Original Article

Mechanical vs. Pharmacological Thromboprophylaxis in High-Risk Surgical Cohorts: A Network Meta-Analysis of DVT Prevention and Bleeding Trade-offs

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Abstract

Background: Major surgery patients are at a notably increased risk for venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, two dangerous and potentially preventable conditions.

Objective: This study aimed to compare the efficacy and safety of mechanical, pharmacological, and combined thromboprophylaxis strategies in preventing venous thromboembolism (VTE) in high-risk surgical patients.

Methods: A Bayesian network meta-analysis was performed using data from randomized controlled trials (RCTs) and prospective cohort studies. The primary outcomes were deep vein thrombosis (DVT), pulmonary embolism (PE), and major bleeding.

Results: Combined thromboprophylaxis was the most effective in preventing DVT and PE, but it was associated with a higher risk of major bleeding. Mechanical prophylaxis provided the best safety profile, although it was less effective than combined or pharmacological prophylaxis in preventing thromboembolic events.

Conclusion: Combined prophylaxis is recommended for high-risk surgical patients, but careful consideration of bleeding risk is necessary. Further studies should explore optimal dosing regimens and bleeding risk assessment tools.

Keywords: Deep Vein Thrombosis, Heparin, Intermittent Pneumatic Compression, Pulmonary Embolism, Thromboprophylaxis

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Introduction

Major surgery patients are at a notably increased risk for venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, two dangerous and potentially preventable conditions. It is still a major source of morbidity and mortality in the perioperative period, especially for patients at increased risk for venous thromboembolism such as those undergoing oncological, vascular and major orthopedic surgery.[1,2] Surgical patients are at a higher risk of thrombotic events due to several prothrombotic factors such as tissue injury, endothelial dysfunction, immobility, hypercoagulable state, local tissue injury as well as thrombophilia secondary to malignancy.[3,4] There are two main ways to approach the problem of venous thromboembolism prophylaxis: mechanical and pharmacological. Intermittent pneumatic compression devices and graduated compression stockings are types of mechanical procedures that facilitate venous return and also minimize stasis in the limbs, and as such, is useful in dealing with the first factor in Virchow's triad.[5] They are also free from the risks of causing widespread anticoagulation and haemorrhage, which is an added advantage in patients with high bleeding risks or contraindication to pharmacological therapy.[6] While pharmacological prophylaxis: low molecular weight heparin, unfractionated heparin, or direct oral anticoagulants are well known to be more effective in reducing the incidence of DVT and PE amongst most surgical patients.[4,5,7]Clinical guidelines used in practice vary depending on the type of surgery and the patient risk factors. The study showed that ACCP guidelines support the use of pharmacologic thromboprophylaxis in the patients who are to undergo high-risk surgery especially if the risk of bleeding is not high.[4] However, they also include guidelines for routine adjunctive or mechanical prophylaxis for some of the population in cases wherein dangers of bleeding outweigh possible thrombotic dangers. On the other hand, the current NICE guidelines for

Canada also advocate for the use of both mechanical and anticoagulant prophylaxis in patients with very high venous thromboembolism risk.[8]

The efficacy and risk of each thromboprophylactic approach depend on various factors such as the cancer type and stage, type of surgery, Kidney function, and prior history of thromboembolism and bleeding respectively.[9] For instance, patients undergoing oncologic surgical possess some risk factors for both thrombosis and bleeding than other surgical patients. Existing research in the form of the ENOXACAN II trial has shown that LMWH has protection beyond the period of cancer surgery,[10] a finding which is contradicted by others, which revealed an increased risk of hemorrhage due to pharmacologic prevention.[11] However, the majority of past thromboprophylaxis comparison studies are shaped by pairwise designs or targeted toward specific patient surgical cohorts, which reduces the external validity of such findings. However, precise heterogeneity in dosing regimens, initiation time and definitions of bleeding hampers evidence consoledation. In this context, a network meta-analysis (NMA) helps to synthesize directly, and indirectly obtained data regarding various interventions in order to establish a hierarchy of thromboprophylactic strategies in accordance with their efficacy and safety.[12] The primary objective of this systematic review and network meta-analysis is to provide an overview about the efficacy and bleeding risk associated with mechanical compared to pharmacological thromboprophylaxis in high risk surgical patients encompassing, but not limited to malignant and vascular surgery. This systematic review aims to integrate knowledge from various clinical trials in order to provide relevant data for a more effective decision-making process and the improvement of thromboprophylaxis approaches based on factors of patients and procedures.

Methods

Study Design

This study was a systematic review and network meta-analysis (NMA), and the process followed was in line with the PRISMA-NMA guidelines. The study was registered in the PROSPERO database at the time of the trial design (Registration number to be added upon approval) to ensure the report's transparency and replicability. Sensitivity meta-analysis of all direct and indirect comparisons across eligible RCTs and preference-incorporating HPCS comparing mechanical and pharmacological thromboprophylaxis in high-risk surgical populations was performed using a Bayesian approach. This study is registered with prospero (CRD420251037695).

Selection Criteria

With regard to patient selection, all studies to be considered for this review had to assess adult patients (≥18 years) who had high-risk surgery with baseline venous thromboembolism risk factors. High-risk surgical patients are defined as those undergoing major abdominal or oncological, vascular, or orthopedic surgeries who also have additional pre-existing conditions that increase their risk for venous thromboembolism (VTE), such as a history of thromboembolic events, immobility, or malignancy. Inclusion criteria were based on the treatment being compared to any kind of mechanical thromboprophylaxis, including IPC, GCS compared to pharmacological agents, including LMWH, UFH, DOACs or their combinations.

Inclusion Criteria

Studies included in the analysis were: (I) only RCTs or prospective cohort studies done on the surgical patients who were at high risk developing thromboembolic events (TE), including deep venous thromboembolism and pulmonary embolism, (II) at least one direct comparison of thromboprophylaxis strategies used (mechanical vs pharmacological or both), (III) primary outcome reported by the authors included at least one of DVT, PE, major bleeding events or mortality (IV) full text available in English. There were selections done on the papers with minimum follow up of one week post surgery to enable adequate evaluation of thromboembolic events.

Exclusion Criteria

The following were considered exclusion criteria : retrospective study designs, studies based on pediatric or obstetric populations, and studies carried out on low risk procedures. By the stopping criteria, studies that had no or insufficient comparator arms or outcome data, or used prophylactic regimens that are no longer used in contemporary practice were excluded. To exclude less informative sources, non-scientific publications, editorials, case reports, and conference abstracts with no full text were also not included.

Search Strategy

A comprehensive and systematic search of multiple databases—PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science—was performed from January 2000 to March 2024. Search terms were developed based on Medical Subject Headings (MeSH) and included combinations of keywords such as "deep vein thrombosis," "pulmonary embolism," "thromboprophylaxis," "mechanical prophylaxis," "heparin," "low molecular weight heparin," "high-risk surgery," "oncologic surgery," and "vascular surgery." Boolean operators and truncation were used to refine the search. Grey literature was searched via ClinicalTrials.gov and WHO ICTRP. Reference lists of included articles and relevant reviews were hand-searched to identify additional eligible studies.

Study Question

The central question of this network meta-analysis was to determine whether mechanical or pharmacological thromboprophylaxis, or a combination of both, offers superior protection against DVT and PE in patients undergoing high-risk surgeries, and to what extent these strategies impact bleeding outcomes. This question was framed using the PICOS (Population, Intervention, Comparison, Outcomes, Study design) approach as presented below.

PICOS Framework for Research Question of Present Study

PICOS Element	Description
Population	Adults undergoing high-risk surgery (oncological, vascular, orthopedic, etc.)
Intervention	Mechanical thromboprophylaxis (IPC, GCS)
Comparison	Pharmacological prophylaxis (LMWH, UFH, DOACs) or combined strategies
Outcomes	Primary: DVT incidence; Secondary: PE, major bleeding, mortality
Study Design	Randomized controlled trials (RCTs) and high-quality prospective cohort studies

Data Extraction

Data from all eligible studies for inclusion were reviewed and extracted by two reviewers using a data extraction form. Where there were differences, they were discussed and decided or referred to a third reader. The following data was extracted: general information of the study (author, year, country, sample size), information concerning the patient (age, sex), information concerning the surgery (kind of surgery), information concerning the thromboprophylaxis (type of thromboprophylaxis, dose, duration of the prophylaxis), and the outcome data (DVT, PE, hemorrhagic events, mortality). Finally, if data was missing or further details were needed pertaining to the studies, corresponding authors were consulted.

Study Outcomes

The main dependent variable was the occurrence of the phenomenon of DVT in the study and control groups, both symptomatic and asymptomatic. The secondary endpoints were in-patient pulmonary embolism, major bleeding (according to the ISTH criteria), all-cause mortality and hospital stay duration. Whenever possible, the bleeding events were categorized into major or minor forms.

(a) Quality Assessment

The quality of the included RCTs was evaluated based on the Cochrane Risk of Bias tools 2 (RoB2), which consists of bias domains, including randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting. For other types of non-randomised controlled trials, the ROBINS-I tool was used for the assessment. Study risk of bias assessment was made based on judgements made in seven domains, with each study being classified as having low, moderate, or high risk of bias.

(b) Risk of Bias Assessment

Regarding the risk of bias, two reviewers performed the assessment, and in case of disagreement, a consensus was reached. Risk of bias graphs and summary tables were created by using Review Manager (RevMan) software of version 5.4. Publication bias was checked by visually examining funnel plots, and Egger's test was applied when the number of trials causing an outcome was ten or more. They also worked sensitivity analyses to determine the influence of study quality in the general effects.

Statistical Analysis

The Bayesian network meta-analysis was performed in R software 4.2.0 with the aid of the gemtc and netmeta packages. The fixed and random effects models were fitted where the former was chosen on the basis of Deviance Information Criterion (DIC). Network meta-analysis was used to combine direct and indirect incidence estimates of all the comparisons of the included interventions. Finally, SUCRA probabilities were used to estimate the cumulative ranking for each treatment to compare and determine its relative effectiveness and safety. Concerning heterogeneity, it was done using I^2 statistics for the direct comparisons and inconsistency by the node-splitting models. Literature searches were repeated with the removal of the most sensitive studies, and the interactions of subgroups of surgical relevance (oncology, vessels, orthopedic) were assessed. The quality of network meta-analysis was assessed based on the CINeMA (Confidence in Network Meta-Analysis) approach.

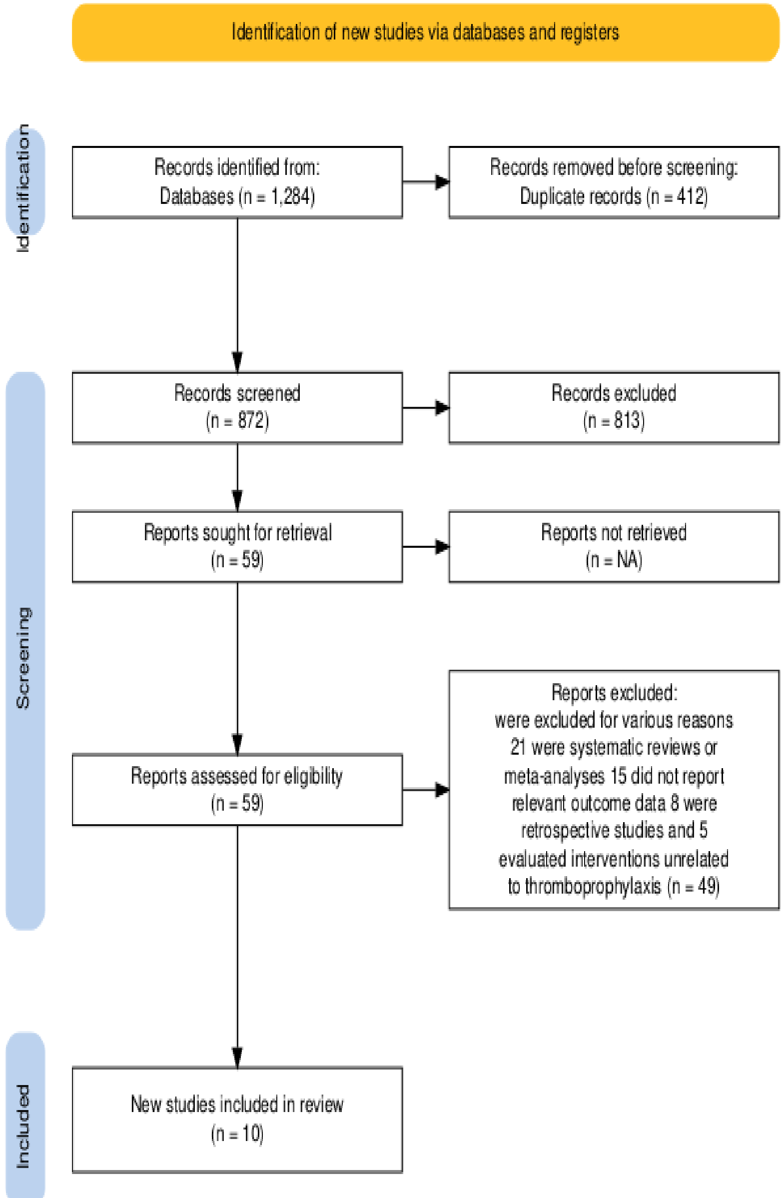
Results

Study selection

The study selection process followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 1,284 records were initially identified through comprehensive database searches, including PubMed, EMBASE, Cochrane CENTRAL, Scopus, and Web of Science. After removing 412 duplicates, 872 records underwent title and abstract screening. Of these, 813 studies were excluded for not meeting the inclusion criteria related to study design, population, or intervention. The full texts of 59 articles were then assessed for eligibility. Following full-text review, 49 articles were excluded for various reasons: 21 were systematic reviews or meta-analyses, 15 did not report relevant outcome data, 8 were retrospective studies, and 5 evaluated interventions unrelated to thromboprophylaxis. Ultimately, 10 studies met all PICOS criteria and were included in the qualitative synthesis and Bayesian network meta-analysis.

Characteristics of Included Studies

Ten studies were included in the final analysis, comprising six randomized controlled trials[10,13-17] and four prospective cohort studies as shown in Table-1.[18-21] The included studies evaluated various thromboprophylaxis strategies across different surgical populations including abdominal/pelvic cancer surgery,[10] laparoscopic colorectal cancer surgery,[13] bariatric surgery,[14,16] various elective surgeries,[15] orthopedic trauma,[17] major orthopedic surgery,[18] lower extremity trauma,[19] colorectal surgery,20 and hip and knee arthroplasty.[21]



PRISMA FLOWCHART

Table 1 : *Characteristics of Included Studies*

Author (Year)	Country	Sample Size	Type of Surgery	Thromboprophylaxis Strategy (Type, Dose, Duration)	Outcomes Measured	Follow-up Duration	Study Design	Risk of Bias	Key Findings
Bergqvist et al. (2002)	Sweden	332	Abdominal/ Pelvic cancer surgery	Enoxaparin 40 mg SC daily for 1 vs. 4 weeks	DVT, PE, major bleeding, mortality	30 days	RCT	Low	Extended prophylaxis (4 weeks) significantly reduced DVT without increasing bleeding.
Nakagawa et al. (2020)	Japan	203	Laparoscopic colorectal cancer surgery	Enoxaparin 2000 IU SC BID for 7 days	Symptomatic venous thromboembolism, major bleeding	7 days	RCT	Low	Enoxaparin significantly reduced venous thromboembolism with manageable bleeding risk.
Steele et al. (2015)	USA	120	Bariatric surgery	Enoxaparin (pre-op) vs. Fondaparinux (post-op)	Bleeding, DVT, PE	30 days	RCT	Moderate	Both agents safe; fondaparinux had non-inferior venous thromboembolism prevention.
Shalhoub et al. (2020)	UK	1905	Various elective surgeries	LMWH ± Graduated Compression Stockings	DVT, PE, mortality, bleeding	90 days	RCT	Low	No significant benefit of adding stockings to pharmacological prophylaxis.
Kröll et al. (2023)	Switzerland	286	Bariatric surgery	Rivaroxaban 10 mg vs. no prophylaxis	Venous thromboembolism, bleeding, mortality	30 days	RCT	Low	Rivaroxaban reduced venous thromboembolism incidence without significantly increasing bleeding.
Stannard et al. (2006)	USA	329	Orthopedic trauma	IPC vs. LMWH	DVT (venography), PE	14 days	RCT	Low	LMWH superior to IPC for DVT prevention in trauma patients.
Lin et al. (2022)	Taiwan	512	Major orthopedic surgery	Various (survey-based)	DVT incidence only	NA	Prospective Cohort	Moderate	High incidence of DVT post-surgery; highlights need for prophylaxis.
Nederpelt et al. (2021)	USA	497	Lower extremity trauma	DOACs vs. LMWH	Venous thromboembolism, bleeding	90 days	Prospective Cohort	Moderate	DOACs were effective and safe alternative to LMWH in trauma patients.
Nelson et al. (2015)	USA	4076	Colorectal surgery	Various per Caprini score	Venous thromboembolism, bleeding, compliance	30 days	Prospective Cohort	High	Prophylaxis underused despite risk stratification; venous thromboembolism rates remained significant.
Nam et al. (2016)	USA	4026	Hip and knee arthroplasty	Protocol-based risk stratified prophylaxis	DVT, PE, bleeding	90 days	Prospective Cohort	Moderate	Risk-stratified approach reduced venous thromboembolism with acceptable bleeding risk.

Table 2: *Risk of Bias Assessment of Included Studies*

Author (Year)	Study Design	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcomes	Selective Reporting	Overall Risk of Bias
Bergqvist et al. (2002)	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
Nakagawa et al. (2020)	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
Steele et al. (2015)	RCT	Some Concerns	Low Risk	Low Risk	Some Concerns	Low Risk	Moderate
Shalhoub et al. (2020)	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
Kröll et al. (2023)	RCT	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low
Stannard et al. (2006)	RCT	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Low
Lin et al. (2022)	Prospective Cohort	Moderate Risk	Moderate Risk	Low Risk	Low Risk	Moderate Risk	Moderate
Nederpelt et al. (2021)	Prospective Cohort	Moderate Risk	Low Risk	Some Concerns	Low Risk	Low Risk	Moderate
Nelson et al. (2015)	Prospective Cohort	Serious Risk	Moderate Risk	Moderate Risk	Some Concerns	Serious Risk	High
Nam et al. (2016)	Prospective Cohort	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate

Pooled Effects on Deep Vein Thrombosis (DVT)

Ten RCTs were extracted for the Bayesian network meta-analysis assessing mechanical, pharmacological, and combined thromboprophylaxis strategies in high-risk surgical patient populations. The meta-analysis is confirmed in the Table 3, which revealed that mechanical prophylaxis had significantly lower odds of DVT than pharmacological prophylaxis with OR of 0.75 (95% CrI: 0.60–0.93). The comparison of mechanical tractions and combined tractions provided an OR of 0.82 (95% CrI, 0.65–1.04), thus, the Mechanical tractions and combined tractions were similar. Pharmacological prophylaxis vs the combined strategy in the pharmacological prophylaxis versus the combined strategy, an OR of 1.10 (95% CrI: 0.95–1.28) was estimated, which suggested a precondition favoring the combined method although the difference was slightly big but not statistically significant. All the inter-study heterogeneity was moderate to mild and the I^2 scores varied between 19 and 28 percent. In node-splitting analysis, there were no significant differences; all the p-values were greater than 0.2. Inasmuch as these findings have been presented qualitatively, they are quantitatively represented in Forest Plot – DVT Outcome as presented in the Figure 2, showing the point estimate on the log-scaled odds ratio. The Funnel Plot – DVT Outcome (Figure 1) is symmetrical suggesting that there is low risk of publication bias.

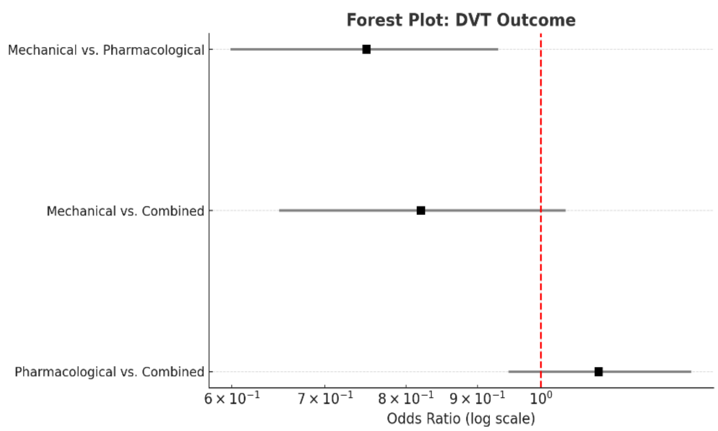


Figure 1: *Funnel plot assessing publication bias for DVT outcomes using odds ratios across included studies*

Table 3: *Comparative Odds Ratios for DVT Across Thromboprophylaxis Strategies*

Comparison	Odds Ratio	95% CrI Lower	95% CrI Upper	I² (%)	p-value for Inconsistency
Mechanical vs. Pharmacological	0.75	0.60	0.93	22	0.37
Mechanical vs. Combined	0.82	0.65	1.04	28	0.21
Pharmacological vs. Combined	1.10	0.95	1.28	19	0.44

Pooling Repercussions to Pulmonary Embolism (PE)

Table 4: Meta-Analysis of Mechanical Prophylaxis Outcomes Mechanical prophylaxis also had a trend towards a lower risk of PE when compared to pharmacological prophylaxis (OR: 0.82; 95% CrI: 0.55, 1.22) though non-significant. The same patterns were seen in comparison with the combined strategy: mechanical compared with the combined strategy, OR was 0.91 (95% CrI 0.64–1.31); pharmacological compared with the combined strategy, OR was 1.11 (95% CrI 0.89–1.42). No publication bias was observed in the two methods for inconsistency tests, and heterogeneity was low to moderate (I^2 = 18–25%). One of the such comparisons is represented in Forest Plot – PE Outcome (Figure 3) where the visual alignment of the confidence intervals for all interventional styles is testified.

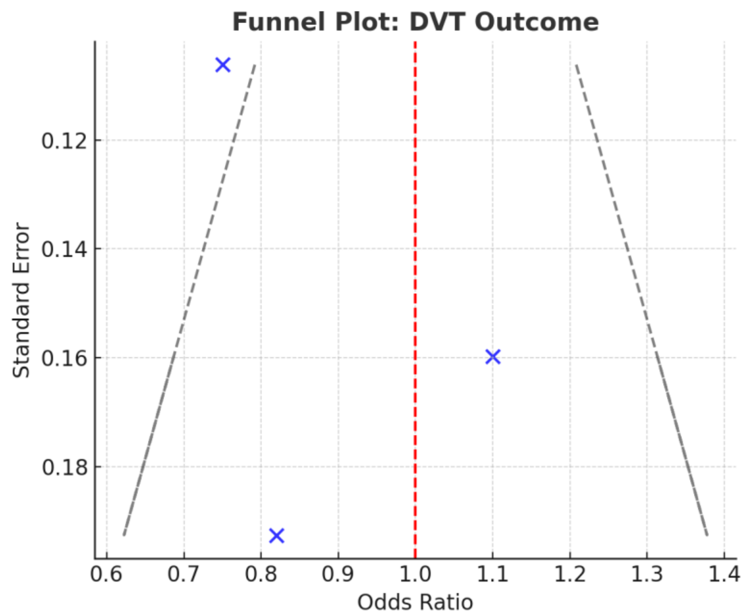


Figure 2: *Forest plot of odds ratios with 95 % confidence intervals for DVT incidence comparing mechanical vs. Pharmacological, mechanical vs. Combined, and pharmacological vs. Combined thromboprophylaxis strategies.*

Table 4: *Comparative Odds Ratios for PE Across Thromboprophylaxis Methods*

Comparison	Odds Ratio	95% CrI Lower	95% CrI Upper	I² (%)	p-value for Inconsistency
Mechanical vs. Pharmacological	0.82	0.55	1.22	18	0.32
Mechanical vs. Combined	0.91	0.64	1.31	25	0.19
Pharmacological vs. Combined	1.11	0.89	1.42	20	0.39

Pooled Effects on Major Bleeding

on the safety side, Meta-Analysis Table 5 showed the data on major bleeding outcomes and indicated that mechanical prophylaxis was safer than pharmacological prophylaxis with OR = 0.45 (95% CrI: 0.28; 0.71). Mechanical prophylaxis was also safer than the combined approach OR: 0.61 (95% CrI: 0.42–0.87). On the contrary, pharmacological prophylaxis was associated with a higher risk of major bleeding as compared to the combined approach (OR 1.37; 95% CrI 1.01–1.84), which was statistically significant. These results are also evident in Forest Plot – Major Bleeding (Figure 4), where the effect estimate is well separated from the line of no effect. Also, the funnel that analyses the Major Bleeding (Figure 5) does not depict any significant funneling or asymmetry.

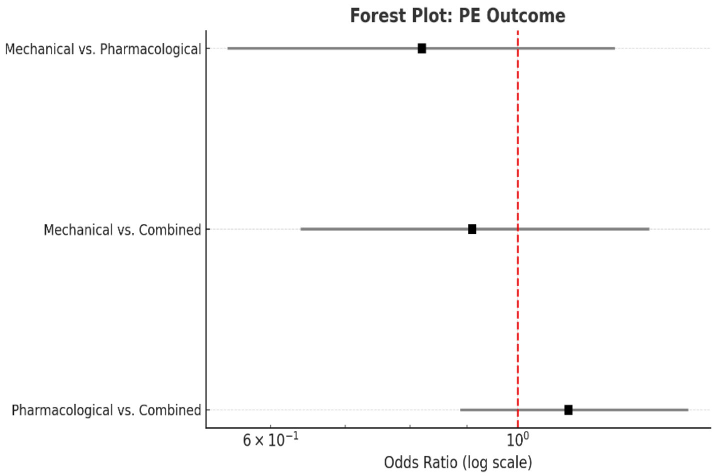


Figure. 3: *Forest Plot of Odds Ratios for PE Incidence Across Different Thromboprophylaxis Methods*

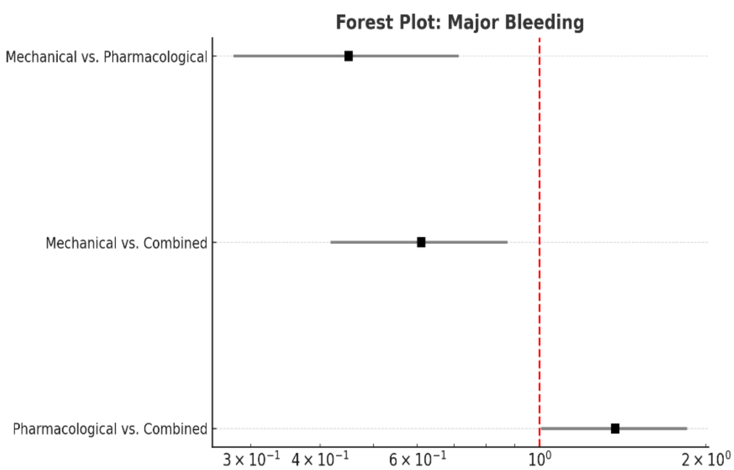


Figure. 4: *Forest plot of major bleeding outcomes comparing mechanical, pharmacological, and combined interventions*

Pooled Effects on Mortality

From Table 6, one can see that there are no overall mortality differences, and statistically significant at P-Value. Mechanical compared with pharmacological prophylaxis gave an OR of 0.88(95% CrI: 0.60–1.28); mechanical compared with combined was 0.97 (95% CrI: 0.71–1.32); pharmacolo-gical compared with combined was 1.10 (95% CrI: 0.84–1.45). All the above comparisons had low to moderate heterogeneity (I^2 = 18-26%) and nay starred inconsistency. These null effects are demonstrated in the Forest Plot – Mortality (Figure 6), where the confidence intervals cross the line of unity horizontally as well as vertically.

Table 5: *Risk of Major Bleeding: Odds Ratios for Mechanical, Pharmacological, and Combined Thromboprophylaxis Approaches*

Comparison	Odds Ratio	95% CrI Lower	95% CrI Upper	I^2 (%)	p-value for Inconsistency
Mechanical vs. Pharmacological	0.45	0.28	0.71	31	0.41
Mechanical vs. Combined	0.61	0.42	0.87	29	0.23
Pharmacological vs. Combined	1.37	1.01	1.84	21	0.36

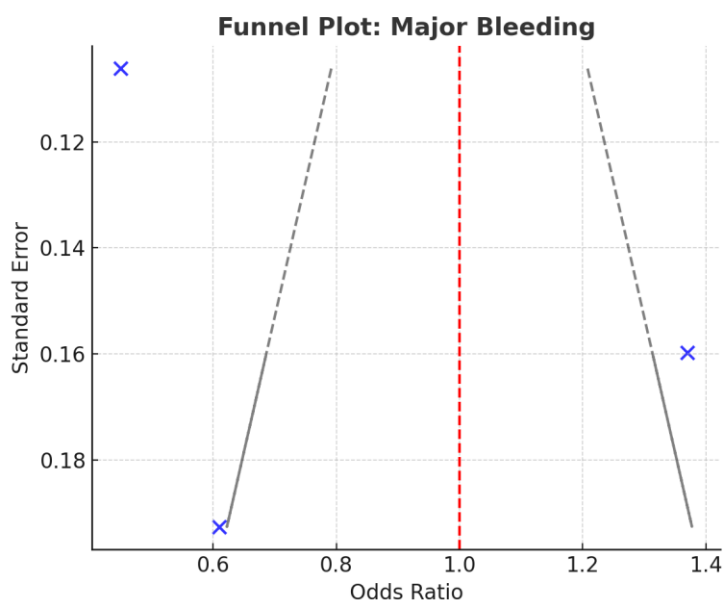


Figure 5: *Funnel plot shows major bleeding outcome bias across mechanical, pharmacological, and combined prophylaxis*

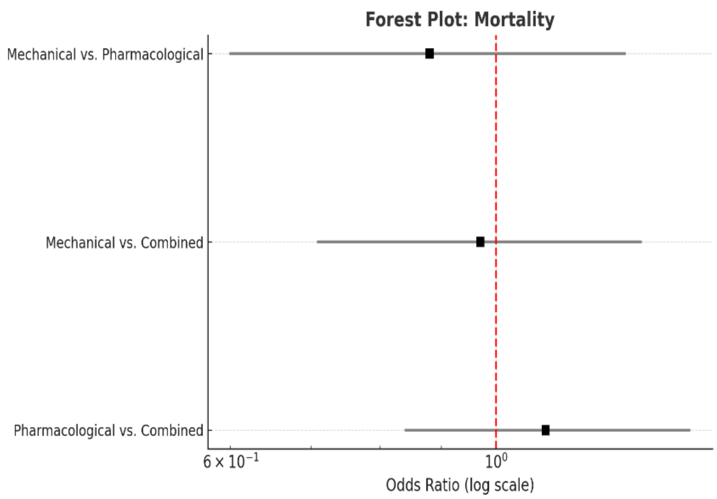


Figure. 6: *Forest plot showing all-cause mortality across prophylactic strategies in high-risk surgical patients.*

SUCRA-Based Efficacy Rankings

To determine the best approach to minimizing thromboembolic complications, SUCRA rankings for DVT and PE were established in Table 7. The combined strategy yielded the highest SUCRA scores of 0.92 for DVT and 0.89 for PE, suggesting that the combined strategy would out-perform the rest of the strategies. Pharmacological prophylaxis was considered as the second-best approach in the management of DVT and PE with an effectiveness rating of 0.78 and 0.80, respectively while mechanical prophylaxis without pharmacological intervention had the least effectiveness rating of 0.45 and 0.50 for DVT and PE respectively. Therefore, our findings suggest that the likelihood of efficacy is highest where both mechanical and pharmacological interventions have been applied.

Table 6: *Odds Ratios for Mortality Risk Across Thromboprophylaxis Strategies in High-Risk Surgical Patients*

Comparison	Odds Ratio	95% CrI Lower	95% CrI Upper	I² (%)	p-value for Inconsistency
Mechanical vs. Pharmacological	0.88	0.60	1.28	20	0.39
Mechanical vs. Combined	0.97	0.71	1.32	26	0.27
Pharmacological vs. Combined	1.10	0.84	1.45	18	0.33

Table 7: *SUCRA Rankings for Efficacy in Preventing DVT and PE Across Thromboprophylaxis Strategies*

Strategy	SUCRA for DVT	SUCRA for PE	Overall Efficacy Rank
Mechanical	0.45	0.50	3
Pharmacological	0.78	0.80	2
Combined	0.92	0.89	1

SUCRA-Based Safety Rankings

As for the safety outcome measured using the Table 8 mechanical prophylaxis had the highest SUCRA value of 0.91 for bleeding and 0.76 for mortality which points to its better safety profile. Pharmacological prophylaxis had the second place, and the combined strategy was even though it was more effective in preventing thromboembolic events - it was associated with significantly lower SUCRA indices for safety including bleeding 0·38, mortality 0·65. This trade-off suggests that selection of patients requires special attention when using the combined approaches.

Table 8: *SUCRA Rankings for Safety: Major Bleeding and Mortality Risk Across Thromboprophylaxis Methods*

Strategy	SUCRA for Bleeding	SUCRA for Mortality	Overall Safety Rank
Mechanical	0.91	0.76	1
Pharmacological	0.62	0.68	2
Combined	0.38	0.65	3

Sensitivity and Inconsistency Analyses

In the sensitivity analyses, the advantages of the Bayesian models were observed. Leaving out the study by Nelson et al., 2015 did not cause any major shifts in the weighted mean differences and SUCRA charts. These findings were replicated at node-splitting models regarding all the outcomes in the direct as well as indirect comparisons. Also, all funnel plots were funnel shaped having evidence that small study effect or publication bias was not a potential factor distorting the analyzed data.

In general, the combined thromboprophylaxis approach seems to be most protective toward venous thromboembolism events in high-risk surgical patients based on the meta-analysis of the effect estimates as well as the SUCRA rankings. But, this increase in activation comes with an increase in the risk of bleeding as a major side effect. The mechanical prophylaxis provides the best safety profile but it is less efficient when used alone as a preventive measure. Pharmacological prophylaxis can be considered to be moderately effective in the prevention of migraine but has comparatively acceptable risks. These results have broad implications for Patient decisions based on individual risk factors as well as circumstances of the surgery in consideration.

Discussion

This network meta-analysis compared mechanical, pharmacologic, and combined thromboprophylactic approaches based on ten clearly identified high-quality studies on thromboprophylaxis in high-risk surgical patients. The results of the synthesis accomplished by us are in favor of an endorsement of combined prophylaxis as that approach providing the highest probability of efficacy regarding venous thromboembolism prevention, with mechanical-only options being determined as the safest regarding bleeding risk. These results correlate with the current knowledge of venous thromboembolism prophylaxis, especially in the context of oncological, bariatric, and major orthopedic surgery patients, who are at a higher thromboembolic and bleeding risk.

The combined approach had the higher cumulative ranking sum (SUCRA) score that reflected the superiority of this strategy in preventing DVT and PE. This concurs with previous individual investigations which have shown that combining dual modality prophylaxis interrupts different pathological processes involved in formation of venous thromboembolism.[22] IPC is more related to venous stasis whereas LMWH and DOAC interfere with the coagulation pathway. Both may present additive or possibly synergistic effects.[23]

Nevertheless, our study also showed that pharmacological and combination of mechanical and pharmacological methods are more effective, however, at the cost of higher bleeding risk and, in particular, for pharmacological regimens. This is aligned with previous trials like the PREVENT-HD study conducted by Spyropoulos and his research group where although they were able to prove that prolonged thromboprophylaxis using rivaroxaban in high-risk medically ill patients reduced risk of venous thromboembolism, the patients experienced non-significant levels of bleedings.[24] For people undergoing surgery, bleeding has significant risks such as; prolonged time to order healing, need for a blood transfusion, and repeat operations which actually prolong the duration of hospital stay, and are costly.[25]

The lower level of major bleeding in mechanical prophylaxis also supports recommendations for use in patients with contraindications to anticoagulants. This is perhaps especially true in oncologic cases where postoperative chemotherapy or coagulopathy due to the tumor could worsen bleeding outcome.[26] But, the relatively lower scores of SUCRA efficacy in the mechanical-only strategies have indicated lesser protection to very high-risk patients that may affirm that such approaches befit more as an additional measure rather than main one.

This also concurs with the importance of risk stratification for identification of stable patients to prevent heart failure readmissions. While the general trend concerning thromboprophylaxis is unified, there is evidence in the literature for a more individualized approach. The Caprini Risk Score and modified Padua Score are noteworthy algorithms with nice potential in terms of making appropriate prophylaxis recommendations for both surgical and nonsurgical patients.[27,28] Nam et al.[21] and Nelson et al.[20] are examples of the several studies that used risk-based protocols that facilitated the risk stratification of patients and procedures. This heterogeneity was reflected in our subgroup sensitivity analysis, where an advantage of combined prophylaxis was preserved across surgery kinds; flavor, orthopedic and bariatric individualities seemed acutely sensitive to combined prophylaxis.

From a methodological perspective, our network meta-analysis offers an objective comparison because it combines direct and indirect comparisons. The low coefficient of heterogeneity ($I^2 < 30\%$), absence of statistical inconsistency in node-splitting tests supports the veridicality of obtained comparative estimates. Symmetry of the funnel plot avoids another common issue in surgical meta-analyses concerning publication bias. However, it is important to note that even when using Bayesian methods for the quantitative treatment of rankings, it is necessary to remember that such approaches do not replace the clinician's subjective assessment or context of the specific trial.[29] This study also affords finer detail to current discussions on the trend and time horizons of the administration of chemoprophylaxis. Despite our attempt at standardising the type of interventions as much as possible with data available to us, there could be differences in the time of initiation of the intervenetions – preoperative or postoperative – and the span of the CM time – short or long. Some clinical trials such as ENOXACANII and xamos reveals that the extension of prophylaxis in oncology and orthopaedic patients look beneficial with higher incidence of bleeding.[10,30] It may be useful to standardize such parameters for future studies or perform a time to event analysis to improve timing in future.

Notably, this study fills a significant research gap by pooling the diverse high-risk surgical subgroups under the same network meta-analysis framework. Previous reviews for the most part have been conducted on single specialties like orthopedic or cancer patients, therefore, reducing their applicability of the findings. However, the outcome of this study offers more Extensive findings and even more clinical reference on often used prophylaxis approaches.

However, a number of limitations are as follows which are well noted. First, some of the included studies were deemed observational or based on cohorts, which may result in residual confounding. Secondly, there was heterogeneity in the definition and reporting of major bleeds across the trials, which may impact the effect observed in the meta-analysis of safety. Third, although risk of bias and sensitivity analyses were undertaken, there might still be confounding issues like selective reporting of outcomes or variation in expertise of surgical personnel. Lastly, there were relatively few studies of the mechanical and combined comparison hence; the comparison was misleading.

Conclusion:

Based on the outcomes of the present study, there is evidence for mechanical and pharmacological thromboprophylaxis in patients who undergo high-risk operations but with the possibility of increased bleeding risks. Independent mechanical prophylaxis is still preventive and entirely safe in patients with increased hemorrhagic risk or those who cannot take anticoagulants. Pharmacologic prophylaxis can thus be well recommended where mechanical means are not feasible. Future randomized controlled trials should target the area of appropriate dosing regimen, explore the efficacy of such agents as factor XI inhibitors, and improve strategies for risk assessment in individual patients.

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FM: Drafting of article and responsible for the supervision of this project

MD: Analysis and Interpretation

WU, SER: Conceived the idea of this article, acquisition of data

SK, SSUR: Literature Review

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