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Letter to the Editors-in-Chief

Extended vs. standard-duration thromboprophylaxis in acutely ill medical patients: A systematic review and meta-analysis

Venous thromboembolism (VTE) is the leading preventable cause of death in hospitalized patients. The risk of developing VTE remains elevated for up to 90 days after hospitalization [1]. Several randomized controlled trials (RCTs) comparing in-hospital and extended-duration thromboprophylaxis, either with LMWH or direct oral anticoagulants (DOACs), have been conducted. However, the benefits and risks of extended-duration thromboprophylaxis remain unclear.

We conducted a systematic review and meta-analysis to evaluate the benefits and risks of extended versus standard-duration pharmacologic thromboprophylaxis.

We searched PubMed, EMBASE, the Cochrane Library Databases, and Clinicaltrials.gov from inception to October 26, 2018. The search queries are presented in the supplemental data (Appendix 1). Reference lists of relevant studies and review articles were screened for potentially eligible studies.

Two authors (T.C. and C.R.E.) independently searched the literature, screened titles and abstracts, reviewed full texts to identify eligible studies, extracted data and appraised the methodological quality in duplicate. Disagreements were resolved by consensus or a third reviewer (A.C.).

Eligible studies were RCTs of adults hospitalized with acute medical illness in which extended-duration thromboprophylaxis (28–45 days) was compared with standard-duration thromboprophylaxis (≤14 days). Studies were required to report the rate of symptomatic VTE (confirmed by standard diagnostic tests), VTE-related death, and major bleeding in both groups. Studies were excluded if non-medical patients were enrolled. The primary efficacy outcome was the composite of symptomatic VTE and VTE-related death. The primary safety outcome was International Society on Thrombosis and Haemostasis (ISTH) major bleeding. The revised Cochrane risk-of-bias tool for randomized trials version 2 was used for quality appraisal. The study protocol is registered on PROSPERO (CRD42019130748).

Data analysis was performed using Review Manager 5.3. Pooled risk ratio (RRs) and 95% confidence intervals (CIs) were calculated using the random-effects model. Inter-study heterogeneity was evaluated using the I^2 statistic. Absolute risk reduction/increase (ARR/ARI) and number needed to treat/harm (NNT/NNH) were calculated. Funnel plots of odds ratio versus standard error were used to assess for the presence of publication bias.

The PRISMA flow diagram is shown in Fig. S1. A total of 577 records were retrieved. After screening by title and abstract, 495 records were excluded. The remaining 82 references underwent full-text review, 5 of which met eligibility criteria and were included in the analysis. These studies (EXCLAIM, ADOPT, MAGELLAN, APEX, and MARINER [2–6]) collectively enrolled 20,046 patients in the intervention (extended-duration) group and 20,078 patients in the control (standard-duration) group. There was excellent agreement between the two independent reviewers with respect to study selection ($\kappa = 1$).

The characteristics of included studies are summarized in Table 1 and Tables S1–S2. All studies were multicenter, placebo-controlled, double-blinded, randomized controlled trials. The list of inclusion and exclusion criteria is provided in Table S1.

A composite of asymptomatic or symptomatic VTE and VTE-related death during the active treatment period served as the primary efficacy outcome in all studies except MARINER, in which the primary efficacy outcome was restricted to symptomatic VTE and VTE-related death (Table S1). In all studies except MARINER, screening compression ultrasonography to detect asymptomatic DVT was undertaken at certain time point (varying from day 5 to day 42 after randomization). Efficacy outcomes were analyzed in the modified intention-to-treat population. In these studies, 16–32% of patients randomized to each treatment group were excluded from the analysis due to lack of or inadequate ultrasonographic assessment for asymptomatic VTE. In MARINER, all randomized patients were included in the intention-to-treat analysis.

In the four most recent studies, major bleeding was defined according to ISTH criteria. In EXCLAIM, the definition of major bleeding was more restrictive, requiring a decrease in hemoglobin level of ≥3 g/dL. However, a threshold decrease of 2 g/dL was used in a post-hoc analysis. In our meta-analysis, the results from the post-hoc analysis were used.

For quality appraisal, all five studies were assessed to have low risk of bias across all five domains (Table S3).

Results from individual studies are listed in Table S4. The summary of primary and efficacy outcomes is listed in Table S5.

Compared to standard-duration prophylaxis, extended-duration prophylaxis significantly decreased the risk of symptomatic VTE or VTE-related death (RR 0.62; 95%CI, 0.46–0.83, $I^2 = 45\%$, ARR = 0.4%, NNT = 250) (Fig. 1A) and symptomatic VTE (RR = 0.52; 95% CI, 0.36–0.76, $I^2 = 38\%$), but not VTE-related death (RR = 0.80; 95% CI, 0.60–1.09, $I^2 = 0\%$) (Fig. S1A-B). Among symptomatic VTE events, extended-duration prophylaxis was associated with a significant reduction in symptomatic DVT and symptomatic non-fatal PE (Fig. S1C-D).

Among EXCLAIM, ADOPT, MAGELLAN and APEX, extended-duration prophylaxis significantly decreased the risk of total VTE (asymptomatic or symptomatic) or VTE-related death (Fig. S1E).

Extended-duration prophylaxis significantly increased the risk of

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Table 1
Characteristics of included studies.

	EXCLAIM 2010	ADOPT 2011	MAGELLAN 2013	APEX 2016	MARINER 2018
Setting	International, multicenter	International, multicenter	International, multicenter	International, multicenter	International, multicenter
Study design	RCT	RCT	RCT	RCT	RCT
Intervention	Enoxaparin 40 mg once daily for 10 ± 4 days then enoxaparin 40 mg once daily for an additional 28 ± 4 days	Apixaban 2.5 mg twice daily for 30 days	Rivaroxaban 10 mg once daily for 35 ± 4 days	Betrixaban 80 mg once daily for 35–42 days (loading dose of 160 mg)[a]	Rivaroxaban 10 mg once daily for 45 days
Control	Enoxaparin 40 mg once daily for 10 ± 4 days then placebo for an additional 28 ± 4 days	Enoxaparin 40 mg once daily during hospitalization and for a minimum of 6 days	Enoxaparin 40 mg once daily for 10 ± 4 days	Enoxaparin 40 mg once daily for 10 ± 4 days	Placebo for 45 days
Screening compression ultrasound (Day after randomization)	Day 28 ± 4	Between Day 5 and Day 14	Day 35 ± 4	Day 35 to 42	Not required
Number of participants (intervention/control)	2975/2988	3255/3273	4050/4051	3759/3754	6007/6012
Mean age, years (intervention/control)	67.9/67.5	66.8/66.7	71/71 (median)	76.7/76.2	69.7/69.7
Heart failure, % (intervention/control)	18.4/18.9	39.0/38.1	32.3/32.4	44.6/44.5	40.6/39.9
Respiratory failure, % (intervention/control)	30.4/30.1	37.1/37.1	27.3/28.7	11.9/12.6	26.2/26.8
Infection, % (intervention/control)	32.8/33.6	21.5/22.8	45.8/45.1	29.6/28.2	17.5/17.4
Percentage of participants excluded due to missing outcome data (intervention/control)	16/16	32/30	25/22	16/15	All randomized patients were analyzed
Follow up duration	180 days	90 days	35 days	42 days	45 days

RCT, randomized controlled trial.
[a] Reduced-dose betrixaban (40 mg) for patients with severe renal insufficiency or receiving concomitant P-glycoprotein inhibitor.

major bleeding (RR = 2.04; 95%CI, 1.42–2.91, I^2 = 23%, ARI = 0.3%, NNT = 333) (Fig. 1B). Among the ISTH criteria for major bleeding, extended-duration prophylaxis significantly increased the risk of bleeding leading to fall in hemoglobin of ≥2 g/dL and bleeding leading to transfusion of ≥2 units of blood. There was no significant difference between extended-duration and standard-duration prophylaxis with respect to fatal bleeding or critical-site bleeding (Fig. S2A-D).

There was no significant difference in the rate of all-cause mortality (RR = 0.97; 95% CI, 0.87–1.08, I^2 = 0%, ARR 0.1%, NNT = 935) (Fig. 1C).

Extended-duration prophylaxis significantly decreased the risk of symptomatic non-fatal PE or VTE-related death (Fig. S1F). There was no significant difference in fatal or critical site bleeding (Fig. S2E).

All funnel plots were symmetrical (Fig. S4), suggesting absence of publication bias.

When only the four studies [2–5] that required screening compression ultrasonography to detect asymptomatic DVT were analyzed, extended-duration prophylaxis was associated with a significant reduction in risk of symptomatic VTE or VTE-related death (RR = 0.55, 95%CI, 0.37–0.83, I^2 = 52%) and a significantly increased risk of major bleeding (RR = 2.09, 95%CI, 1.33–3.27, I^2 = 42%). These results are comparable to findings in MARINER.

Our results confirm those of a recently published meta-analysis by Bajaj et al. [7]. We also sought to extend their findings by breaking down efficacy and safety outcomes into their component parts and by focusing on the most patient-important outcomes. For example, major bleeding events in the included studies consisted primarily of bleeding that led to a hemoglobin fall of ≥2 g/dL or transfusion of ≥2 units. Although important, these events rarely lead to significant morbidity or mortality. To further evaluate the benefit:risk ratio of extended-duration prophylaxis, we analyzed the composite of symptomatic non-fatal PE and VTE-related death compared to the composite of fatal and critical-site bleeding. Extended prophylaxis decreased the risk of symptomatic non-fatal PE or VTE-related death (ARR 0.25%, NNT = 403). Conversely, the ARI of fatal or critical-site bleeding was 0.056% (NNH = 1785). These findings suggest that, when the most patient-important outcomes are considered, the benefit:risk ratio of extended-duration prophylaxis may be more favorable.

Despite strategies to enrich the study populations with patients at increased risk of VTE, the relatively low incidence of the primary outcome in the included studies may underestimate the potential benefits of extended thromboprophylaxis. These observations emphasize the potential for more selective risk stratification strategies to identify patient subgroups at highest VTE risk in order to optimize the benefits of extended-duration prophylaxis in medical patients.

Our study has several limitations. Firstly, four studies used a modified intention-to-treat analysis, which involved post-randomization exclusion of a considerable proportion of participants due to missing or inadequate outcome data. Although this strategy could have introduced bias, the number of excluded participants was balanced between the extended and standard-duration thromboprophylaxis groups in these studies, suggesting that the results were unlikely to be affected. Secondly, patients in all studies were highly selected based on age, medical conditions, and baseline risk of VTE, making broad comparisons across the general medical population difficult. Thirdly, the use of screening compression ultrasonography to detect asymptomatic DVT in four of the five trials may have led to initiation of therapeutic-intensity anticoagulation, thus altering the natural history of symptomatic VTE. This could have decreased the rate of symptomatic VTE and VTE-related death while magnifying the incidence of major bleeding. Reassuringly, a sensitivity analysis showed that the results in these four trials were similar to those of the overall analysis as well as those of MARINER.

The close balance between benefits and harms with extended-duration thromboprophylaxis highlights the need for an individualized

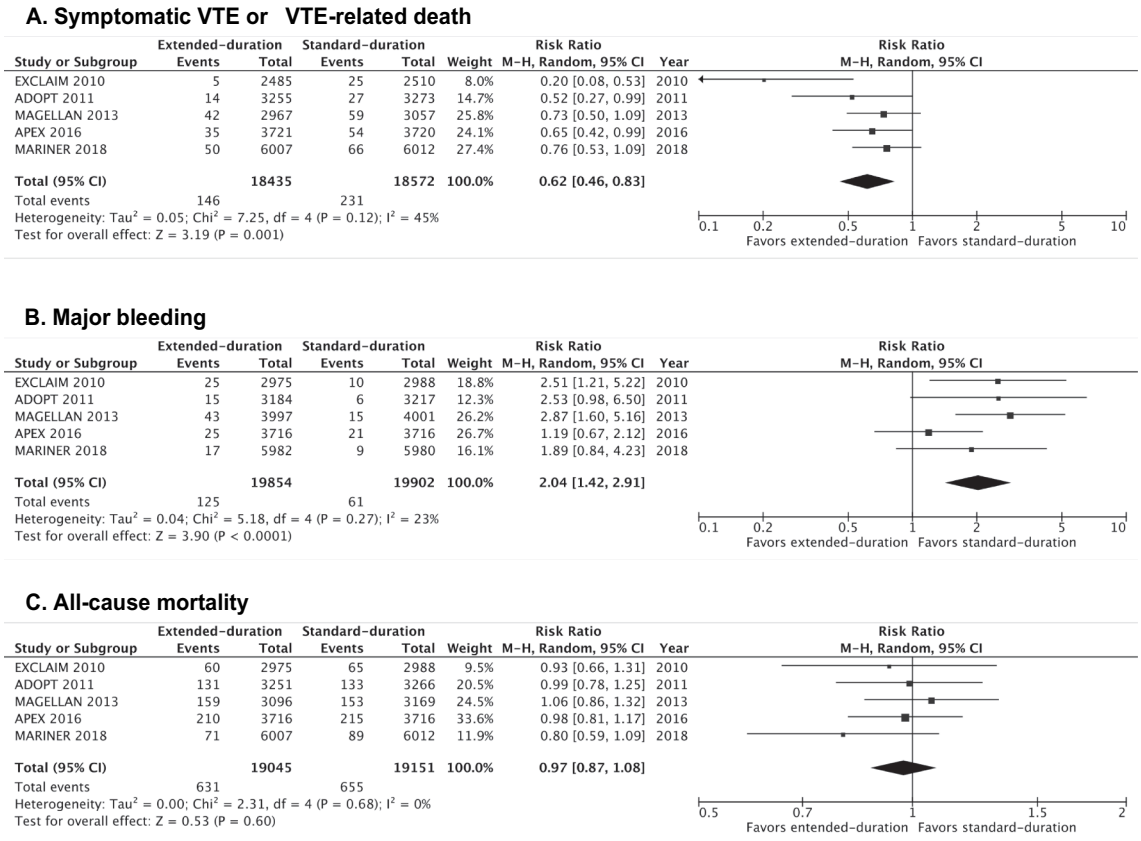

Fig. 1. Forest plot showing pooled risk ratio of (A) symptomatic VTE or VTE-related death, (B) major bleeding, and (c) all-cause mortality in patients receiving extended-duration versus standard-duration thromboprophylaxis. VTE, venous thromboembolism; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

approach to management. Whereas the American Society of Hematology clinical practice guidelines [10] recommend against the routine use of extended-duration thromboprophylaxis, our results suggest that a more nuanced approach may be appropriate that incorporates individualized assessment of thrombotic and bleeding risk, patient values and preferences, and cost considerations.

In summary, in acutely ill medical patients, extended-duration thromboprophylaxis is associated with approximately a 40% reduction in symptomatic VTE and VTE-related death and a two-fold increase in major bleeding compared with standard-duration thromboprophylaxis with no effect on overall mortality, highlighting the need for an individualized approach to management.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.10.027.

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