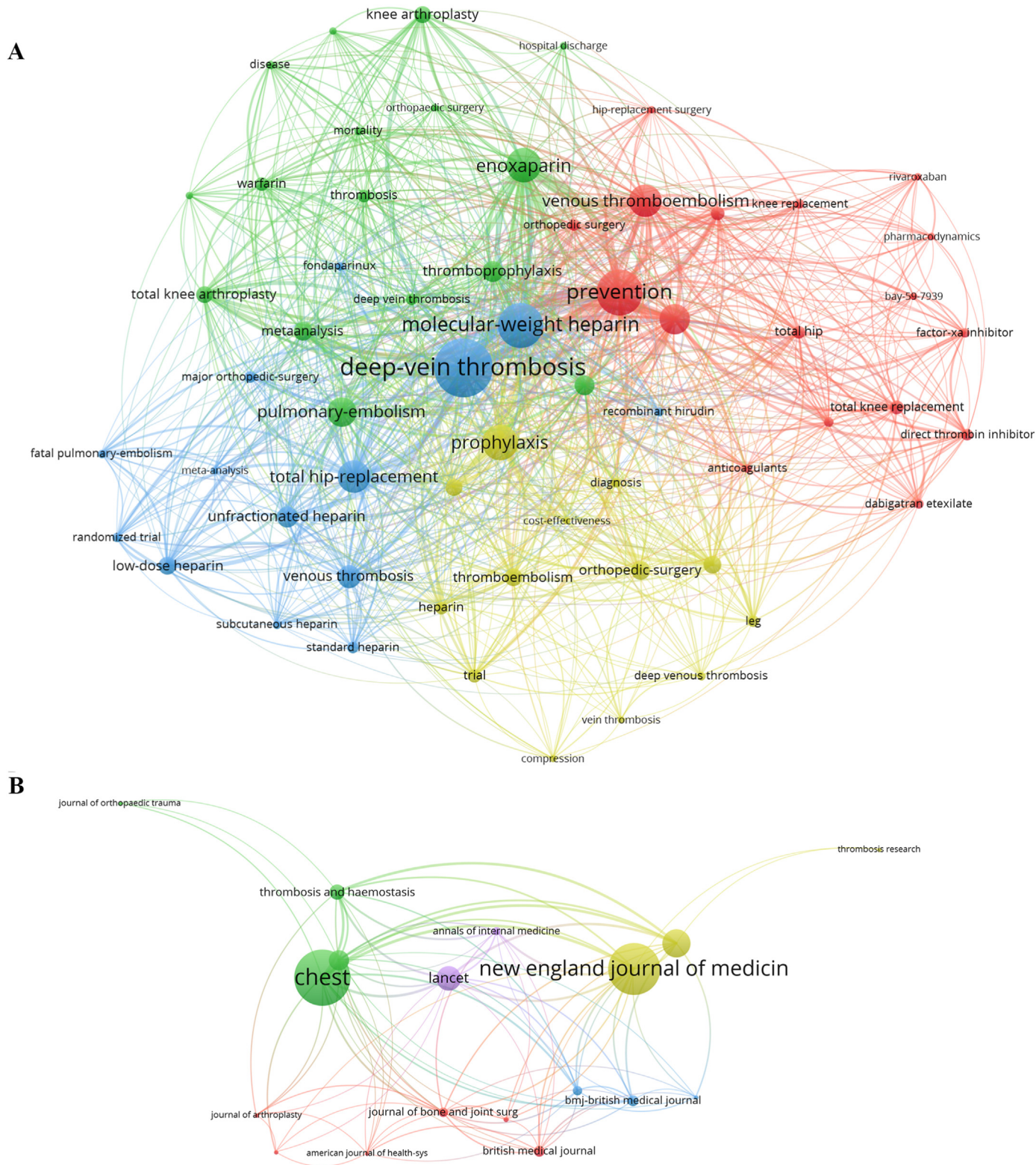
With the increasing use of LMWH regimens<sup>36,37,39</sup> in mid 1990's these medications became a mainstay in orthopaedics. The Fourth American College of Chest Physicians Conference in 1995 further affirmed the LMWHs of the day, however routine thromboprophylaxis was not still widely practiced. Follow up studies from the late-1990's showed there was a lack of adherence to any thromboprophylaxis regimen, as the 1995 Grade A recommendations had not been widely accepted.<sup>40</sup> One study looking at 1907 patients across 10 sites from January 1st, 1996 to February 28th, 1997 showed only 58.3% of Total Hip Replacement (THR) and 53.3% Hip Fracture Repair (HFR) patients received at least some DVT prophylaxis at discharge.<sup>41</sup> By the late-1990's, LMWHs like dalteparin and enoxaparin<sup>42</sup> had become the most commonly used LMWH used in post-operative venous thromboprophylaxis. In the early 2000's, numerous studies revealed there were fewer incidences of Heparin Induced Thrombocytopenia (HIT) with the use of fondaparinux as compared to other LMWHs.<sup>43</sup> Our analysis showed a strong uptick in the number of articles in the early 2000's focusing on demonstrating superiority of fondaparinux against LMWHs.<sup>44–50</sup>

In 2000, the "Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial"<sup>51</sup> was published, which is the largest trial on venous thromboprophylaxis randomized control trial (RCT) in Orthopaedics with over 17,000 subjects. This trial revealed a 43% decrease in PE with the use of low-dose aspirin against placebo in hip fracture patients.<sup>51</sup> This trial has long since sparked debate within the orthopaedic community and caused disagreements across orthopaedic organizations. In 2007 The American Academy of Orthopaedic Surgeons (AAOS) changed opinion regarding

standalone aspirin use and recommended the use of low-dose aspirin for low VTE risk patients undergoing elective TKR or THR procedures if they were at no more increased risk than the surgery itself. This recommendation and its moderate grade was further clarified in a 2011 update,<sup>52</sup> stating there were difficulties in the comparability of studies included in analysis and not enough high-quality studies.

In 2008, the 8th edition American College of Chest Physician (ACCP) Guidelines, Prevention of venous thromboembolism, the most cited article of our analysis, maintained a position against the use of aspirin as monotherapy "for any patient group," continuing the controversy. A later update in the 9th edition by the ACCP in 2012<sup>9</sup> the fourth most cited article of our analysis, recommended the use of aspirin after elective TKR or THR surgeries, realigning with the prior AAOS recommendation. Numerous other articles in our analysis focused on the variations between the AAOS and ACCP guidelines over the years, highlighting the controversy over aspirin's efficacy and lower-bleeding potential.<sup>8,53–55</sup> More recent studies have reinvigorated the debate of using aspirin<sup>55–57</sup>.

Interestingly, the 8th edition ACCP guidelines remained the most cited, and the new 9th edition, though cited 4th on the list has less than one-third the number of citations (2802 vs 909).<sup>9,16</sup> Even on further analysis of the annual citation rate since year of publication, the 8th edition demonstrated a higher annualized rate against the 9th edition (215.5 vs 101). This discrepancy could be due to the fewer number of years since publication of the 9th edition, in turn not allowing the recommendations to gain enough traction, or this could reveal a reluctance to adapt the newer 9th edition guidelines. This is an inherent limitation of bibliometric reviews, as objective analysis of impact of an article necessitates the use of total number of times cited as a measure for impact, naturally articles that are more recently published, might not have had the time to accrue adequate number of citations to be represented highly on the list.



**Fig. 2.** Visualization of Similarities (VoS) analysis of Keywords (2A) and Journals relative to number of citations (2B).

With the advent of the novel Xa inhibitors<sup>25,26,29,30,58–61</sup> and Direct thrombin inhibitors,<sup>31,62–67</sup> there has been increasing focus on these agents in DVT prophylaxis. More recent studies have focused on comparing these two new agents and their efficacy in orthopaedic surgery.<sup>24,27,28</sup> Of these new anticoagulants, the ACCP’s most recent 9th edition recommendations recognize dabigatran,

and apixaban as viable alternatives to patients who refuse injections (Grade 1B Recommendation).

Lastly, ANOVA analysis of an article’s LOE against its respective number of citations revealed a statistically significant relationship favoring articles with an LOE of I. It is known that a majority of orthopaedic research typically is of lower quality due to limitations



# Orthopaedics Overall

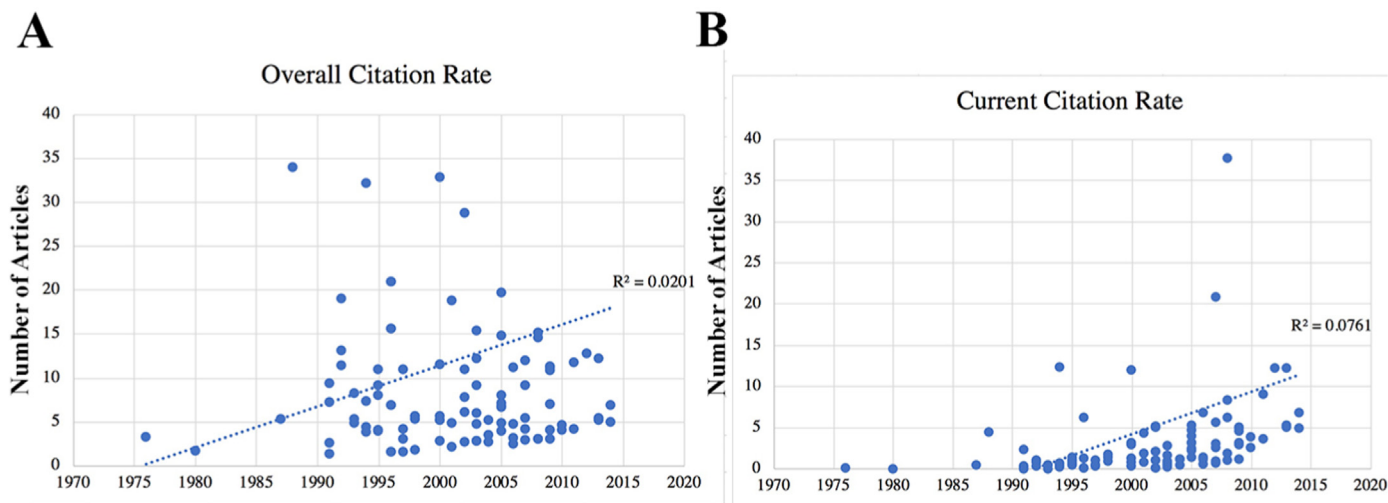


Fig. 3. Linear regression analysis of Overall and Current Citation Rates.

## Top 100 Orthopaedics Overall

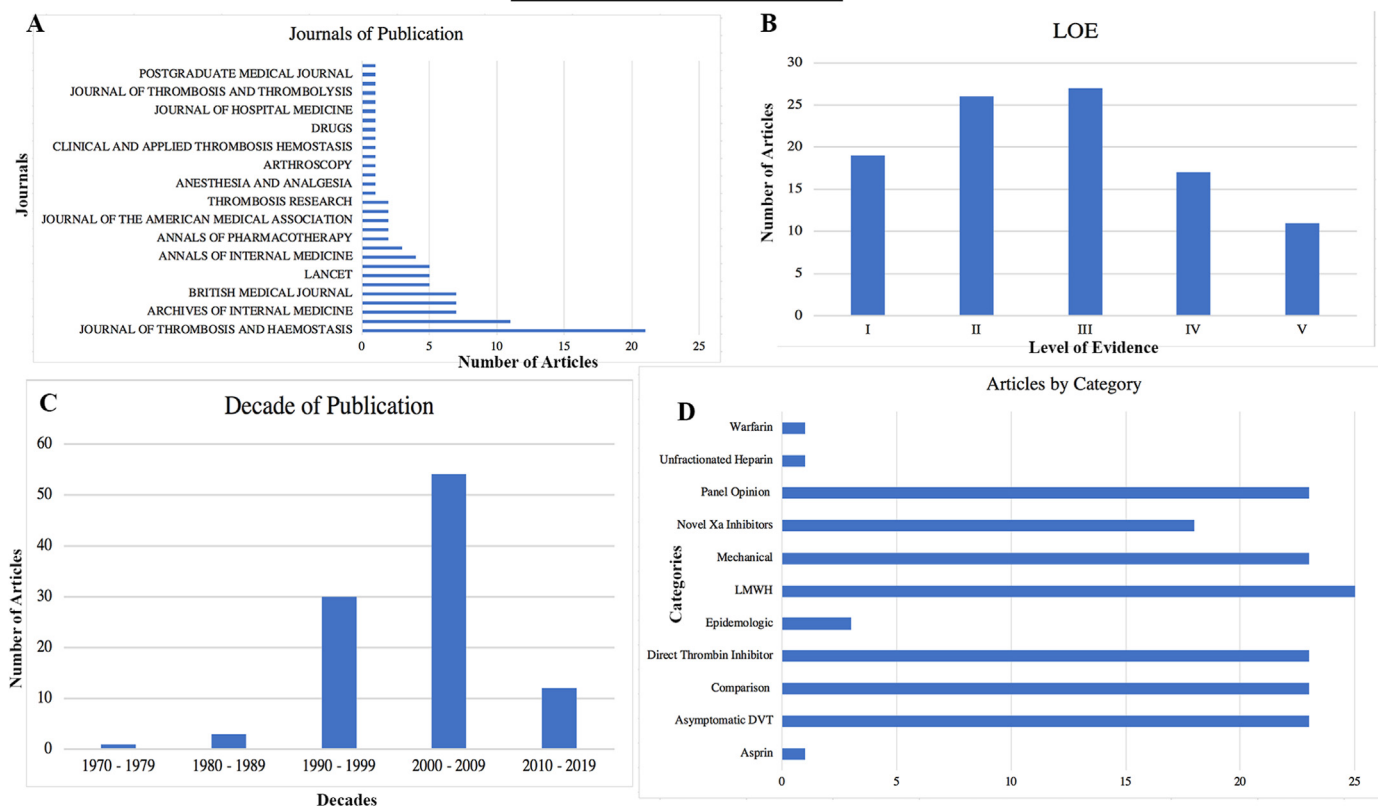


Fig. 4. Characteristics of the top 100 most cited articles.

in adequately randomizing and the ethical implications of not providing certain treatments for the sake of randomization. This predominance of high-quality research highlights the amount of resources and enduring commitment to enhancing thromboprophylaxis in orthopaedics, which is rarely seen with other topics of research in orthopaedics.

### 5. Conclusions

Orthopaedic thromboprophylaxis is an ever-changing field that is at the forefront of orthopaedic literature. The significant trend favoring high quality research within orthopaedic thromboprophylaxis demonstrates the importance of this topic. Given the endorsement and subsequent rejection of anticoagulation regimens, there was a need for a guide to best understand the evolution of DVT prophylaxis.

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