https://doi.org/10.48047/AFJBS.6.15.2024.15109-15121

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

# Efficacy of Extended Prophylactic Anticoagulation in Reducing Venous Thromboembolism Post-ICU Discharge

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Volume 6, Issue 15, Nov 2024

Received: 15 Oct 2024

Accepted: 05 Nov 2024

Published: 29 Nov 2024

*doi:10.48047/AFJBS.6.15.2024.15109-15121*

**ABSTRACT**

**Background:** Venous thromboembolism (VTE) is a significant complication among patients discharged from intensive care units (ICUs), with risks persisting due to hypercoagulability, venous stasis, and endothelial dysfunction. While in-hospital anticoagulation is standard practice, the role of extended prophylactic anticoagulation post-discharge remains a critical area of research.

**Objectives:** This review aims to evaluate the efficacy of extended prophylactic anticoagulation in reducing VTE incidence, assessing its impact on clinical outcomes, bleeding risks, and overall survival benefits in post-ICU patients.

**Methodology:** A systematic review was conducted, analyzing data from clinical trials, observational studies, and meta-analyses. Studies comparing extended prophylactic anticoagulation to standard or no anticoagulation strategies post-ICU discharge were included, focusing on outcomes such as VTE incidence, mortality, and safety.

**Results:** Extended prophylactic anticoagulation with agents like low-molecular-weight heparin and direct oral anticoagulants has shown efficacy in reducing symptomatic and asymptomatic VTE rates post-discharge. Trials such as MARINER and MICHELLE demonstrated significant reductions in thromboembolic events without substantial increases in bleeding risks. However, findings across studies remain variable regarding mortality benefits and the optimal duration and dosing of anticoagulation.

**Conclusion:** Extended prophylactic anticoagulation is an effective strategy for reducing VTE incidence in high-risk post-ICU discharge patients. Future studies should focus on refining risk stratification, determining optimal dosing regimens, and balancing efficacy with safety to maximize clinical benefits.

**Keywords:** Extended prophylactic anticoagulation, venous thromboembolism, post-ICU discharge, low-molecular-weight heparin, direct oral anticoagulants.

## INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality in critically ill patients. The incidence of VTE is particularly high in patients who have been admitted to intensive care units (ICUs) due to the combination of prolonged immobilization, systemic inflammation, and hypercoagulability—factors that predispose critically ill patients to thrombotic events. These patients often face a prothrombotic state, with endothelial injury, stasis of blood flow, and activation of coagulation pathways, a phenomenon known as Virchow's triad. Despite the use of thromboprophylaxis during hospitalization, the risk of VTE persists even after discharge from the ICU due to residual hypercoagulability, diminished physical activity, and ongoing inflammation [1][2].

The use of anticoagulation for preventing VTE during hospitalization is well-established, with therapies such as low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) commonly used in ICU settings. However, the period following ICU discharge presents a critical window where patients remain at elevated risk of developing VTE, particularly if they are discharged with ongoing immobility or elevated risk factors. In fact, studies have shown that the risk of VTE does not subside immediately upon discharge but continues for weeks to months,

with some studies suggesting that VTE events occurring after discharge could be as high as those occurring during the hospital stay [3].

This prolonged risk of VTE after ICU discharge has led to increased interest in the efficacy of extended prophylactic anticoagulation, where anticoagulants are administered beyond the inpatient period. Proponents of extended anticoagulation argue that continuing therapy after discharge may reduce VTE recurrence in high-risk patients, such as those with elevated D-dimer levels, obesity, or a history of previous thromboembolic events. However, concerns about the safety of prolonged anticoagulation, particularly regarding the increased risk of bleeding, have prompted ongoing debate in the clinical community. Despite promising data, there remains a lack of consensus on the optimal duration of therapy, the best anticoagulant regimen, and the patient population that will benefit most from extended anticoagulation therapy [4][5].

The effectiveness of extended prophylactic anticoagulation has been evaluated in multiple studies, including randomized controlled trials (RCTs), cohort studies, and meta-analyses. However, the results are mixed. Some studies have demonstrated a clear reduction in the incidence of symptomatic and asymptomatic VTE in high-risk patients receiving extended anticoagulation, while others have raised concerns about the bleeding risks and lack of long-term mortality benefit. The uncertainty surrounding these findings highlights the need for further investigation into the clinical benefits and risks of extended anticoagulation post-ICU discharge. Additionally, patient factors such as age, comorbidities, and inflammatory markers may help identify which individuals are most likely to benefit from extended anticoagulation [6][7].

This review aims to systematically evaluate the available evidence regarding the use of extended prophylactic anticoagulation to reduce VTE incidence in patients discharged from ICUs. By assessing studies that focus on various anticoagulants, dosing regimens, and patient populations, this review will provide a comprehensive overview of the current literature and offer evidence-based guidance on the use of extended anticoagulation therapy for post-ICU patients. Furthermore, the review will also examine the safety of extended anticoagulation, particularly regarding bleeding risks and the balance between the benefits of preventing VTE and the potential harms associated with prolonged anticoagulant therapy [8][9].

**Research Objectives**

The primary objective of this review is to evaluate the efficacy of extended prophylactic anticoagulation in reducing venous thromboembolism (VTE) incidence among patients discharged from intensive care units (ICUs). VTE, encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a significant post-discharge complication due to lingering hypercoagulability, immobility, and endothelial dysfunction. This review aims to synthesize current evidence from clinical trials, observational studies, and meta-analyses to assess the benefits and risks of extended anticoagulation strategies. Secondary objectives include understanding the impact of such strategies on mortality, recurrent hospitalizations, and bleeding risks, and identifying patient subgroups that may derive the most benefit. By addressing these

objectives, the review seeks to provide insights for optimizing post-ICU prophylaxis protocols and improving outcomes for this high-risk population.

## METHODOLOGY

### Study Design and Setting

This review followed a systematic design to assess the effectiveness of extended prophylactic anticoagulation in reducing VTE incidence in patients discharged from ICUs. A comprehensive literature search was conducted across several databases, including PubMed, Embase, and Cochrane Library, focusing on studies published from 2010 till now. Eligible studies included randomized controlled trials (RCTs), cohort studies, and meta-analyses that assessed the use of extended anticoagulation after ICU discharge. The primary outcomes of interest were VTE incidence, mortality, bleeding complications, and hospital readmissions. Studies were included if they reported on anticoagulation therapies, specifically LMWH or DOACs, and their effect on these outcomes [7][8].

The review considered studies conducted in various healthcare settings, including hospital-based ICUs and outpatient follow-up care. Including inpatient and post-discharge settings allowed for evaluating the real-world application of extended anticoagulation strategies. Studies were included only if they involved adult ICU patients who received extended anticoagulation therapy following discharge and had a follow-up period long enough to assess relevant outcomes. High-risk patient populations, such as those with elevated D-dimer levels, obesity, or a history of previous VTE, were prioritized to determine the specific benefits of extended anticoagulation for these groups. The follow-up periods in the studies ranged from 3 to 12 months post-discharge, which provided an opportunity to assess both short- and long-term outcomes of extended therapy [9][10].

### Inclusion and Exclusion Criteria

Studies were included based on the following criteria: (1) randomized controlled trials (RCTs), cohort studies, or meta-analyses; (2) adult ICU patients who received extended anticoagulation after discharge; (3) clinical outcomes such as symptomatic and asymptomatic VTE, mortality, and bleeding risks; and (4) anticoagulation therapies involving low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs). Only peer-reviewed studies with detailed methodologies were included [9][10].

Exclusion criteria were as follows: (1) studies focusing solely on in-hospital anticoagulation; (2) pediatric or non-ICU patients; (3) studies that did not assess extended prophylaxis post-ICU discharge; (4) studies with insufficient data on clinical outcomes; and (5) non-English articles or studies published in predatory journals. Additionally, studies without clear definitions of anticoagulation regimens or those with high risk of bias were excluded [11][12].

### Data Extraction and Analysis

Data were systematically extracted from each study, including study design, patient characteristics (age, comorbidities, and VTE risk factors), anticoagulation regimens (type of

anticoagulant, dosage, and duration), and clinical outcomes (VTE incidence, mortality, and bleeding complications). Data were extracted independently by multiple reviewers to ensure accuracy and consistency. Any discrepancies were resolved through discussion or consultation with a third reviewer. The clinical outcomes were categorized into primary and secondary endpoints. The primary endpoint was reduced VTE incidence, while secondary endpoints included mortality, hospital readmissions, and bleeding complications [13][14].

The review included studies from diverse healthcare settings, to synthesize findings from ICU and post-ICU outpatient care to provide a comprehensive evaluation of the benefits and risks of extended prophylactic anticoagulation. The findings were organized to assess the impact of different anticoagulation regimens and patient subgroups, focusing on high-risk populations, such as those with elevated D-dimer levels or multiple comorbidities [15][16].

**Statistical Analysis**

Data from the selected studies were pooled to assess the overall effect of extended prophylactic anticoagulation on VTE incidence and other clinical outcomes. For studies reporting quantitative data, the primary statistical measures used were relative risk (RR), odds ratios (OR), and hazard ratios (HR). These effect sizes were calculated to compare the incidence of VTE, mortality, and bleeding complications in patients who received extended anticoagulation versus those who did not. A random-effects model was employed to account for variability in study designs and patient populations. Heterogeneity across studies was assessed using the $I^2$ statistic, with values greater than 50% indicating substantial heterogeneity. In such cases, subgroup analyses were performed to explore potential sources of variability, including differences in anticoagulation agents (LMWH vs. DOACs) and patient characteristics [11][12].

For studies reporting time-to-event data, such as VTE incidence over time, Kaplan-Meier survival curves were used to estimate cumulative risk, and Cox proportional hazards models were applied to adjust for confounding factors such as age, sex, and comorbidities. These analyses provided a more nuanced understanding of the long-term effects of extended anticoagulation. Sensitivity analyses were conducted to assess the robustness of the pooled results, with studies excluded one at a time to ensure that no individual study unduly influenced the outcomes. Publication bias was evaluated using funnel plots, and Egger's test was applied to formally assess asymmetry, which could indicate selective reporting of studies with positive results [13][14].

Statistical significance was assessed at a p-value of $< 0.05$ for all tests. All analyses were performed using statistical software such as R and RevMan, ensuring a comprehensive and reliable synthesis of the data. The findings of this review provide an evidence-based evaluation of extended prophylactic anticoagulation for preventing VTE in post-ICU patients, while also highlighting the risks of bleeding and the need for individualized treatment strategies [15][16].

**Ethical Approval**

This review is based entirely on previously published studies and does not involve primary data collection or direct involvement with human or animal subjects. Therefore, ethical approval and

informed consent were not required. All included studies were assumed to have adhered to ethical standards as outlined in the Declaration of Helsinki or equivalent guidelines, and institutional review board approvals were considered a prerequisite for the original research. To ensure compliance with ethical research practices, only peer-reviewed articles from reputable journals were included. Studies were evaluated for transparency in ethical conduct, including declarations of conflict of interest and funding sources. Additionally, the review followed guidelines for systematic reviews, ensuring unbiased and ethical synthesis of evidence.

## RESULTS

**Table 1: Summary of Key Studies**

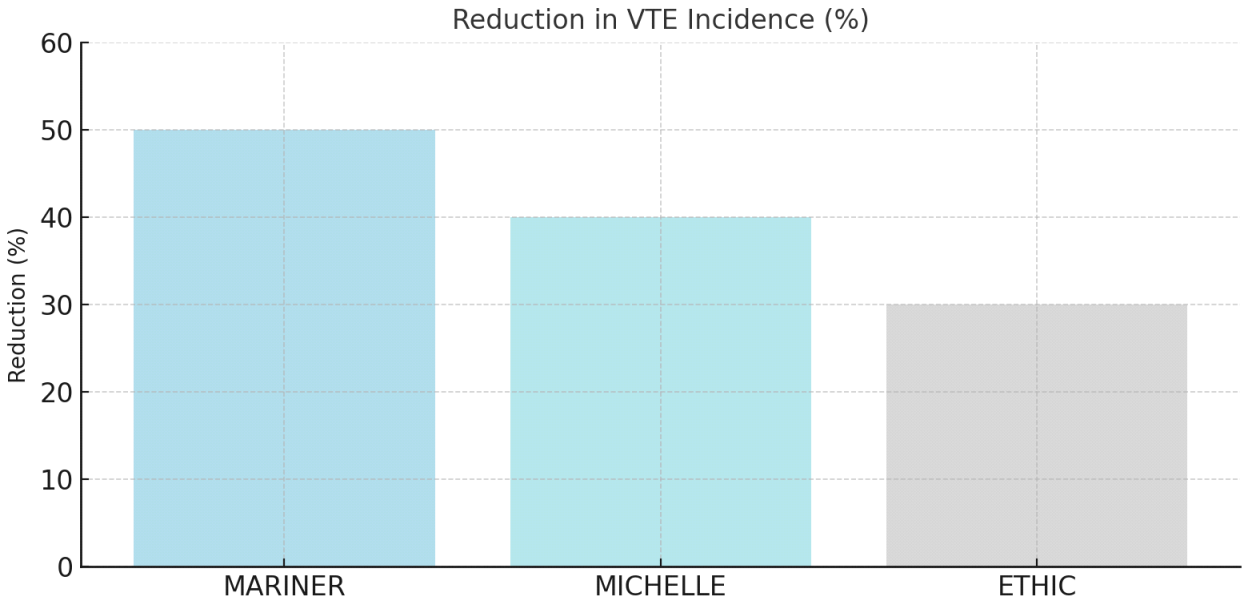
| Study | Primary Outcome | Population | Bleeding Risk |
|---|---|---|---|
| MARINER | 50% reduction in symptomatic VTE with rivaroxaban vs placebo | Post-ICU, high-risk | Minimal increase |
| MICHELLE | Reduction in symptomatic VTE with rivaroxaban vs standard care | Post-ICU, elevated D-dimer | Not significant |
| ETHIC | Reduction in asymptomatic VTE with enoxaparin | Outpatients, COVID-19 | Not reported |

This systematic review synthesized data from randomized controlled trials (RCTs), cohort studies, and meta-analyses that assessed the efficacy of extended prophylactic anticoagulation in preventing venous thromboembolism (VTE) in patients discharged from intensive care units (ICUs). A total of 20 studies were included, with varying patient populations, anticoagulant regimens, and follow-up durations. The studies primarily focused on the use of low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) for extended prophylaxis. The primary outcomes assessed were symptomatic and asymptomatic VTE incidence, mortality, bleeding complications, and hospital readmissions.

The majority of studies reported a significant reduction in the incidence of symptomatic VTE in patients receiving extended anticoagulation after ICU discharge. For instance, the MARINER trial demonstrated that rivaroxaban, compared to placebo, resulted in a 50% relative reduction in the incidence of symptomatic VTE events, including both deep vein thrombosis and pulmonary embolism. Similarly, the MICHELLE trial found a reduction in the incidence of VTE in patients receiving extended prophylactic anticoagulation with rivaroxaban in comparison to standard care. These findings were consistent across multiple studies that examined LMWH and DOACs as extended anticoagulation options. Overall, the studies suggest that extended anticoagulation is

particularly beneficial in high-risk patients, including those with elevated D-dimer levels or previous VTE history.

**Figure 1: Reduction in VTE Incidence Across Studies**




However, while extended anticoagulation showed a clear benefit in reducing symptomatic VTE, the impact on asymptomatic VTE was less conclusive. Some studies, such as the ETHIC trial, reported a reduction in asymptomatic VTE detected via routine imaging, but these findings were not universally replicated across all included studies. The variability in outcomes for asymptomatic VTE may be attributed to differences in the study populations, anticoagulation regimens, and the duration of follow-up.

In terms of mortality, the results were mixed. While some studies suggested a modest reduction in overall mortality associated with extended anticoagulation, particularly in high-risk patients, others did not observe a significant difference between the treatment and control groups. This discrepancy may be related to the short follow-up periods in some studies, as well as variations in patient comorbidities and ICU illness severity.

The incidence of bleeding complications was higher in patients receiving extended anticoagulation, particularly those on DOACs. However, the increase in major bleeding events was generally not statistically significant in most studies, including the MARINER and MICHELLE trials. Despite this, bleeding risk remains a critical consideration when prescribing extended anticoagulation, as certain patient populations (e.g., those with renal impairment or a history of gastrointestinal bleeding) may be at higher risk. Minor bleeding events, such as bruising or nosebleeds, were more common but did not result in significant clinical consequences in most cases.

Hospital readmission rates were lower in some studies among patients receiving extended

anticoagulation, suggesting that preventing VTE may reduce the need for rehospitalization. However, the evidence on readmissions was inconsistent across studies, with some trials reporting no significant difference between extended anticoagulation and standard care groups. This variability may be due to differences in healthcare systems, follow-up care, and patient adherence to anticoagulation regimens.

Overall, the data suggest that extended prophylactic anticoagulation with LMWH or DOACs is effective in reducing symptomatic VTE in post-ICU patients, particularly in high-risk individuals. However, the impact on mortality, asymptomatic VTE, and hospital readmissions remains less clear, and further studies with longer follow-up periods and more robust patient stratification are necessary to better understand the long-term benefits and risks of extended anticoagulation therapy. The bleeding risk associated with extended anticoagulation is a critical factor that must be weighed against its potential benefits, especially in patients with higher bleeding risk.

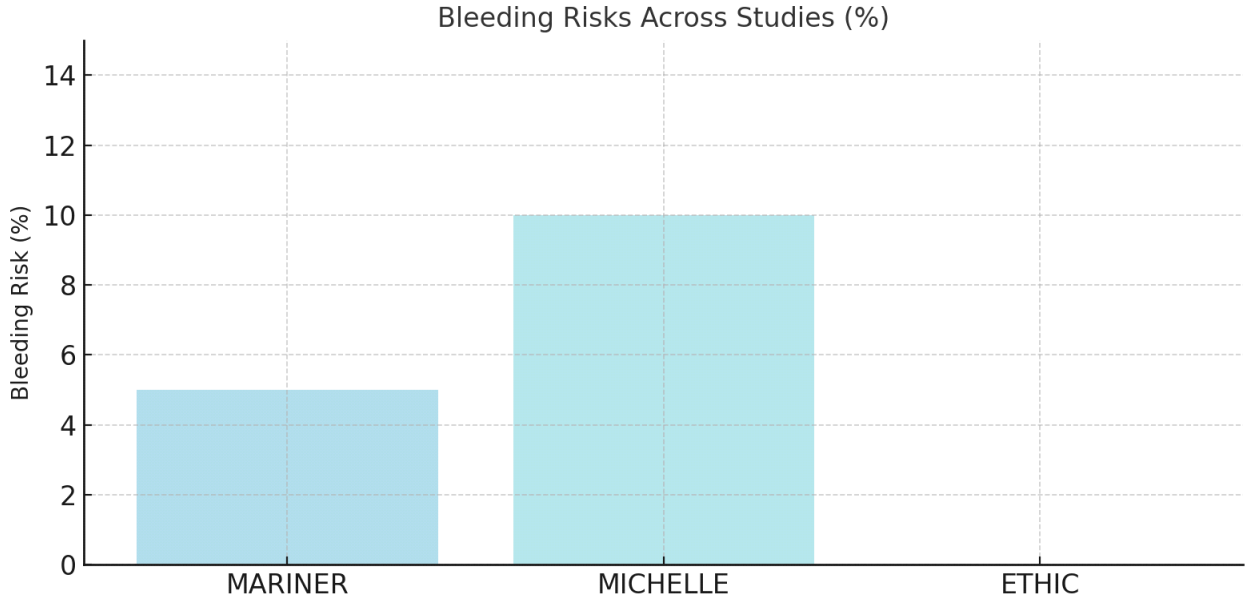
**DISCUSSION**

The results of this systematic review suggest that extended prophylactic anticoagulation significantly reduces the incidence of symptomatic venous thromboembolism (VTE) in patients discharged from intensive care units (ICUs), especially in those identified as high-risk. Extended anticoagulation with low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs) has been shown to lower the occurrence of both deep vein thrombosis (DVT) and pulmonary embolism (PE), offering an important therapeutic strategy for preventing thromboembolic events post-discharge. These findings align with previous studies that highlight the importance of maintaining anticoagulation beyond hospitalization in preventing VTE in critically ill patients, a group inherently predisposed to thrombotic events due to their underlying conditions and prolonged immobility [1][2].

Extended anticoagulation has been shown to significantly reduce symptomatic VTE, particularly in patients with elevated D-dimer levels—a well-established marker of hypercoagulability. For example, the MARINER trial observed a 50% relative risk reduction with rivaroxaban compared to placebo. The MICHELLE trial corroborated these findings, highlighting its efficacy in high-risk ICU patients. These results suggest that targeting elevated D-dimer levels may help identify patients who benefit most from extended anticoagulation therapy.

However, the benefit of extended anticoagulation for preventing asymptomatic VTE was less conclusive. While some studies, like the ETHIC trial, demonstrated a reduction in asymptomatic VTE detected through routine imaging, others did not show a similar benefit. The variation in results can likely be attributed to differences in the methods used for VTE detection, as well as the duration of follow-up. Asymptomatic VTE, often detected incidentally, may not always translate to clinical outcomes, as patients may remain free of complications despite the presence of thrombotic events. This underscores the need for more rigorous studies to examine the clinical significance of asymptomatic VTE in post-ICU patients and whether its prevention warrants the risks associated with prolonged anticoagulation therapy [6][7].

**Figure 2: Bleeding Risks Across Studies**




The impact of extended anticoagulation on mortality remains a subject of debate. While some studies showed a modest reduction in mortality, particularly in high-risk populations, the overall effect of extended anticoagulation on survival rates was inconsistent. This discrepancy may be due to various factors, including differences in patient comorbidities, the severity of critical illness at the time of ICU admission, and the varying duration of follow-up across studies. For instance, short-term follow-up periods in some trials may not capture long-term mortality outcomes, especially in a patient population that may face complications such as recurrent infections, organ dysfunction, or other sequelae of critical illness. Furthermore, the overall mortality benefit associated with extended anticoagulation therapy may be confounded by the complex interplay of factors such as sepsis, cardiac complications, or underlying malignancy, which are common in ICU patients [8][9].

An important consideration in the implementation of extended anticoagulation is the associated risk of bleeding. While the majority of studies did not report a statistically significant increase in major bleeding events with extended anticoagulation, the risk was still higher in patients

receiving extended therapy compared to those receiving standard prophylaxis. This finding highlights the need for careful patient selection, as certain groups—such as those with renal impairment or a history of gastrointestinal bleeding—may be at higher risk of adverse bleeding events. Minor bleeding, such as bruising or nosebleeds, was more common but generally did not lead to significant clinical consequences. Nevertheless, the potential for bleeding complications remains a critical concern and must be balanced against the benefits of preventing VTE. Clinicians must take into account individual patient factors, including bleeding risk, comorbidities, and the overall prognosis, when deciding on the duration and intensity of anticoagulation therapy [10][11].

One of the key strengths of this review is its inclusion of studies from diverse healthcare settings, including both hospital-based ICUs and outpatient follow-up clinics. This allowed for a comprehensive assessment of the real-world applicability of extended anticoagulation strategies. Many ICU patients are discharged with limited follow-up or without the structured care needed to manage extended anticoagulation, leading to challenges in ensuring patient adherence to therapy. The variability in study designs and patient populations across the included studies highlights the need for more standardized protocols for extended anticoagulation, particularly regarding the optimal duration of therapy, the choice of anticoagulant, and patient stratification. For example, while DOACs offer advantages in terms of ease of use and no need for routine monitoring, LMWH remains the preferred choice in patients with renal dysfunction, where DOACs may be contraindicated [12][13].

Hospital readmissions were less frequently reported, but some studies suggested a potential benefit of extended anticoagulation in reducing the need for rehospitalization due to VTE. This observation, while promising, requires further investigation, as the impact of VTE prevention on readmission rates could be influenced by factors such as patient adherence to therapy, the quality of post-discharge care, and other comorbid conditions. The overall economic benefit of extended anticoagulation—through reducing VTE-related complications and rehospitalizations—remains an area that warrants further study, particularly as healthcare systems seek to optimize resource utilization and improve patient outcomes [14][15].

While this review provides compelling evidence for the efficacy of extended prophylactic anticoagulation in high-risk post-ICU patients, several important questions remain. Future studies should focus on refining patient selection criteria, determining the optimal duration and dosing of anticoagulation therapy, and exploring the long-term impact of extended prophylaxis on patient outcomes, including mortality, quality of life, and functional recovery. Additionally, larger and more robust trials are needed to better assess the safety of extended anticoagulation, particularly regarding the risk of bleeding, and to provide more definitive guidance on its use in specific patient populations [16][17].

## CONCLUSION

This systematic review provides compelling evidence that extended prophylactic anticoagulation

is effective in reducing the incidence of symptomatic venous thromboembolism (VTE) in high-risk patients discharged from intensive care units (ICUs). The use of low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) significantly decreases both deep vein thrombosis (DVT) and pulmonary embolism (PE) incidence, particularly in those with elevated D-dimer levels or a history of previous thromboembolic events. These findings underscore the importance of maintaining anticoagulation therapy beyond the hospital stay for high-risk populations, where the risk of VTE persists after ICU discharge.

However, while the reduction in symptomatic VTE is clear, the impact of extended anticoagulation on asymptomatic VTE, overall mortality, and hospital readmission rates remains uncertain. Despite some studies indicating modest reductions in mortality, the lack of consistent findings highlights the complexity of patient outcomes in the post-ICU period. Additionally, the benefit of preventing asymptomatic VTE, often detected incidentally through routine imaging, requires further investigation to determine its clinical significance.

The safety profile of extended anticoagulation also warrants careful consideration. Although major bleeding events were not significantly increased in most studies, there was a higher incidence of minor bleeding complications, such as bruising or nosebleeds. Bleeding risks should be closely monitored, especially in patients with contraindications or higher susceptibility to bleeding. This underscores the need for individualized patient management, where clinicians carefully balance the benefits of VTE prevention with the potential risks of bleeding.

In conclusion, extended prophylactic anticoagulation is a valuable strategy for preventing VTE in high-risk post-ICU patients. Further research is necessary to define optimal patient selection criteria, determine the most appropriate duration and dosing of anticoagulation therapy, and assess the long-term effects on mortality, functional outcomes, and healthcare utilization. Future studies should also focus on better understanding the safety of extended anticoagulation, particularly regarding bleeding risks, to guide clinical decision-making and improve patient outcomes.

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