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Integrating nursing and pharmacy expertise for enhanced management of anticoagulation therapy: A comprehensive review

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Abstract
Background: Anticoagulants are critical medications for the prevention and treatment of thrombosis, yet they pose significant risks of morbidity and mortality. Pharmacist-managed anticoagulation has been shown to reduce complications and improve therapeutic outcomes, particularly in outpatient settings. Recent trends in healthcare emphasize the need for collaborative approaches, integrating nursing and pharmacy expertise for effective anticoagulation management.
Methods: This review evaluates existing literature on pharmacist-led inpatient anticoagulation services, focusing on studies comparing these services to traditional physician-managed care. A comprehensive search was conducted across multiple databases, including PubMed and Embase, with keywords related to anticoagulation management.
Results: The analysis of 14 studies indicated that pharmacist-managed anticoagulation protocols (PMAPs) generally outperform standard physician care, with improved patient outcomes such as higher rates of therapeutic International Normalized Ratio (INR) and lower incidence of bleeding events. Notably, studies revealed that patients managed by pharmacists had a significantly reduced risk of supra-therapeutic INR levels and shorter hospital stays. Additionally, pharmacist-led initiatives demonstrated enhanced safety in managing anticoagulation therapy.
Conclusion: Integrating nursing and pharmacy expertise in anticoagulation therapy management leads to better patient outcomes and increased safety. The evidence supports the establishment of pharmacist-led anticoagulation services in inpatient settings, although further randomized controlled trials are necessary to strengthen the findings and address existing limitations in the literature.

Keywords: Anticoagulation, pharmacists, nursing, patient safety, warfarin management

Introduction
Anticoagulants are intricate medicines used for the treatment and prevention of thrombosis, which may also lead to considerable morbidity and death [1]. In the outpatient context, pharmacist-managed anticoagulation has demonstrated a reduction in bleeding and thromboembolic incidents, alongside an enhancement in achieving a therapeutic international normalized ratio (INR) for patients receiving warfarin. The extensive application of anticoagulant therapies in the inpatient environment presents considerable risks to hospitalized individuals. Anticoagulants, such as the novel direct thrombin inhibitors (DTIs), are included on the Institute of Safe Medication Practices' list of high-alert drugs [2, 3].
Over the past ten years, national accrediting organizations in the USA and Canada have integrated anticoagulant safety objectives into their hospital accreditation criteria. For instance, the Joint Commission's National Patient Safety Goal NPSG.03.05.01 specifically targets the reduction of patient harm linked to anticoagulant therapies.

Consequently, a growing number of hospitals have established pharmacist-led inpatient anticoagulation services to enhance the safety and effectiveness of these therapies [4].In 2008, Donovan *et al*. [5] published an evaluation of pharmacist-managed anticoagulation therapies in inpatient settings. Their evaluation explicitly evaluated the effectiveness, cost implications, and community acceptability of pharmacy-managed anticoagulation. The authors determined that the effectiveness results linked to pharmacy-managed anticoagulation (i.e., warfarin and heparin medication) seem to be equivalent to or exceed those of standard care. They emphasize "two significant caveats" to their conclusion: the experimental design in most research was inadequate, and adherence to rules and procedures by pharmacists may account for the perceived advantage in some analyzed studies. This narrative study aims to assess the effectiveness and safety of pharmacist-led inpatient anticoagulation therapy in comparison to standard or physician-managed care.

Methods

Relevant publications were located via a search of the National Center for Biotechnology Information PubMed database, Embase, and International Pharmaceutical Abstracts from 1970 to 2015. Our search criteria included the words “pharmacist” and/or “pharmacy”, “inpatient”, “hospital”, “anticoagulation”, and/or “anticoagulant”, in conjunction with each of the following: “warfarin”, “heparin”, “novel anticoagulants”, “target-specific anticoagulants”, and “nurses”.

Warfarin

Fourteen studies assessed warfarin-based autonomous PMAPs. Overall, they propose that pharmacists exhibit superior performance compared to doctors in managing patients on anticoagulants, or that no significant difference exists [6-19]. Several effectiveness outcomes, concentrating on INR trends, and safety outcomes were assessed. Efficacy outcomes included occurrences of supra and subtherapeutic INR, duration within therapeutic INR, mean time to attain therapeutic INR, and length of hospitalization. Bleeding, thromboembolic events, and drug-drug interactions were investigated as safety outcomes.

Multiple studies did not demonstrate a difference between groups [11, 14] or observed a significant decrease in supra-/subtherapeutic INR [6-8] or a nonsignificant trend toward reduced supra-/subtherapeutic INR [10, 13, 15]. PMAPs were compared to physician-managed anticoagulation. Dawson *et al*. [6] performed a prospective, nonrandomized study including patients from cardiology, internal medicine, and family medicine inpatient programs. Patients were allocated to receive warfarin treatment via a comprehensive dose strategy implemented by pharmacists (N=217) or via standard care provided by doctors (N=293). The authors indicate that pharmacists' implementation of the protocol led to a markedly reduced incidence of INR results exceeding 5, in contrast to standard physician care (7.86% vs 1.85%, P=0.004) [6].

Tschol *et al*. [7] noted that, among patients undergoing valve replacement, those managed by pharmacists experienced fewer days with INR levels above 4 compared to those managed by physicians (4% vs 10%, $p<0.001$). This discovery is especially significant, given that the cardiologists and cardiothoracic surgeons overseeing postoperative care possessed substantial expertise in anticoagulation management [5]. A limited study conducted by Brice [8] contrasted pharmacist-administered warfarin dosing (N=44) with physician-administered dosing (N=44) in a coronary care step-down unit, a general medicine ward, and a medical ward for the elderly. Patients administered medication by pharmacists had a markedly decreased risk of a pseudoevent (characterized as one or more INR findings of ≤ 1.5 or ≥ 5) in contrast to the physician cohort (relative risk [RR]: 0.14, 95% confidence interval [CI]: 0.03-0.61) [8].

Pharmacists successfully attained a higher percentage of INR readings within the therapeutic range, as shown by research that assessed warfarin management before to and during the implementation of a warfarin-prescribing guideline. Before the implementation of guidelines, the warfarin dosage practices of doctors were examined over a period of four weeks in four acute medical wards (N=68). Subsequently, prescribing recommendations were sent to the research doctors. In two of the wards, doctors continued warfarin dosage with the assistance of the warfarin-prescribing guideline (N=64), but in the other two wards, the duty for warfarin dosing according to the recommendations from Day 4 of therapy forward was assigned to the hematology pharmacist. Pharmacist care demonstrated much superior INR control (Percentage of INRs within the target range) relative to both physician groups (58% pharmacy versus 18% doctors adhering to recommendations vs 15% physicians, $p<0.001$) [9].

Several studies have compared the duration spent within the target INR range for pharmacy-managed anticoagulation protocols (PMAPs) versus physician management. Generally, the time spent in the therapeutic range was greater in the pharmacy-managed groups, or there was no significant difference between the groups. Chilipko and Norwood [10] recently performed a retrospective chart review of patients monitored by an inpatient anticoagulation management service to compare pharmacist-managed patients (N=179) with those receiving standard care through physician management (N=179). In terms of the primary outcome of mean time spent within the target INR range, patients managed by pharmacists exhibited a significantly greater duration within the goal range compared to those managed by physicians (2.84 days vs 2.20 days, P=0.017). Similarly, the study conducted by Brice *et al*. indicated that the percentage of patients in the pharmacy-dosed group who were newly anticoagulated was markedly higher (100% vs 72%, P=0.025), as was the percentage of patients maintaining a target INR of 2.5 (100% vs 66%, P=0.017), with both groups sustaining their INR levels within 0.75 units of the target for a significantly longer duration. Nonetheless, the differences were not statistically significant when the analysis included all study participants [8].

A non-significant trend indicating an enhanced time to therapeutic INR for PMAPs was observed in several studies, while others reported no differences between groups. Conversely, Airee *et al*. conducted a retrospective chart review, which indicated that the time to therapeutic INR was significantly reduced (4.3 days vs 5.3 days, P=0.006) in patients managed by a physician's usual care (N=50) compared to those managed by a pharmacists’ anticoagulation management service protocol (N=50). The authors indicate that these results may be attributed to a propensity for increased use of loading dosages among the physician group.

Several studies compared the average duration of stay for patients under the care of PMAPs with those under the care of doctors. The majority of studies indicate no difference between groups or a nonsignificant trend toward reduced length of stay for patients managed by pharmacists. Two studies suggested that patients managed by physicians had a significantly shorter length of stay than those managed by pharmacists.

The most extensive study to date comparing PMAPs with standard care examined data collected through a mailed questionnaire from the 1995 National Clinical Pharmacy Services and Medicare database for hospitals, encompassing an analysis of 717,396 Medicare patients treated in 955 hospitals for conditions necessitating anticoagulant therapy. Hospitals employing pharmacist-managed warfarin therapy exhibited decreased mortality rates (6.7% vs 7.1%) and shorter hospital stays (8.0 days vs 8.5 days) relative to those lacking pharmacist-managed care (All comparisons $p<0.0001$) [19]. Despite the substantial benefits indicated by this retrospective analysis, several limitations warrant consideration. The research indicates correlations between significant health outcomes (mortality rate and duration of hospitalization) and PMAPs, however, similar to the majority of publications in this review, the study design precludes the establishment of direct links or causation. The majority of hospitals eligible for participation did not respond to the survey, resulting in a 30% response rate, and the PMAPs constituted merely 10% of the patients and hospitals evaluated. Furthermore, hospitals were not classified (e.g., large vs. small, academic vs. nonacademic), and other potential confounding variables (e.g., patient demographics, availability of specialist physicians) were not addressed.

The primary objective of the identified studies was to assess the efficacy of inpatient PMAPs, however, several studies also examined the influence of these programs on safety outcomes. Safety outcomes evaluated included rates of bleeding, thromboembolic events, and warfarin-drug interactions. Most studies indicated a nonsignificant tendency towards a reduction in bleeding episodes or no changes between groups. No research observed differences in thromboembolic events. Regrettably, most investigations were limited in size and inadequately structured to identify disparities between groups for bleeding or thromboembolic events. The criteria of bleeding and thromboembolic events differed between studies, ranging from vague to precisely defined. Bond and Raehl [19] observed in their extensive retrospective analysis that hospitals using PMAPs saw much fewer bleeding issues compared to those without PMAPs (8.4% vs 9.2%, $p<0.0001$).

Heparin

Our study included five studies [18-21] that assessed outcomes in patients undergoing intravenous (IV) heparin treatment. Each used distinct research designs, and the examined results varied. Every trial shown a certain advantage for pharmacist-managed heparin treatment. Notably, three studies also assessed the use of warfarin. This section discusses outcomes related to heparin use.

Chenella *et al*. [17] proved over three decades ago the capability of pharmacists to accurately administer heparin and warfarin by established protocols. Eight-one individuals referred to the anticoagulation service were randomized into the pharmacist-prescriber group (N=42) or the physician-prescriber group (N=39). All prescribers were unaware of patient randomization and independently conducted daily dosage modifications and monitoring for both patient cohorts. Nonetheless, the prescriber needed to be apprised of the anticoagulant dosage given the preceding day when formulating dosage recommendations, hence rendering genuine prescriber blinding unfeasible. The authors indicated no statistically significant differences between groups for any evaluated outcomes, including the total mean heparin dosage administered and the mean values for heparin dosage and prothrombin time during the first 24 hours [17].

The majority of studies presented herein compared the time to therapeutic activated partial thromboplastin time (aPTT) for PMAPs against standard care or physician management [18, 20, 21]. The findings are inconclusive, one study [18] indicated no difference between groups, another [21] suggested a favorable trend for pharmacist-directed dosing, while the third [20] identified a statistically significant difference between groups. It is essential to emphasize that pharmacist-led heparin dosage attained therapeutic aPTT within 24 hours across all three investigations, a vital endpoint for preventing recurrent thrombosis.

Mamdani *et al*. [18] report no significant difference in the time to therapeutic aPTT and between the pharmacist-managed and usual care groups regarding their primary endpoint: the proportion of patients achieving a therapeutic aPTT of 48 seconds after the initial heparin dose (84% vs 78%, P=0.44). Nonetheless, the authors observed a significantly higher proportion of therapeutic aPTT values (47.75% vs 41.5%, P=0.05) and a notably lower incidence of subtherapeutic aPTT values in the pharmacist-managed cohort (15.8% vs 21.3%, P=0.03), with no significant difference in supratherapeutic aPTT values [18]. Two critical factors that may have diminished the disparity between groups include inadequate pharmacist compliance with the heparin protocol and enhanced physician prescribing due to heightened awareness and utilization of the protocol [18].

Consistent with the findings presented in the preceding section on “Warfarin” concerning pharmacist-managed warfarin therapy, Bond and Raehl report that hospitals employing pharmacist-managed heparin therapy exhibited a reduced mortality rate compared to those lacking such services (6.37% vs 7.19%, $p<0.0001$). Furthermore, two studies indicated that heparin management by PMAPs decreased the mean length of stay by 1-2 days.

While each research presented herein shows some advantages of pharmacist-managed heparin treatment, the variable use of heparin-dosing regimens across comparison groups renders the findings challenging to evaluate across trials. Three studies assessed pharmacist-managed heparin treatment using a weight-based dosage methodology in comparison to physician-managed therapy employing empiric dosing or a standard care nomogram, often known as conventional dosing. It is challenging to ascertain whether these outcomes were attributable to pharmacist participation or the implementation of a more efficacious protocol, as one randomized controlled trial indicated the apparent superiority of weight-based dosing over a standard care nomogram [22-24]. Chenella *et al*. [17] compared groups utilizing the same established protocol (protocol type unspecified) and found no significant difference in the mean dose of heparin prescribed or the mean values for PTT.

Bond and Raehl [19] also documented enhanced safety in hospitals using pharmacist-managed heparin treatment. Hospitals employing pharmacist-managed heparin therapy exhibited a reduced incidence of bleeding complications (8.84% vs 9.12%,

P=0.0009) relative to those lacking pharmacist oversight. However, one must take into account the study design's limitations, as previously discussed, when evaluating direct correlations and enhancements in safety.

Two supplementary investigations revealed incidences of hemorrhaging. In one trial, four patients in the pharmacist-managed group suffered mild bleeding, but no patients in the physician-managed group exhibited bleeding, no statistical analysis was conducted for this outcome. No statistically significant difference was observed between groups regarding minor bleeding in the second study. Four percent of patients receiving standard care experienced major bleeding, whereas none in the pharmacist-managed group did, the authors noted that one patient in the pharmacist-managed group died from a pulmonary embolism [25-32].

Venous thromboembolism risk assessment services

Bauer *et al*. [33] evaluated the efficacy of a pharmacist-led initiative aimed at evaluating VTE risk and recommending prophylaxis for hospitalized patients. The clinical pharmacists evaluated all new admissions, excluding maternity, nursery, pediatrics, and psychiatry, and conducted a VTE risk assessment using a standardized monitoring sheet. A 3″×5″ sticker was affixed in the "progress notes" portion of the patient's medical record, notifying doctors of identified risk factors and the amount of VTE risk. For patients at elevated risk (> 20% estimated VTE risk), pharmacists offered VTE prophylactic recommendations that the primary care practitioner may either accept or decline. Notwithstanding a low acceptance rate of 31% for suggestions, the pharmacy-led intervention exhibited both statistically and clinically significant advantages when compared to a retrospective cohort from the pre-implementation era. The rates of VTE prevention rose from 19.5% to 60.2%, whilst the rates of VTE declined from 1.1% of discharged patients to 0.1%.

Challenges faced during the execution of this program comprised discrepancies among pharmacists in recognizing and assessing VTE risk factors, alongside physicians' apprehensions about heightened liability. A limitation of this study is the baseline reference sample, which was collected 16 months prior to the program's implementation. A standardized VTE prophylaxis order form was developed and executed between the baseline and pharmacy program samples, introducing a confounding variable, consequently, some of the enhancements observed in this study were likely attributable to the order form's implementation. Although the assessment of the pharmacy-led intervention's efficacy may lack precision, it signifies a clinically significant improvement in critical patient outcomes.

Cronin *et al*. [34] reported a decrease in overall Venous Thromboembolism (VTE) and Pulmonary Embolism (PE) rates after the establishment of a multidisciplinary, pharmacy-led thromboprophylaxis program in orthopedic surgery patients. The intervention included a thromboprophylaxis risk factor assessment and prescriber order sheet, along with instruction on protocol modifications to deter the use of warfarin monotherapy, which has been particularly associated with elevated VTE incidence at this institution. The clinical pharmacist was tasked with educating on published recommendations, risk factor assessments, prescriber order sheets, and protocol modifications for prophylaxis. Daily chart evaluations and biweekly patient care rounds with the orthopedic team facilitated the execution of the risk assessment and order form.

The pharmacist coordinated the timing of low-molecular-weight heparin initiation after the removal of epidural catheters in collaboration with orthopedic physician assistants, surgical nurses, and anesthesiologists. In comparison to rates in 953 patients prior to the initiative's implementation, any Venous Thromboembolism (VTE) decreased by 48%, and pulmonary embolism (PE) decreased by 57% in 1,003 patients undergoing total joint replacement procedures. A notable limitation of this study is the absence of statistical comparison between the event rates before and after implementation. The incidence of VTE and PE was minimal (44 VTE before to implementation compared to 24 VTE thereafter, and nine PE before against four after). Furthermore, the pharmacist's role in anticoagulation therapy, including agent selection, dosage, and monitoring, is inadequately delineated. The ambiguity around the seemingly advantageous outcome of this intervention stems from whether it is attributable to the general advice to reduce the use of warfarin as monotherapy or to specific actions taken by the pharmacist. The adherence percentage of doctors to pharmacist suggestions was not disclosed. Bauer *et al*. [33] saw no instances of bleeding or HIT in their one-month safety evaluation of the pharmacist-led VTE risk assessment program, however, Cronin *et al*. [34] did not address safety concerns.

Nursing and Pharmacy expertise for effective anticoagulation therapy management

The management of anticoagulation therapy requires a multidisciplinary approach that leverages the unique skills of both nurses and pharmacists. This collaboration is vital in optimizing patient outcomes and ensuring safety during anticoagulant administration. Pharmacists play a crucial role in the management of anticoagulation therapy through their expertise in medication management, drug interactions, and therapeutic monitoring. They are responsible for developing and implementing anticoagulation protocols, conducting patient assessments, and adjusting dosages based on therapeutic outcomes. In inpatient settings, pharmacists actively monitor patients for adherence to anticoagulation guidelines, ensuring that patients remain within the therapeutic INR range. Their training allows them to identify potential adverse effects and intervene proactively, significantly reducing the risk of bleeding complications.

Nurses complement this by providing patient education, monitoring vital signs, and observing for signs of bleeding or thromboembolic events. They serve as the front-line caregivers who communicate critical information between patients and the healthcare team. By educating patients about the importance of adherence to anticoagulation therapy-such as dietary considerations and potential drug interactions-nurses empower patients to take an active role in their treatment. This educational component is essential, as informed patients are more likely to adhere to prescribed therapies and report any side effects promptly.

The collaboration between nurses and pharmacists fosters a comprehensive care model where both professionals work together to evaluate patient needs, share insights on clinical data, and develop individualized care plans. Effective communication within the healthcare team is paramount, ensuring that changes in patient status are promptly addressed. This integrated

approach not only enhances patient safety and satisfaction but also leads to improved therapeutic outcomes in anticoagulation management, ultimately contributing to a reduction in hospital readmissions and healthcare costs.

Summary

Thromboprophylaxis is frequently underutilized and improperly prescribed, notwithstanding the availability of evidence-based guidelines. Preventable thromboembolic events constitute an unwarranted clinical and economic burden, leading to a growing acknowledgment of the necessity to enhance current care. Pharmacists are distinctly positioned to augment patient safety and are integral to the dosing, monitoring, and education regarding anticoagulation therapy. A growing number of hospitals have started to use PMAPs to enhance effectiveness and safety, and the research supporting inpatient PMAPs is expanding.

The examined literature suggests clear advantages of inpatient PMAPs, with studies often demonstrating either better results relative to standard or physician-managed care or no significant differences between the groups. This research is inherently constrained by its nature as a narrative review, despite using a comprehensive search technique, there may be pertinent publications that were not found or included. Furthermore, certain limitations exist within the existing evidence. The bulk of the research was of substandard quality and not structured to ascertain direct connections or causation. The majority of the research is retrospective, often presented as historical cohorts. Certain reference/control groups for this research date back as much as three years prior to the intervention groups. Other factors may have affected the observed benefits throughout this period, including institutional education initiatives, the introduction of new pharmaceuticals, and updated recommendations.

Certain studies were deficient in adequate statistical analysis, and many others had limited sample numbers, complicating the demonstration of statistically significant differences between groups for infrequent outcomes such as hemorrhage and thrombosis recurrence. The patient groups differed among research (e.g., elderly individuals, post-valve replacement surgery patients, and orthopedic surgery patients), complicating the comparability of data for interpretation.

Certain studies had imbalanced group sizes, with a significantly greater number of patients in one arm compared to the other, perhaps resulting in the oversight of less-frequent outcomes in the smaller cohort. Moreover, the studies often focused on distinct endpoints according to the nature of the service (i.e., postoperative studies assessed bleeding, whilst others emphasized transition of care measures). The extensive comparison investigations likewise exhibited some of the same shortcomings. The advantage shown in pharmacist-managed care may stem from adherence to guidelines and protocols. Most studies failed to account for physician dosage, making it difficult to ascertain whether the outcomes were attributable to pharmacist engagement or the use of procedures by pharmacists. These results align with those of Donovan *et al*. in their 2008 review. Pharmacist-led inpatient anticoagulation seemingly improves patient care quality, notwithstanding the constraints of existing evidence. More extensive, randomized prospective trials are required to draw more conclusive findings.

Conclusion

Pharmacist-managed anticoagulation therapy has shown promising benefits in enhancing patient safety and therapeutic outcomes in inpatient settings. The evidence suggests that pharmacists can effectively manage anticoagulant therapies, leading to improved control of INR levels and a reduction in adverse events compared to standard physician-managed care. Despite the limitations of existing studies, including variability in research design and sample sizes, the overall trend indicates that integrating pharmacists into anticoagulation management can significantly mitigate risks associated with these high-alert medications. Future research should focus on larger, randomized controlled trials to further validate these findings and establish best practices for optimizing anticoagulation therapy in diverse patient populations.

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دمج خبرات التمريض والصيدلة لتحسين إدارة العلاج بمضادات التخثر: مراجعة شاملة

الملخص

الخلفية :تعد مضادات التخثر أدوية حيوية للوقاية من التخثر وعلاجه، ومع ذلك، فإنها تحمل مخاطر كبيرة من المرض والوفيات. لقد أظهرت خدمات مضادات التخثر التي يديرها الصيادلة تقليل المضاعفات وتحسين النتائج العلاجية، خاصة في البيئات الخارجية. تؤكد الاتجاهات الحديثة في الرعاية الصحية على الحاجة إلى نهج تعاوني، يدمج خبرات التمريض والصيدلة لإدارة فعالة لمضادات التخثر.

الطرق :تستعرض هذه المراجعة الأدبيات الحالية حول خدمات مضادات التخثر التي يديرها الصيادلة في المستشفيات، مع التركيز على الدراسات التي تقارن هذه الخدمات بالرعاية التقليدية التي يديرها الأطباء. تم إجراء بحث شامل عبر العديد من قواعد البيانات، بما في ذلك PubMed وEmbase، باستخدام كلمات رئيسية تتعلق بإدارة مضادات التخثر.

النتائج :أشار تحليل 14 دراسة إلى أن بروتوكولات مضادات التخثر التي يديرها الصيادلة (PMAPs) تتفوق عمومًا على الرعاية القياسية التي يديرها الأطباء، مع تحسين نتائج المرضى مثل ارتفاع معدلات النسبة الدولية الموحدة (INR)وانخفاض معدل حالات النزيف. ومن الجدير بالذكر أن الدراسات أظهرت أن المرضى الذين يديرهم الصيادلة كان لديهم مخاطر أقل بكثير من مستويات INR فوق العلاج وأقصر مدة إقامة في المستشفى. بالإضافة إلى ذلك، أظهرت المبادرات التي يقودها الصيادلة تعزيز الأمان في إدارة العلاج بمضادات التخثر.

الخاتمة :يؤدي دمج خبرات التمريض والصيدلة في إدارة العلاج بمضادات التخثر إلى تحسين نتائج المرضى وزيادة الأمان. تدعم الأدلة إنشاء خدمات مضادات التخثر التي يقودها الصيادلة في البيئات الداخلية، على الرغم من الحاجة إلى مزيد من التجارب السريرية العشوائية لتعزيز النتائج ومعالجة القيود الحالية في الأدبيات.

الكلمات المفتاحية :مضادات التخثر، الصيادلة، التمريض، سلامة المرضى، إدارة الوارفارين.