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Original article

Effect of extended duration of thromboprophylaxis for medically ill patients

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ABSTRACT

Background: There are knowledge gaps regarding the comparative efficacy and safety of various venous thromboprophylaxis regimens with extended timing in patients hospitalized for acute medical illnesses. This study aims to investigate the optimal regimen for the prevention of venous thromboembolism in these patients.
Methods: We conducted a Bayesian network meta-analysis of randomized controlled trials (RCTs) comparing different venous thromboprophylaxis regimens for acutely ill medical patients. Outcomes included venous thromboembolism, major bleeding, and all-cause mortality. Risk ratios (RR) and associated 95% credible interval (CrI) were estimated. In addition, we assessed the most effective interventions in a subgroup of patients with stroke.
Results: We identified five RCTs involving 40,124 patients. Extended thromboprophylaxis with direct oral anticoagulant (DOAC) (RR 0.78, 95% CrI 0.68 to 0.89) and low molecular weight heparin (LMWH) (RR 0.62, 95% CrI 0.45 to 0.84) were superior to standard therapy in the prevention of venous thromboembolism. However, both of them (DOAC: RR 1.99, 95% CrI 1.38 to 2.92; LMWH: RR 2.56, 95% CrI 1.26 to 5.68) lead to a significant increase in major bleeding). Moreover, both LMWH (RR 0.76, 95% CrI 0.57 to 1.00) and DOAC (RR 0.86, 95% CrI 0.76 to 0.98) with extended thromboprophylaxis showed favorable net clinical benefit compared to standard therapy.
Conclusions: Extended thromboprophylaxis, especially with LMWH, showed better efficacy in venous thromboembolism reduction with increased risk of major bleeding. The beneficial effect of LMWH with extended timing has also been shown in stroke patients. Overall, extended thromboprophylaxis is associated with a positive net clinical benefit.

1. Introduction

Patients hospitalized for acute medical illnesses such as stroke, infections, heart attack, and COVID-19 are at increased risk for venous thromboembolism [1–3]. The situation is even worse in patients hospitalized for stroke; researchers have reported that medical sequelae due to neurological impairment such as immobilization may triple the risk of venous thromboembolism [4,5]. Moreover, previous research has observed that the risk of venous thromboembolism in patients with acute medical illnesses persists even after their discharge from the hospital [6].

In light of these findings, current clinical guidelines recommended the application of extended thromboprophylaxis in the selected group of patients, such as patients undergoing hip fracture surgery, total knee replacement, or total hip replacement [7,8]. However, no studies have supported the regular application of extended thromboprophylaxis in a broader population of patients. More importantly, there is uncertainty regarding the choice of drug (e.g. low molecular weight heparin [LMWH], and direct oral anticoagulant [DOAC]) for prolonged venous thromboprophylaxis in these patients. In addition, it remains unclear whether specific subgroups of patients with acute medical illnesses, such as those with acute stroke remain at higher risk of venous thromboembolism after hospital discharge, and may thereby benefit from extended thromboprophylaxis [9,10].

Based on this knowledge gap, we designed a systematic review with network meta-analysis of existing randomized controlled trials (RCTs) to integrate current evidence and evaluate the comparative safety and of efficacy various venous thromboprophylaxis regimens with extended timing in patients hospitalized for acute medical illnesses.

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2. Materials and methods

2.1. Search strategy and data sources

The Ovid EMBASE, the Cochrane Central Register of Controlled Trials, and the Ovid MEDLINE databases were searched from inception to December 31, 2022, without language restriction. The bibliography of the selected articles and published systematic reviews on the same topic were also systematically searched to identify any additional studies. The search strategy was developed and implemented by an experienced researcher (Table S1). We registered this study on the Open Science Framework Portal (https://osf.io/v4ywk) and PROSPERO database (CRD42023395040).

2.2. Eligible criteria

Eligible studies conformed to the following criteria with respect to participants, interventions, comparators, outcomes, and study design: (1) Population: patients admitted to the hospital for acute medical illness. (2) Intervention: extended venous thromboprophylaxis with any type of anticoagulant agents including unfractionated heparin, low molecular weight heparin, direct oral anticoagulant, etc. (3) Comparison: standard venous thromboprophylaxis with any type of anticoagulant, or a placebo. (4) Outcome: the primary outcome was venous thromboembolism defined by each trial. The secondary outcome included major bleeding and all-cause mortality. (5) Study design: randomized controlled trials.

Besides, we excluded observational studies, single-arm trials, and trials that compared anticoagulants with other pharmacologically active agents.

2.3. Selection process

According to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension Statement for network Meta-analyses [11], we excluded ineligible publications based on title and abstract after deleting duplicate articles. Next, we excluded studies based on the eligible criteria after screening full-text articles.

Two independent authors examined the publications and completed this procedure collaboratively. When conflicts or disagreements arose during this process, the other independent author made the ultimate decision.

2.4. Data extraction

Data associated with the following fields were extracted onto a standard sheet: (1) study characteristics: study name, publication year, geographical location, and registration information; (2) treatment characteristics: medication information, dosage, and duration of treatment; (3) patient characteristics: age, sex, and the disease for hospitalization.

Two independent authors examined the publications and completed this procedure collaboratively. When conflicts or disagreements arose during this process, the other independent author made the ultimate decision.

2.5. Assessment of the risk of bias and certainty of the evidence

Cochrane Collaboration Risk of Bias tool was used to evaluate the risk of bias for all RCTs among seven aspects: blinding of study participants; selective reporting; incomplete outcome data; allocation concealment; blinding of outcome assessment; random sequence generation; and other potential bias [12]. Each field was rated as low, unclear, or high risk of bias. If necessary, the investigators of the original study will be contacted by email for more information.

We employed the framework developed by the Working Group on Recommendations Assessment, Development, and Evaluation (GRADE) to assess the quality of the evidence for each outcome estimate, prioritizing the quality of the evidence [13]. Overall, each estimate was rated as very low, low, moderate, or high certainty of evidence.

2.6. Statistical analysis

The methods and reporting of this network meta-analysis followed the PRISMA-NMA guideline [11]. We applied a Bayesian hierarchical model via Monte Carlo algorithms to incorporate direct and indirect comparisons of relative treatment effects. For the primary analysis, we used the parameters with four parallel Markov chains of 30,000 samples after a 10,000-sample burn-in. Trace plots and Gelman-Rubin diagnostic statistics were used to check the convergence of Markov chains. Model fit was assessed by comparing the posterior total residual deviance with the number of unconstrained data points. We calculated and pooled relative risks (RRs) with 95% credible interval (CrI) for dichotomous outcomes, and mean differences (MDs) between treatment arms for continuous outcomes.

Furthermore, the surface under the cumulative ranking curve (SUCRA) and forest plots, were performed to evaluate and summarize the main results. The SUCRA value ranges between 0 and 1. Treatments with the highest and lowest SUCRA values are deemed to be the most and least effective. We estimated the overall ranks of treatments by calculating the overall SUCRA score for each treatment. The rank probabilities were also determined. Heterogeneity was measured by using Cochran's Q and quantified using I^2 statistics, which ranges between 0% and 100%. The global statistical heterogeneity across all comparisons was obtained from the established model.

Risk–benefit analysis was performed semi-quantitatively considering SUCRAs of the benefit (lowering risk of venous thromboembolism) and the risk (increasing risk of major bleeding). The higher SUCRA of the venous thromboembolism and major bleeding represented the maximal efficacy and minimal safety concerns. The plot was divided into four quadrants, in which the right upper quadrant reflected the intervention with optimal efficacy and safety, whereas the left lower quadrant represented the intervention with the worst efficacy and safety. Quantitative risk-benefit analysis was conducted by calculating the number needed to treat (NNT) and the number needed to harm (NNH). Treatment regimens with lower NNT and higher NNH values are considered to be associated with a more favorable treatment profile [14]. Net clinical benefit of the different treatment regimens was additionally evaluated, which was defined as the number of venous thromboembolism events and major bleeding events [15].

All analyses were done in R software (release version 4.2.2), SPSS (release version 26) and RevMan (5.4.0; The Cochrane Collaboration). A two-sided p-value of < 0.05 was considered to be statistically significant.

3. Results

3.1. Study population and qualitative analysis

The literature retrieval process is presented in Fig. 1. In brief, a total of 2021 potentially eligible articles were retrieved from the Medline, Cochrane CENTRAL, and Embase databases. Of these, 699 records were duplicates. The titles and abstracts of the 1322 records were screened, and then we excluded 1301 studies according to the predefined criteria. In the full-text screenings, we further excluded 16 studies. Finally, a total of 5 trials were included in this meta-analysis [16–20], of which 4 reported data in stroke patients [16–18,21].

The baseline characteristics of the included studies are shown in Table 1. These studies were published between 2011 and 2018. The sample size across the included studies ranged from 5963 to 12,019. Overall, 40,124 patients with acute medical illness were included, of whom 4164 were stroke patients (10.4%) and 20,245 (50.5%) were male patients. Patients came from the USA (3 trials), France (1 trial), and

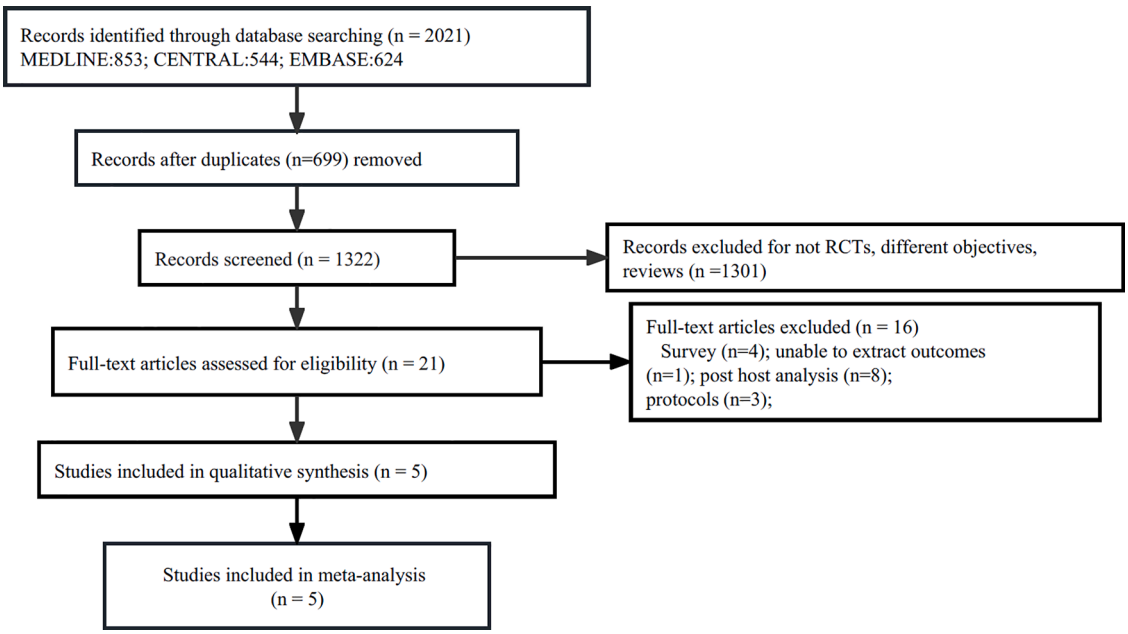

Fig. 1. Study flow diagram and reasons for exclusion of studies. RCT randomized clinical trial.

Table 1
Characteristics of studies included in the systematic review and meta-analysis.

Study	Registration	Country	No. of patients	Stroke patients (%)	Extended treatment		Standard treatment		Primary outcomes	Duration of follow up
					Treatment Regimen	Age (% male)	Treatment Regimen	Age (% male)		
MARINER 2018	NCT02111564	USA	12,019	1555 (12.9)	Rivaroxaban 10 mg once daily for 45 days	69.7 (52.1)	Oral placebo	69.7 (52.5)	A composite of symptomatic venous thromboembolism or death due to venous thromboembolism	3 months
APEX 2016	NCT01583218	USA	7513	837 (11.1)	Betrixaban 80 mg once daily for 35 to 42 days	76.6 (45.4)	Enoxaparin 40 mg once daily for 10±4 days	76.2 (45.8)	A composite of asymptomatic proximal deep-vein thrombosis and symptomatic venous thromboembolism	3 months
EXCLAIM 2013	NCT00077753	Canada	5963	389 (6.5)	Enoxaparin 40 mg an additional 28 ±4 days	67.9 (49.3)	Enoxaparin 40 mg once daily for 10±4 days	67.5 (49.4)	A composite of symptomatic or asymptomatic proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism	3 months
MAGELLAN 2012	NCT00571649	USA	8101	1383 (17.1)	Rivaroxaban 10 mg once daily for 35±4 days	71.0 (55.6)	Enoxaparin 40 mg once daily for 10±4 days	71.0 (52.7)	A composite of asymptomatic proximal or symptomatic venous thromboembolism	1 month
ADOPT 2011	NCT00457002	France	6528	NA	Apixaban 2.5 mg twice daily for 30 days	66.8 (50.0)	Enoxaparin 40 mg once daily for 6 days	66.7 (48.2)	A composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis	3 months

USA: United States of America; NA: not available;.

Canada (1 trial) populations. The mean or median age ranged from 66.8 to 76.6 years in the extended thromboprophylaxis group and from 66.7 to 76.2 years in the standard thromboprophylaxis group. The mean follow-up from disease onset was 2.6 months (range: 1–3 months). The most commonly administered regimen of extended thromboprophylaxis was rivaroxaban 10 mg. The most commonly administered regimen of standard thromboprophylaxis was enoxaparin 40 mg.

3.2. Risk of bias

In summary, the risk of bias was low across the included trials. The overall and individual risks of bias are shown in Figure S1–2 in the Supplement. The GRADE certainty of the evidence for the primary outcome was rated low to moderate quality. The certainty of evidence assessments for the primary outcome is shown in Table S2 in the Supplement. The most common reasons for downgrading the evidence quality were indirectness, and imprecision of estimates.

3.3. Venous thromboembolism outcome

Five studies were suitable for meta-analysis, involving 16,782 patients treated with extended thromboprophylaxis, and 17,037 patients

treated with standard thromboprophylaxis (Figure S3 in the Supplement). Incidence of venous thromboembolism following acutely ill medically ranged from 0.8 to 5.3% in the extended thromboprophylaxis group vs. 1.1 to 7.0% in the standard thromboprophylaxis group (Fig. 2). Due to the negligible heterogeneity (I^2=0), we applied a fixed-effects model to pool the results. Extended thromboprophylaxis with DOAC (RR 0.78, 95% CrI 0.68 to 0.89; moderate certainty; Table S2) and extended thromboprophylaxis with LMWH (RR 0.62, 95% CrI 0.45 to 0.84; moderate certainty; Table S2) both led to a significant decrease in venous thromboembolism compared with standard thromboprophylaxis with LMWH.

SUCRA values further suggest that extended thromboprophylaxis with LMWH is associated with the lowest risk of venous thromboembolism (SUCRA, 0.96), followed by extended thromboprophylaxis with DOAC (SUCRA, 0.67) and standard thromboprophylaxis with LMWH (SUCRA, 0.19).

Four trials involving 3873 patients reported venous thromboembolism in patients with stroke (Figure S4). Incidence of venous thromboembolism following stroke ranged from 1.0 to 5.1% in the extended thromboprophylaxis group vs. 0.9 to 9.1% in the standard thromboprophylaxis group (Fig. 3). Our analyses revealed that extended thromboprophylaxis with LMWH resulted in significant improvement in venous thromboembolism for patients with stroke (RR 0.28, 95% CrI 0.08 to 0.82; moderate certainty; Table S2). Similar results were noted in the comparison of extended thromboprophylaxis with DOAC and standard thromboprophylaxis with LMWH (RR 0.68, 95% CrI 0.45 to 1.01; moderate certainty; Table S2); however, the results did not reach a statistical difference.

3.4. Major bleeding outcome

Five trials involving 39,756 patients reported major bleeding (Figure S5). Major bleeding after acute medical illness occurred in 0.3–1.1% of patients treated with extended thromboprophylaxis, compared with 0.2–0.6% in patients treated with standard thromboprophylaxis (Fig. 4). In comparison with standard thromboprophylaxis with LMWH, extended thromboprophylaxis with DOAC (RR 1.99, 95% CrI 1.38 to 2.92) and extended thromboprophylaxis with LMWH (RR 2.56, 95% CrI 1.26 to 5.68) both lead to a significant increase in major bleeding.

SUCRA values further suggest that extended thromboprophylaxis with LMWH is related to the highest risk of major bleeding (SUCRA, 0.11), followed by extended thromboprophylaxis with DOAC (SUCRA, 0.26).

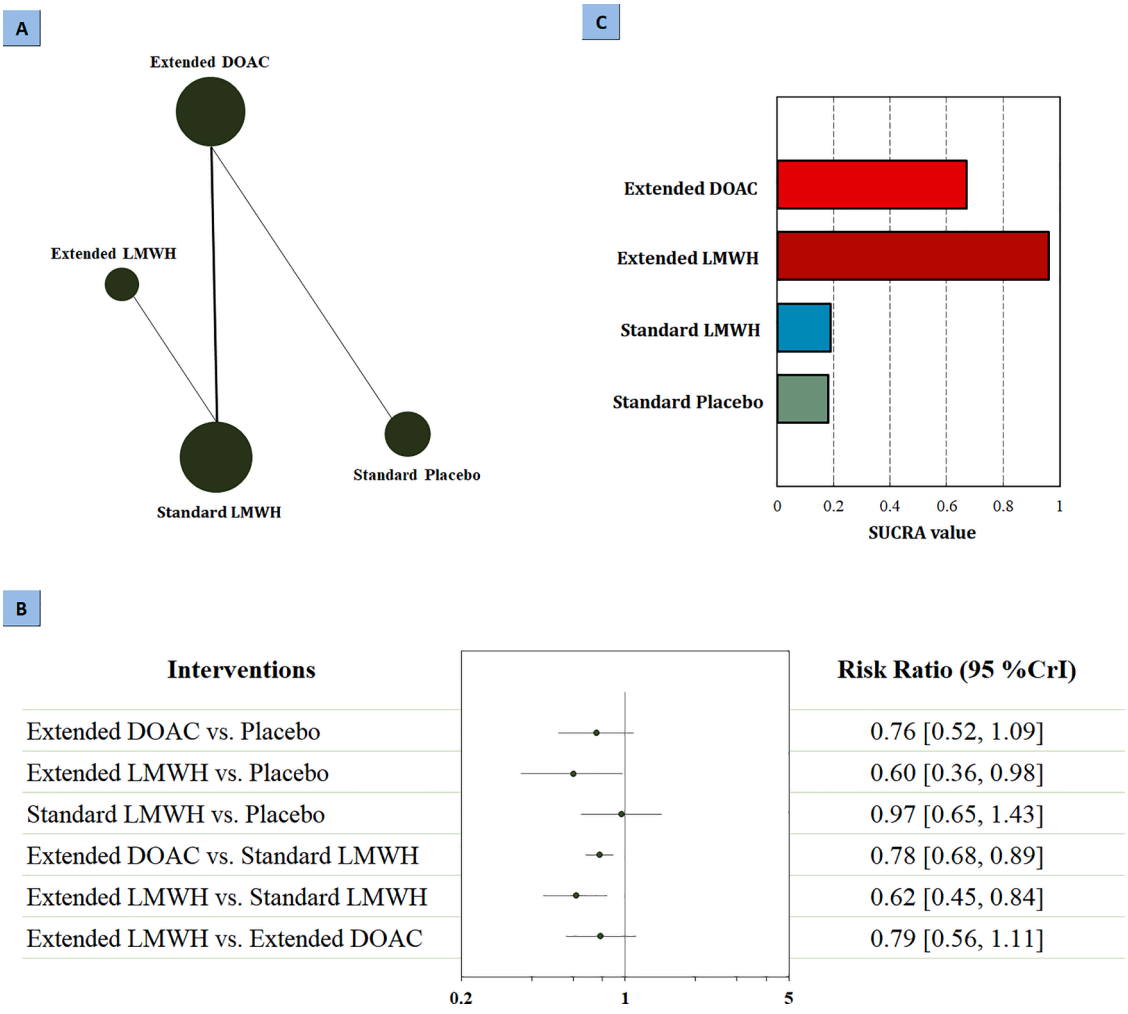

Fig. 2. Summary of the venous thromboembolism outcome. A. Network plot of venous thromboembolism. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. B. The forest plot shows the risk ratio (RR) and credible interval (CrI). C. Ranking probabilities graph of each treatment agent. The SUCRA values for each treatment were as follows: 96% for extended thromboprophylaxis with LMWH; 67% for extended thromboprophylaxis with DOAC; 19% for standard thromboprophylaxis with LMWH; 18% for standard thromboprophylaxis with placebo. SUCRA: surface under the cumulative ranking curve.

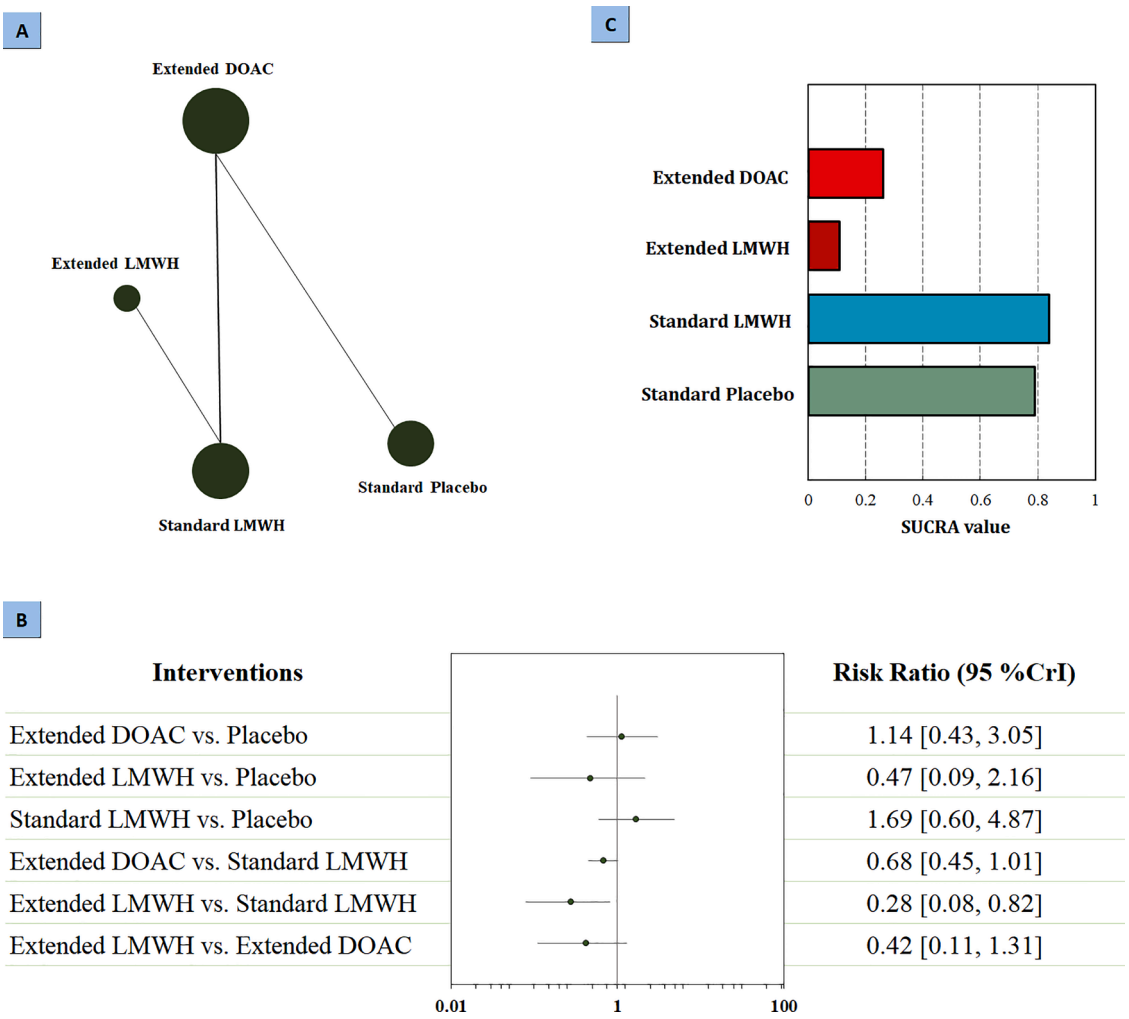

Fig. 3. Subgroup analysis of the venous thromboembolism outcome for stroke patients. A. Network plot of venous thromboembolism. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. B. The forest plot shows the risk ratio (RR) and credible interval (CrI). C. Ranking probabilities graph of each treatment agent. The SUCRA values for each treatment were as follows: 91% for extended thromboprophylaxis with LMWH; 54% for standard thromboprophylaxis with placebo; 48% for extended thromboprophylaxis with DOAC; 7% for standard thromboprophylaxis with LMWH. SUCRA: surface under the cumulative ranking curve.

3.5. Mortality outcome

Five trials including 38,053 patients reported all-cause mortality (Figure S6). Following acute medical illness, all-cause mortality varied from 1.2 to 5.7% in patients treated with extended thromboprophylaxis, compared with 1.5–5.8% in patients treated with standard thromboprophylaxis (Fig. 5). The meta-analysis suggested that compared with the standard thromboprophylaxis group, the extended thromboprophylaxis group had no difference in all-cause mortality (extended thromboprophylaxis with DOAC: RR 1.01, 95% CrI 0.90 to 1.14; extended thromboprophylaxis with LMWH: RR 0.93, 95% CrI 0.66 to 1.32).

3.6. Risk/benefit assessment and net clinical benefit analysis

In terms of the cluster ranking plot combined SUCRA values for preventing venous thromboembolism versus increased risk of bleeding events, extended thromboprophylaxis, especially treatment with LMWH, showed better efficacy in reducing venous thromboembolism with suboptimal profile in the risk of major bleeding (Fig. 6a). To quantify whether the benefit of prolonged thromboprophylaxis to reduce the risk of venous thrombosis overwhelms the increased risk of bleeding, NNT and NNH of different treatment pairs were calculated (Table 2). The NNH/NNT of the comparison between extended treatment with LMWH and extended treatment with DOAC was 7.36, and the NNH/NNT of the comparison between extended treatment with LMWH and standard treatment with LMWH was 3.05, indicating that extended treatment with LMWH is superior to extended treatment with DOAC and standard treatment with LMWH in terms of the combined benefit-risk ratio. In addition, meta-regression analysis was performed to test the interaction between the risk of venous thromboembolism and major bleeding. The results did not reach statistical differences (Fig. 6b and c).

To assess the net clinical benefit, composite clinical outcomes of venous thromboembolism and major bleeding were integrated (Fig. S7). The results showed that extended thromboprophylaxis with DOAC (RR 0.86, 95% CrI 0.76 to 0.98; moderate certainty; Fig. 6d) and extended thromboprophylaxis with LMWH (RR 0.76, 95% CrI 0.57 to 1.00; moderate certainty; Fig. 6d) both led to a significant decrease in the composite clinical outcome compared with standard thromboprophylaxis. Moreover, LMWH with extended duration ranked first in net clinical benefit (SUCRA, 0.87), followed by extended thromboprophylaxis with DOAC (SUCRA, 0.65; Fig. 6e).

4. Discussion

In this Bayesian network meta-analysis, we integrated direct and

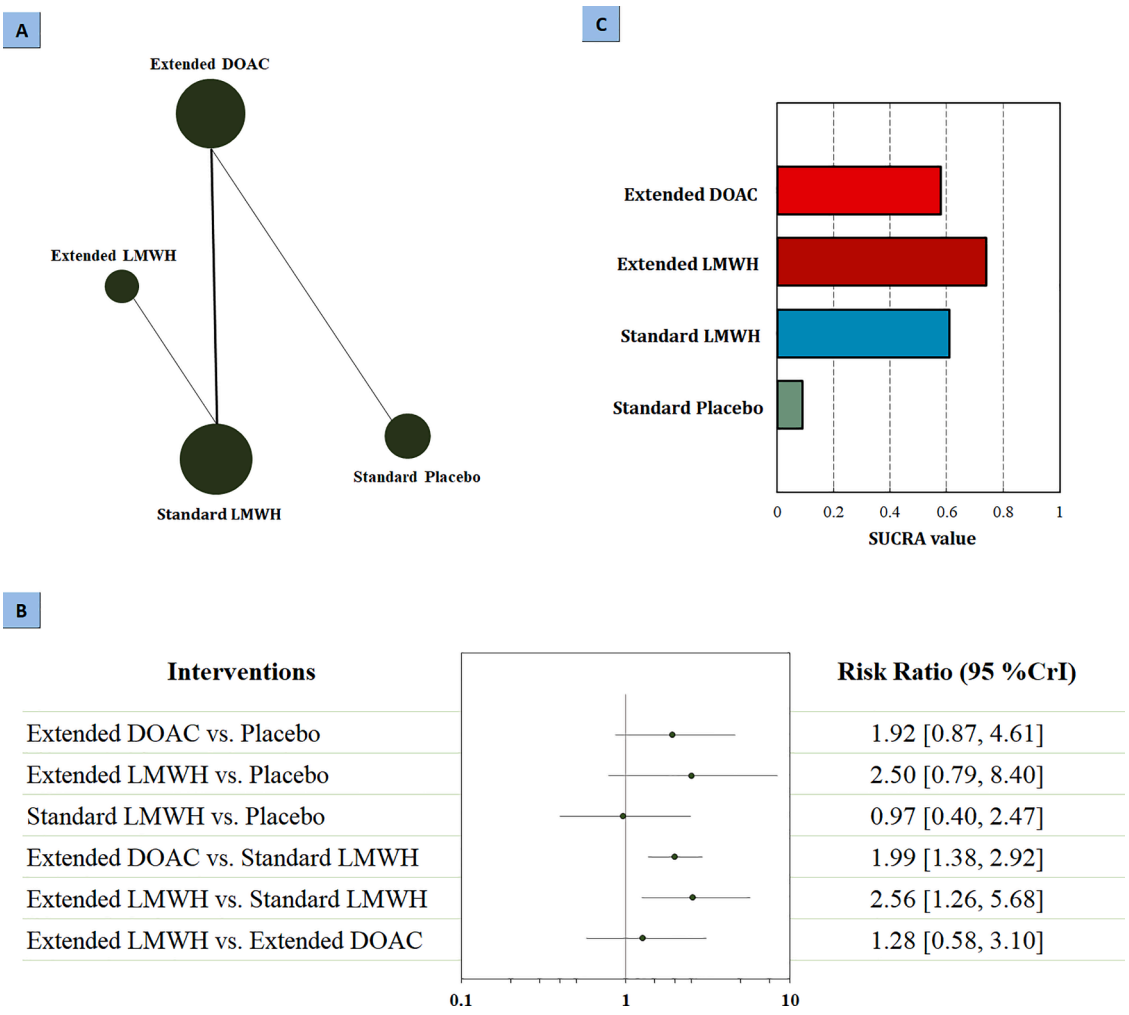

Fig. 4. Summary of the major bleeding outcome. A. Network plot of major bleeding. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. B. The forest plot shows the risk ratio (RR) and credible interval (CrI). C. Ranking probabilities graph of each treatment agent. The SUCRA values for each treatment were as follows: 84% for standard thromboprophylaxis with LMWH; 79% for standard thromboprophylaxis with placebo; 26% for extended thromboprophylaxis with DOAC; 11% for extended thromboprophylaxis with LMWH. SUCRA: surface under the cumulative ranking curve.

indirect evidence from five randomized clinical trials including 40,124 patients with acute medical illness. Both extended thromboprophylaxis with DOAC and LMWH was associated with a greater reduction in venous thromboembolism than standard thromboprophylaxis. However, these treatment regimens also led to a significant increase in major bleeding. Regarding patients with stroke, extended thromboprophylaxis with LMWH resulted in significant improvement in venous thromboembolism. Overall, extended thromboprophylaxis was more effective than standard thromboprophylaxis, but attention should be paid to the increased incidence of major bleeding. Besides, extended thromboprophylaxis with either DOAC or LMWH is a safe prevention option that does not increase mortality.

The ranking probabilities calculated using the SUCRA approach indicate the following order of magnitude in terms of the primary outcome: extended thromboprophylaxis with LMWH had the highest SUCRA value (suggesting it is probably the best treatment), followed by extended thromboprophylaxis with DOAC. On the other hand, in terms of major bleeding, thromboprophylaxis with LMWH had the lowest SUCRA value (suggesting it is probably the worst treatment).

We also evaluated the risk and benefit of prolonged thromboprophylaxis, as well as the net clinical benefit, in consideration of the reduction of venous thromboembolism and the associated increase of major bleeding. The analysis yielded a positive net clinical benefit for patients treated with extended thromboprophylaxis compared with standard thromboprophylaxis. In addition, extended thromboprophylaxis with LMWH was associated with the most favorable benefit–risk profile for the treatment of medically ill patients.

4.1. Comparison with other studies

Compared with existing pairwise meta-analyses and randomized clinical trials on this topic, our findings were expanded by investigating the comparative benefits and harms of various thromboprophylaxis regimens for patients with acute medical illness, particularly in patients with stroke [22–24]. Concerning evidence certainty and study limitations, a direct meta-analysis performed by Zayed et al. suggested that prolonging venous thromboprophylaxis is effective, but its clinical utility could be limited by safety profiles in increasing risk of bleeding [23]. Taken together, our network estimates also noted no harm in prolonging venous thromboprophylaxis for the treatment of individuals with acute medical illness. This network meta-analysis provided a broader representation of both comparative and absolute estimates of a variety range of clinically important outcomes.

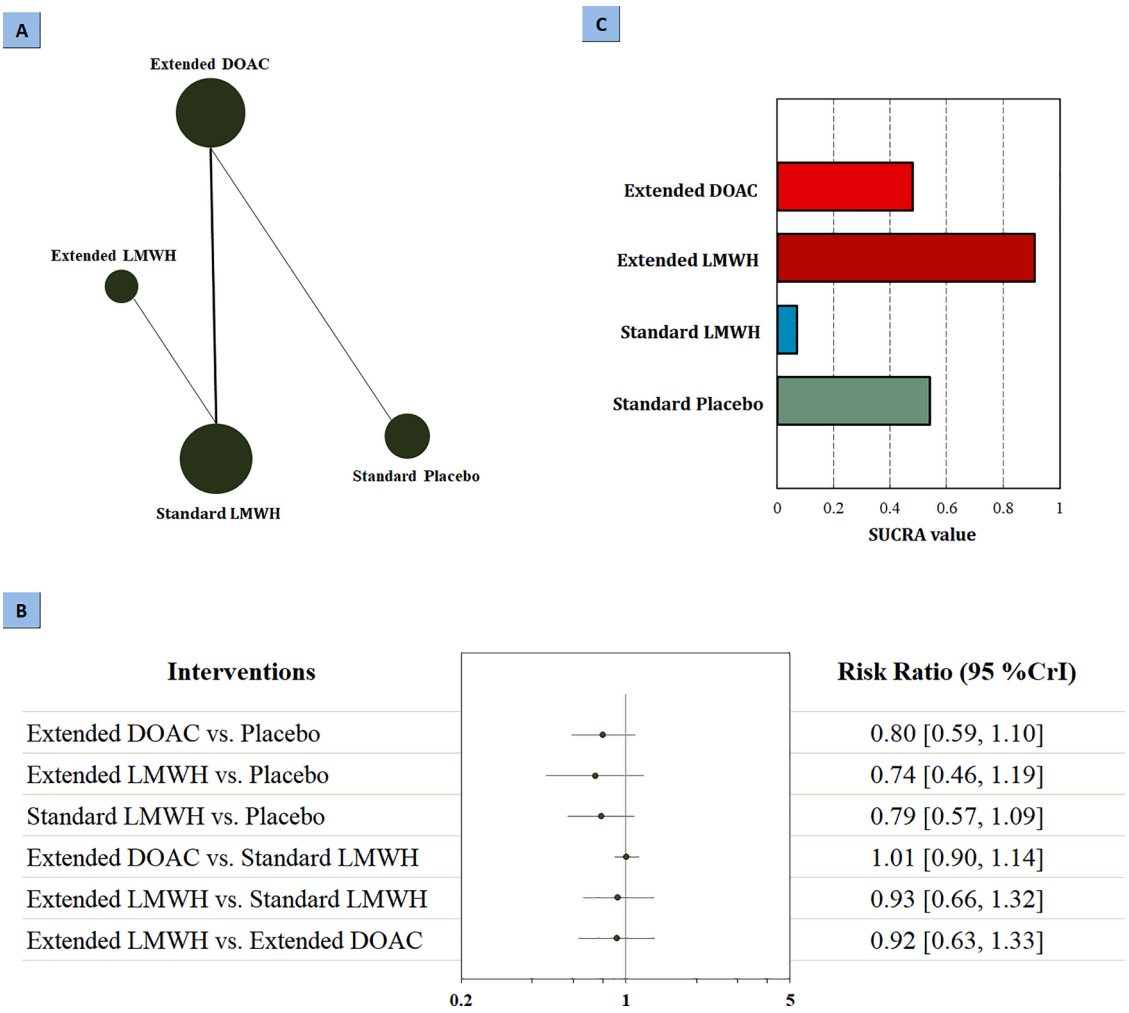

Fig. 5. Summary of the all-cause mortality outcome. A. Network plot of all-cause mortality outcome. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. B. The forest plot shows the risk ratio (RR) and credible interval (CrI). C. Ranking probabilities graph of each treatment agent. The SUCRA values for each treatment were as follows: 74% for extended thromboprophylaxis with LMWH; 61% for standard thromboprophylaxis with LMWH; 58% for extended thromboprophylaxis with DOAC; 9% for standard thromboprophylaxis with placebo. SUCRA: surface under the cumulative ranking curve.

4.2. Study implications

This network meta-analysis of five clinical trials provides detailed information for decision-makers about the benefits and harms of different thromboprophylaxis regimens on important outcomes in acutely ill medical patients. To develop the implications for practice and to determine which thromboprophylaxis regimen is most clinically beneficial, we incorporated the direct and indirect effectiveness derived from randomized clinical trials. Collectively, extended thromboprophylaxis with LMWH (probably large beneficial effect), and extended thromboprophylaxis with DOAC (probably moderate beneficial effect), may be proposed as first-choice treatment regimen due to evidence certainty, the magnitude of effect sizes, SUCRA values, risk/benefit assessment, and net clinical benefit analysis.

Our results provided evidence to support guideline recommendations made by the National Institute for Health and Care Excellence (NICE) that LMWH is the first-line pharmacological prophylaxis for venous thromboprophylaxis if the risk of venous thromboembolism outweighs the risk of bleeding risk of venous thromboembolism [25].

4.3. Strengths and limitations

Our review assessed the efficacy and safety of various thromboprophylaxis regimens in the prevention of venous thromboembolism in acutely ill medical patients. The study aimed to address the currently unanswered question of which pharmacological agent was the most effective for thromboprophylaxis in acutely ill medical patients, especially in stroke patients. Our analysis used robust methods, including Bayesian meta-analysis and rigorous quality assessment by GRADE. The strengths of this study comprise a thorough and systematic review of the literature; the integration of large-scale phase 3 trials, and the successful building of a network to evaluate four treatment regimens. In addition, Bayesian hierarchical modeling was applied, with the incorporation of both direct and indirect evidence. We also used the SUCRA method to rank the treatment agents in different outcomes. Moreover, we determined the most effective interventions in a subgroup of patients with stroke. To provide clearer evidence of the benefit-risk assessment, we used several approaches, including the integration of net clinical benefits, implementation of cluster ranking plot, calculation of NNT and NNH of different treatment pairs, and construction of meta-regression analysis. These analyses provide more precise guidance to clinicians on drug selection.

Our study had several limitations. First, studies included in our analysis varied in their definition of venous thromboembolism. For example, in the MARINER trial, researchers only reported symptomatic venous thromboembolism, whereas the other four trials reported both

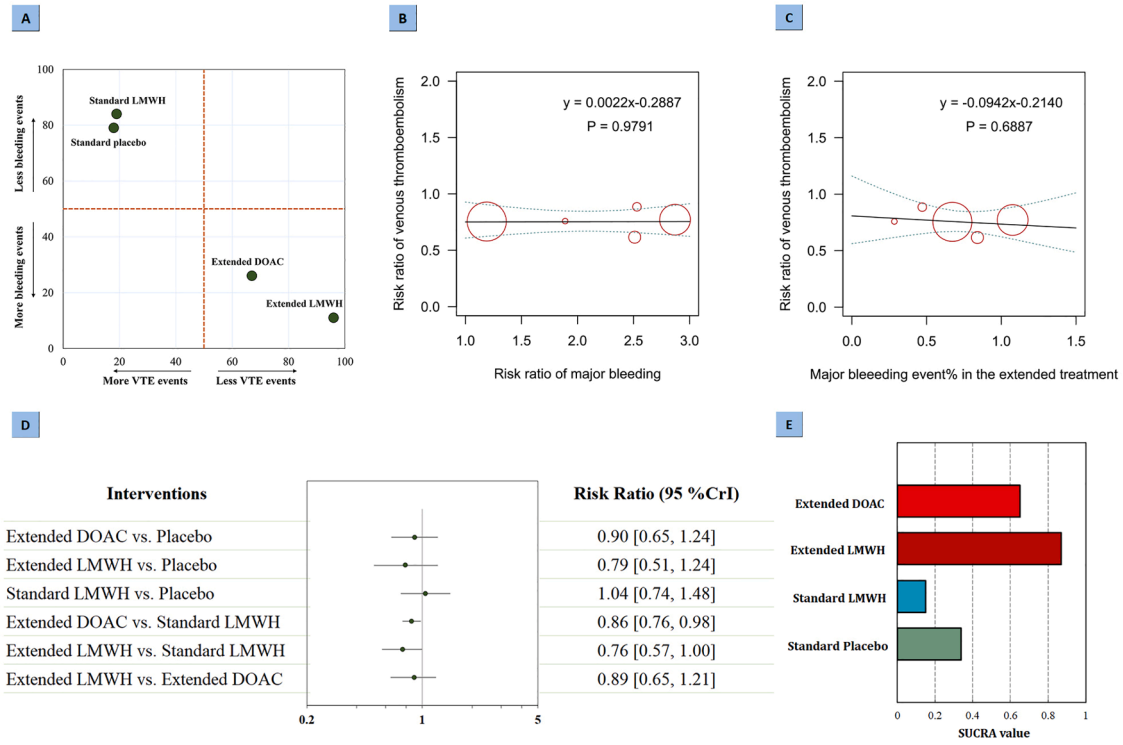

Fig. 6. Summary of the benefit-risk assessment. A. A cluster ranking plot showing SUCRA values for the outcome of preventing venous thromboembolism events versus the risk of bleeding events. The right higher quadrant represents the highest benefit of venous thromboembolism with minimal risk of bleeding. Each symbol represents a group of treatments. B-C. Meta-regression analysis for the interaction of risk ratio of major bleeding (B) and proportion of major bleeding event in the extended venous thromboprophylaxis (C) on the risk of venous thromboembolism. D. Network plot of net clinical benefit of different comparisons. E. Ranking probabilities graph of each treatment agent. The SUCRA values for each treatment were as follows: 87% for extended thromboprophylaxis with LMWH; 65% for extended thromboprophylaxis with DOAC; 34% for standard thromboprophylaxis with placebo; 15% for standard thromboprophylaxis with LMWH. SUCRA: surface under the cumulative ranking curve.

Table 2
Risk/benefit assessment for clinical outcomes in the meta-analysis.

Benefit (venous thromboprophylaxis)	Treatment A	Treatment B	ARR by extended LMWH	95% CI	NNT	95% CI
Extended LMWH over extended DOAC	0.0429	0.0545	0.0120	0.0055–0.0186	83	54–182
Extended LMWH over standard LMWH	0.0245	0.0398	0.0153	0.0052–0.0255	65	39–192
Harm (major bleeding)	Treatment A	Treatment B	ARI by extended LMWH	95% CI	NNH	95% CI
Extended LMWH over extended DOAC	0.0044	0.0028	0.0016	0.0001–0.0032	625	313–10,000
Extended LMWH over standard LMWH	0.0084	0.0033	0.0051	0.0009–0.0095	196	105–1111
Risk/benefit estimate		NNH/NNT				
Extended LMWH over extended DOAC		7.36				
Extended LMWH over standard LMWH		3.05				

ARR: absolute risk reduction; ARI: absolute risk increase; NNT: Number-needed to treat; NNH: Number-needed to harm; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; CI: confidence interval.

symptomatic and detected venous thromboembolism events without physical manifestations. However, given the minimal observed statistical heterogeneity, these variabilities may not have an important impact on our findings.

Second, extended thromboprophylaxis included several treatment regimens such as apixaban, betrixaban, enoxaparin, and rivaroxaban. Nevertheless, we felt it inappropriate to analyze the specific regimen in detail because they lack precision due to limited studies. To demonstrate exactly which pharmacological agents with extended timing is preferable, more RCTs are warranted.

5. Conclusion

These analyses from the 5 pivotal trials in patients with acute medical illness show that extended thromboprophylaxis with LMWH and DOAC decrease the risk of venous thromboembolism and that LMWH has comparatively higher efficacy than DOAC at the prolonged duration of thromboprophylaxis. However, all of the treatment options increase the risk of bleeding. Further analyses show that the benefits of the extended duration of thromboprophylaxis in reducing venous thromboembolism, particularly with LMWH treatment, outweigh the bleeding risk that may occur. Overall, extended thromboprophylaxis is associated with a positive net clinical benefit. These estimates were mainly based on evidence of moderate certainty and therefore can inform decision-making. Our analysis also demonstrated that LMWH with extended duration was consistently superior to standard duration in the prevention of venous thromboembolism for stroke patients. These data reinforce and provide more granular detail describing the beneficial effects of extended thromboprophylaxis in a broad population of patients. Our findings could inform policy on which anticoagulant types and timing

are most effective in the prevention of venous thromboembolism in acutely ill medical patients generally and stroke patients especially.

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Data availability statement

All datasets presented in this study are included in the article.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.03.032.

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