



Making Healthcare Safer IV

Reducing Adverse Drug Events Related to Anticoagulant Use in Adults

Rapid Response



Main Points

1. Anticoagulation medications help prevent life-threatening events such as pulmonary embolism, but they also increase the risks of major bleeding.
2. Patient safety practices such as patient and caregiver education and periodic international normalized ratio testing to increase medication adherence may potentially prevent adverse effects of anticoagulant use during care transitions and in the ambulatory setting.
3. For care transitions, specifically for discharge from the hospital to home, we included three randomized trials and three non-randomized studies, and all six were at high risk of bias. Only one of the six studies (a nonrandomized study) found evidence of a benefit on any adverse event. No included studies addressed other types of care transitions (e.g., within-hospital).
4. Most telemedicine interventions to prevent adverse events of anticoagulation in the ambulatory setting improved time in therapeutic range, and telepharmacy reduced rates of bleeding and hospitalization. Anti-Xa monitoring lowered rates of thromboembolic events while maintaining similar rates of major bleeding compared to usual care. The evidence was inconclusive about the effect of education and remote monitoring on adverse events in people on anticoagulation.
5. We identified two relevant toolkits from AHRQ's Patient Safety Network (both from 2012). One provided general medication guidance for the transition to home, and the other provided six tools either for the delivery or provision of a medication treatment management program or for assessing the effect of such a program.



PATIENT SAFETY



1. Background and Purpose

The Agency for Healthcare Research and Quality (AHRQ) Making Healthcare Safer (MHS) reports consolidate information for healthcare providers, health system administrators, researchers, and government agencies about practices that can improve patient safety across the healthcare system—from hospitals to primary care practices, long-term care facilities, and other healthcare settings. In spring 2023, AHRQ launched its fourth iteration of the [MHS Report \(MHS IV\)](#). Reducing adverse drug events related to anticoagulants was identified as a high priority for inclusion in the MHS IV reports using a modified Delphi technique by a Technical Expert Panel (TEP) that met in December 2022. The TEP included 15 experts in patient safety with representatives of governmental agencies, healthcare stakeholders, clinical specialists, experts in patient safety issues, and a patient/consumer perspective. See the [Making Healthcare Safer IV Prioritization Report](#) for additional details.

Professional organizations widely endorse anticoagulants for preventing and treating blood clots in conditions that have a higher risk of leading to venous thromboembolism and stroke (e.g., chronic atrial fibrillation, artificial heart valves, antiphospholipid syndrome, genetic or acquired thrombophilia, cancer).^{1,2} While anticoagulants may reduce morbidity and mortality in some patients,³⁻⁵ they may also lead to serious adverse effects (e.g., bleeding).^{6,7} The 2014 National Action Plan for Adverse Drug Event Prevention (ADE Action Plan) identified anticoagulants as a leading cause of adverse drug events.⁸ For example, between 2013 and 2014, anticoagulants were implicated in 38.8 percent (95% confidence interval [CI]: 33.7% to 43.8%) of all U.S. emergency department visits for adverse drug events among adults aged ≥ 80 years.⁷

1.1 Purpose of the Rapid Response

Two critical areas for safe anticoagulation are care transitions and ambulatory care. Inpatient care transitions are vulnerable to miscommunication between healthcare staff, but the primary concern is the transition to home, where the patient and/or caregiver must be aware of the purposes and risks of anticoagulation (most prominently, bleeding). Further, for continued management of vitamin K antagonists (VKAs) such as warfarin in the ambulatory setting, periodic international normalized ratio (INR) tests are critical. If INR is not monitored, necessary dose adjustments will not be performed, which could lead to either an increased risk of bleeding if the INR is too high or inadequate anticoagulation and increased risk of thrombotic events if the INR is too low. Interventions to improve ambulatory monitoring of anticoagulants are critical for ensuring patient safety in ambulatory settings.

A third area, covered in the 2020 Making Healthcare Safer report,⁹ is the use of dosing protocols and nomograms for newer direct oral anticoagulants (DOACs, e.g., factor Xa inhibitors, direct thrombin inhibitors). We determined this latter patient safety practice (PSP) to be a lower priority for an evidence update relative to the other

two (the TEP stated that nomograms “may no longer be a major concern in primary care”).

During the immediate post-discharge period, patients are more vulnerable to adverse effects of anticoagulants. One population-based cohort study¹⁰ of over 120,000 patients at a single hospital in Canada compared the rates of short-term hemorrhagic events (first month post-discharge) to the rates at longer time intervals. For those newly prescribed an anticoagulant, the incident rate was about 22 hemorrhagic events per 100 person years in the first month, 11 events at 6 months, and 7 events at 2 years. Similarly, for more experienced patients (those already taking anticoagulants before hospital admission), the rate was about 30 events per 100 person-years in the first month post-discharge, compared to about 17 events at 1 to 2 years. These data underscore the importance of the immediate post-discharge period in managing the risk of bleeding.

Regarding specific anticoagulants, one of the touted advantages of newer DOAC medications (e.g., apixaban, rivaroxaban) over VKAs such as warfarin is the elimination of the need for periodic INR testing. However, the newer medications still require careful dosing and monitoring. Therefore, the scope of this report includes any anticoagulation medication.

This rapid response summarizes the most relevant and recent literature on two PSPs: interventions to support safe care transitions and continuation of anticoagulants post-discharge (PSP 1), and anticoagulation management services in ambulatory settings (PSP 2). Both had been covered in the 2020 MHS III report (which only included literature before 2019), and this report summarizes more recent literature (published in 2019 or later).

1.2 Review Questions

1. What are the frequency and severity of harms associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge among adults?
2. What patient safety measures or indicators have been used to examine the harm associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge?
3. What PSPs have been used to ensure safe transitions and continuation of patients’ anticoagulants after discharge, and in what settings have these practices been applied?
4. What is the rationale for these PSPs that have been used to prevent or mitigate the harm associated with anticoagulant use in the inpatient and outpatient settings and anticoagulation after discharge?
5. What studies have assessed the effectiveness and unintended effects of PSPs (i.e., PSP 1, interventions to support safe care transition for patients with anticoagulation, and PSP 2, anticoagulant management in ambulatory settings), and what new evidence has been published since the search was done for the MHS III report in 2019?

6. What are the common barriers and facilitators to implementing these PSPs?
7. What resources (e.g., cost, staff, time) are required for the implementation of these PSPs?
8. What toolkits are available to support the implementation of the PSPs?



2. Methods

We followed review processes described by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program.¹¹ The rapid response is intended to present the end-user with an answer based on the best available evidence, without formally synthesizing the evidence into conclusions. While the methodological steps are similar to those of a systematic review, the methods are different (i.e., streamlined systematic review methods).

For this rapid response, strategic adjustments were made to streamline traditional systematic review processes and deliver an evidence product in the allotted time. We followed adjustments and streamlining processes proposed by the AHRQ EPC Program. Adjustments included being as specific as possible about the questions, limiting the number of databases searched, modifying search strategies to focus on finding the most valuable studies (i.e., being flexible on sensitivity to increase the specificity of the search), restricting the search to studies published since the last report (i.e., since 2019 when the search was done for the MHS III report) in English, and having each study assessed by a single reviewer.

For Review Questions 1 through 4, we summarized information from the literature without conducting a systematic search for all evidence on the targeted harms and related patient safety measures or indicators. We addressed Review Question 5 using searches for evidence published since the 2020 report. For Review Questions 6 and 7, we examined the barriers, facilitators, and required resources reported in the studies we found for Review Question 5, as well as studies identified in our search that provided relevant information but did not meet the eligibility criteria for Question 5. For Review Question 8, we identified publicly available patient safety toolkits developed by AHRQ or other organizations that could help to support implementation of the PSPs. To accomplish that task, we reviewed AHRQ's Patient Safety Network (PSNet) (<https://psnet.ahrq.gov>) and AHRQ's listing of patient safety related toolkits (see https://www.ahrq.gov/tools/index.html?search_api_views_fulltext=&field_toolkit_topics=14170&sort_by=title&sort_order=ASC). We included any toolkits mentioned in the studies included for Review Question 5. We identified toolkits without assessing or endorsing them.

2.1 Eligibility Criteria for Studies of Effectiveness

We selected evidence on Review Question 5 according to the inclusion and exclusion criteria presented in Table 1. Separately for each of the two PSPs, we planned to decide whether systematic reviews (SRs) would be sufficient to update the evidence on effectiveness. If so, we would rely solely on those reviews. If not, we would examine empirical studies (randomized controlled trials [RCTs] and non-randomized studies with either a comparison group or a pre-post comparison) for possible inclusion.

Table 1. Inclusion and exclusion criteria for Review Question 5 on Effectiveness

Study Parameter	Inclusion Criteria	Exclusion Criteria
Population	Adults (aged 18 years and older) who receive anticoagulants	Studies exclusively conducted with children and adolescents (aged <18 years), pregnant and lactating individuals, prison inmates, and individuals with active cancer
Intervention	PSPs designed or hypothesized to prevent adverse events related to (PSP 1) anticoagulation management services and (PSP 2) interventions to support safe transitions and continuation of patients' anticoagulants post-discharge	None
Comparator	Any comparator (e.g., standard care without specific PSPs), including pre-intervention measurements	<ul style="list-style-type: none"> • No comparator • Comparator group is not appropriate (would not have equivalent need for the intervention)
Outcome	<p>Safety</p> <ul style="list-style-type: none"> • All-cause and cause-specific mortality, bleeding, hemorrhage, stroke, quality of life, adverse events associated with drug-drug interaction, thrombotic events, time in therapeutic range <p>Harms associated with the use of PSPs (i.e., unintended negative consequences)</p> <p>Utilization of healthcare services</p> <ul style="list-style-type: none"> • Emergency department utilization • Hospital admission/readmission <p>Implementation</p> <ul style="list-style-type: none"> • Barriers and facilitators to implementation • Resources (i.e., cost, staff, time) required for implementation. <p>Contextual information</p> <ul style="list-style-type: none"> • Rationale for PSPs • Patient safety measures or indicators • Toolkits and availability 	Other unspecified outcomes
Timing	Any	None
Setting	Transitions between inpatient settings, or transition from hospital to home, or ambulatory care	Studies conducted in emergency medical services settings; specific long-term living facilities (e.g., prisons, inpatient mental health)
Type of studies	All review questions (RQs): Systematic reviews. If systematic reviews are not available: randomized controlled trials, non-randomized studies with a comparison group, including before-after studies, published since 2019, the date of the search done for the MHS III report on this topic	<ul style="list-style-type: none"> • Unspecified study designs or comparison group not described • Not peer-reviewed publications

MHS = Making Healthcare Safer; PSP = patient safety practices; RCT = randomized controlled trial

2.2 Literature Searches for Studies of Effectiveness

A research librarian searched PubMed for systematic reviews published from 1/1/2019 to 8/22/2023 that addressed the effectiveness of either PSP 1 or PSP 2. Due to the lack of relevant systematic reviews on PSP 1, we then searched PubMed for relevant empirical studies using the same time frame.

2.3 Selection of Studies

To efficiently identify articles that met the eligibility criteria, each title/abstract was reviewed by a single team member. A second team member checked a 10 percent sample of citations to verify that important studies were not excluded. The full text of each potentially eligible article was reviewed by a single team member to confirm eligibility, abstract the data (e.g., author, year, study design, number of study participants), and prepare a summary of the study.

2.4 Risk of Bias (Quality) Assessment

For studies included for Review Question 5 (effectiveness of PSPs), the primary reviewer used the Cochrane Collaboration's tool for assessing the risk of bias of RCTs¹² or the ROBINS-I tool for assessing the Risk Of Bias In Non-randomized Studies – of Interventions.¹³ When assessing RCTs, we used the seven items in the Cochrane Collaboration's tool that cover the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. When assessing nonrandomized studies, we used specific items in the ROBINS-I tool that assess bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. The risk of bias assessments focused on the main outcome of interest in each study.

For systematic reviews addressing either PSP, we usually relied on the review authors' assessments of the risk of bias in their included studies. However, in a few cases, we judged the review authors' assessment as underestimating the risk of bias, so we performed our own assessment of the risk of bias.



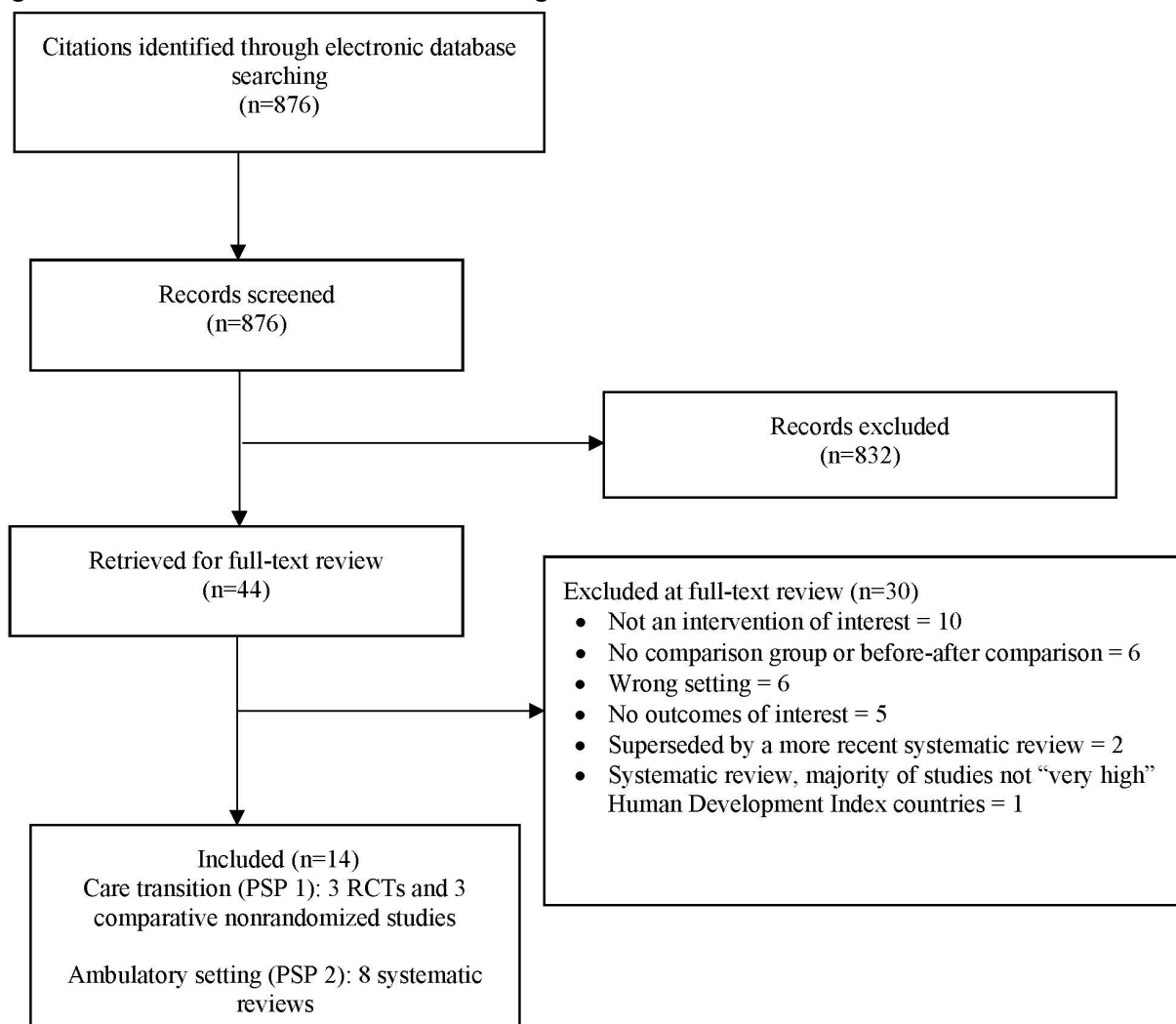
3. Evidence Base

3.1 Number of Studies

Searches yielded 876 potentially relevant references (see Figure 1). For Review Question 5 on effectiveness:

- We excluded 791 at the abstract level and another 30 at the full-text level.
- For PSP 1 (care transitions), systematic reviews were not sufficient to update the evidence, so we included six studies (3 RCTs, 3 controlled nonrandomized studies).
- For PSP 2 (ambulatory services), we included 8 systematic reviews.

Figure 1. Results of the search and screening



3.2 Findings for Review Questions

3.2.1 Question 1. What Are the Frequency and Severity of Harms Associated With Anticoagulant Use in the Inpatient and Outpatient Settings and Anticoagulation After Discharge Among Adults?

The primary risk of anticoagulation is major bleeding. The patient population receiving anticoagulants predominantly comprises older adults, who are at increased risks for falls, and bleeding from a fall is particularly dangerous for those taking anticoagulants. For warfarin as treatment in the context of atrial fibrillation, in a 2022 systematic review developed to support recommendations of the U.S. Preventive Services Task Force, the risk of bleeding was estimated to be 76 percent higher than with placebo (95% CI 15% lower to 266% higher).¹⁴ The newer anticoagulants generally have a lower bleeding risk, but similar or better effectiveness in clot prevention. A 2023 network meta-analysis of over 130,000 patients¹⁵ estimated that, compared with warfarin, new anticoagulants have a 15 percent lower risk of stroke or embolism as well as a 34 percent lower risk of major bleeding and a 47 percent lower risk of intracranial hemorrhage. Another 2023 study estimated that oral anticoagulant-related bleeding resulted in 1.27 million emergency department (ED) visits in the United States between 2016 and 2020, of which 47.8 percent resulted in hospitalization.¹⁶ For every 100 patients who received oral anticoagulants at least once during those years, the study estimated 5.9 ED visits for patients receiving DOACs and 13.0 visits for patients receiving warfarin.

Other risks of anticoagulant use include liver injury,¹⁷ minor bleeding,¹⁸ and dermatologic effects.¹⁹ The degree of risk ranges widely from about 0.1 percent for skin necrosis¹⁹ to 15–20 percent for minor bleeding,¹⁸ but these vary greatly by specific populations and medications. These risks underscore the importance of managing patients through care transitions and in the ambulatory setting.

3.2.2 Question 2. What Patient Safety Measures or Indicators Have Been Used To Examine the Harm Associated With Anticoagulant Use in the Inpatient and Outpatient Settings and Anticoagulation After Discharge?

The most important patient safety measure to assess the harm associated with anticoagulant use is the incidence of major bleeding, which can be fatal in patients taking anticoagulants.¹⁴ Older patients on anticoagulants are vulnerable to major bleeding (particularly intracranial hemorrhage) following a fall. By extension, mortality is an important indicator given the risk of death from major bleeding. Minor bleeding is also an important outcome to monitor in patients on anticoagulants. Monitoring INR is important in the inpatient setting for patients on VKAs, as is

tracking medication errors (dosing and dispensing). Several blood tests are recommended for monitoring of patients on DOACs, including urea and electrolytes (3 monthly to annually), full blood count, and liver function tests (alanine transaminase [ALT]) annually. Renal function should be assessed and monitored using the Cockcroft-Gault formula—creatinine clearance. Hospital readmission rate post-discharge is an indirect indicator of harm from anticoagulant use, but this outcome is complicated because it mixes incidents of major bleeding with thrombotic events. Quality of life can also be monitored as an indirect indicator of harm, as adverse effects of anticoagulation have a negative impact on this outcome. In the outpatient setting, time in therapeutic range (TTR) for warfarin can be used as an indirect indicator of harm, as TTR <65 percent is associated with increased risk of major bleeding, thromboembolic events, and death.²⁰

3.2.3 Question 3. What PSPs Have Been Used To Ensure Safe Transitions and Continuation of Patients' Anticoagulants After Discharge, and in What Settings Have These Practices Been Applied?

Educational programs are often provided before hospital discharge to patients on anticoagulants to promote safe transitions and continuation of anticoagulants. These programs have been applied in inpatient, outpatient, and post-discharge nonhospital settings (in nonhospital settings, education can be delivered via mobile apps or telehealth-related tools [phone or internet]).^{21,22}

Other telemedicine-related interventions are also commonly used for anticoagulation management following hospital discharge. These interventions can include the use of computerized algorithms to assist with dosing, laboratory testing for INR with remote (telephonic or internet-based) assistance for dose adjustment, self-testing for INR with remote or self-managed dose adjustment, and internet-based or mobile app-based clinical decision support for atrial fibrillation management.^{20,23-25}

Remote monitoring of cardiac arrhythmias (which can lead a provider to prescribe or alter the dosage of anticoagulation therapy) has been done using devices such as implantable cardiac defibrillators (ICDs), cardiac resynchronization therapy (CRT) devices, permanent pacemakers, and smart-phone-based rhythm monitoring devices.²⁶

Finally, patients receiving low molecular-weight heparin (LMWH) may undergo anti-Xa monitoring as part of their anticoagulation management.²⁷

3.2.4 Question 4. What Is the Rationale for These PSPs That Have Been Used To Prevent or Mitigate the Harm Associated With Anticoagulant Use in the Inpatient and Outpatient Settings and Anticoagulation After Discharge?

Education on anticoagulation provides information to patients regarding anticoagulant dosing, timing of dosing, diet (foods to avoid, particularly for vitamin K

antagonists), a list of medications that interfere with anticoagulants, the importance of medication adherence to avoid adverse events such as thromboembolic events, and for vitamin K antagonists (e.g., warfarin), the need for regular INR monitoring to ensure that the medication is maintaining the therapeutic range.^{21,22}

Telemedicine interventions are often delivered to assist dosing after laboratory INR testing; patients can learn whether they need to adjust their dosage by receiving test results over the phone or via the internet. This information is necessary to ensure that patients maintain their INR in the therapeutic range. Patients can also choose to self-test at home with an INR test meter, which eliminates the need for travel to a clinic. Multitasking interventions delivered via mobile apps or the internet can provide a combination of anticoagulation therapy indication and management, along with rate or rhythm control, symptom monitoring, and management of other cardiovascular risk factors, thereby reducing risks of adverse events beyond what anticoagulation management alone can offer.²³

Remote monitoring of anticoagulation therapy uses devices that deliver notifications when an arrhythmia (atrial tachycardia or atrial fibrillation) occurs; anticoagulation is prescribed by a provider after arrhythmia detection.²⁶

Patients receiving LMWH for treatment of venous thromboembolism may receive anti-Xa monitoring (the gold standard of LMWH monitoring) to determine that anti-Xa levels remain in the therapeutic range (0.2 to 0.4); levels below 0.2 increase the risk of thromboembolic events, and levels above 0.4 increase the risk of major bleeding.²⁷ LMWH dosage will vary depending on the results of the anti-Xa assay. The alternative is that patients often receive a fixed dose of LMWH with no monitoring.

3.2.5 Question 5. What Studies Have Assessed the Effectiveness and Unintended Effects of PSPs (i.e., PSP 1, Interventions To Support Safe Transition for Patients With Anticoagulation Post-discharge, and PSP 2, Anticoagulant Management in Ambulatory Settings) and What New Evidence Has Been Published Since the Search Was Done for the Making Healthcare Safer (MHS) III Report in 2019?

Evidence Summary for PSP 1: Support Safe Care Transitions

We included three RCTs and three nonrandomized comparative studies for this PSP (Table 1, with RCTs listed first and other studies listed next). All six specifically addressed discharge from hospital to home (i.e., while we would have included studies of other types of transitions, no such studies met our inclusion criteria). Their interventions targeted post-discharge safety of anticoagulation. In one of the three RCTs, the intervention occurred only during the hospital stay (e.g., intensive warfarin patient education before discharge), whereas in the other two studies, the PSP included

some post-discharge activities. In two of the three nonrandomized studies, the intervention occurred only during the hospital stay. Several studies had used a multicomponent intervention involving one-on-one education in the hospital (sometimes with pharmacists, sometimes clinicians, sometimes nurses) and/or followup telephone calls. More aspects of the six studies are listed in Appendix C, Table C-1.

Regarding risk of bias, all three RCTs were rated as High risk of bias, mostly due to a lack of blinding of patients or providers. For one of the RCTs, we also had concerns about high attrition and reporting bias (the latter because the study measured rates of recurrence of venous thromboembolism, major hemorrhage, and readmission to the hospital, but did not report the corresponding data). The three nonrandomized studies were all rated as Critical risk of bias, due primarily to inherently uncontrollable risk of bias arising from the study design (pre/post implementation with historical control); this is of particular concern due to the approval of direct oral anticoagulants shortly before and during the study periods, which may have produced trends in prescribing patterns. In two nonrandomized studies, there were also uncertainties about the classification of patients who were enrolled in the period immediately before implementation of the intervention; additionally, in one study, it appeared that the intervention was adopted incompletely and gradually by providers, making it impossible to judge the effect of the intervention at any stable level of penetration.

Results From RCTs

Manzato 2021²⁸ randomized 52 patients who were initiating warfarin to either post-discharge education (consisting of 5 telephone calls from a researcher) or no calls. The calls were intended to reinforce the education provided to both groups prior to discharge from the hospital. This in-hospital education involved “a portable device (tablet) to show a 26-slide presentation (Power Point® for Windows, version 2007), which included illustrations about the treatment with warfarin. A booklet containing the same figures and information was also delivered to the participants.”²⁸ About the content of the calls to the intervention group, the authors stated, “These contacts were focused on encouraging the self-management of the treatment with warfarin and on reinforcing the information about oral anticoagulant therapy, including signs and symptoms of complications, INR control, concomitant use of other medications that may decrease warfarin effectiveness, use of alcoholic beverages and intake of diets rich in fat and vitamin K. For the telephone calls, we elaborated a script with nine questions about the participant's behaviours regarding the correct use of warfarin. Based on the person's responses, the investigator clarified doubts and misunderstandings and gave positive reinforcement to the correct behaviours already in place.”²⁸ The study reported time in therapeutic range, quality of life, anxiety, depression, and psychological impact (the latter was measured by 8 items on the Duke Anticoagulation Satisfaction Scale), at both three and six months after discharge. Of numerous outcomes, the only one that demonstrated a statistically significant between-group difference was psychological impact at 6 months (better scores in the intervention group than the control group). The authors stated that “the quality of life

and beliefs about the illness and oral anticoagulation therapy have been shown to be associated with the person's behaviour regarding the therapy and, consequently, with the control of INR.”²⁸

Kapoor 2020²⁹ randomized 162 patients prescribed anticoagulation after a new episode of venous thromboembolism to either two anticoagulation interventions after discharge (a home visit from a pharmacist within 7 days of discharge, and a followup call by an anticoagulation expert 8–30 days later) or no reminders. The study measured recurrence of venous thromboembolism (measurement method not reported), major hemorrhage (defined based on either the ISTH 2005 medical definition (either a 2-unit drop in hemoglobin, 2-unit transfusion, or a critical site bleed) or the ISTH 2009 surgical definition (2-unit drop or 2-unit transfusion with increase in length of stay, or hemodynamic compromise, or delay in rehabilitation), readmissions to the hospital, and patient-rated quality of care transition (see the [clinicaltrials.gov](https://clinicaltrials.gov/record/NCT02870296) record for NCT02870296). However, the authors only reported one of these outcomes (quality-of-care transition), and there was no statistically significant difference between groups.

Liang 2020³⁰ randomized 152 patients initiated on warfarin (about 50% for atrial fibrillation, another 20% for deep venous thrombosis) to either intervention (pharmacist-led education and follow-up service, abbreviated, involving 15 minutes of pre-discharge one-on-one warfarin education with a pharmacist, and a booklet, followed by two pharmacist followup telephone calls at 30 and 90 days after discharge, for reinforcement) or usual care (education from their physician at discharge, with control noneducational calls at the same time intervals after discharge). About the booklet in the intervention group, the authors stated that it included “dosage instructions, dietary and lifestyle considerations, actions to be taken in case of bleeding, thromboembolic complications or missed dose, proper pill-cutting technique, and the importance of medication adherence and INR monitoring.”³⁰ About the physician education given to patients in the control group, the study did not provide details. Anticoagulation control (measured in four different ways, specifically the percentage of time in therapeutic range for INR, the percentage of time within the expanded target INR range, the percentage of time with INR less than or equal to 1.5, and the percentage of time with INR less than or equal to 5) did not statistically significantly differ between groups for three of four metrics. The exception was the percentage of time within the expanded target INR range, which was 54 percent versus 42 percent in favor of the intervention.

Results From Nonrandomized Studies

Wu 2022³¹ compared outcomes before and after implementation of a hospital-based pharmacist-managed warfarin therapy service that included: (1) suggesting initial dose and dose adjustment, (2) developing a monitoring plan for INR and adverse reactions, (3) documenting and managing drug-drug and drug-food interactions, (4) identifying causes of supratherapeutic INR and providing suggestions for management, and (5) providing education to patients and their caregivers. Of patients admitted in the pre-implementation period, 62.9 percent had an INR in the

therapeutic range at their first return appointment post-discharge; for patients admitted in the post-implementation period, the percentage was 71.0 percent, a statistically nonsignificant difference.

Drejler 2020³² compared outcomes before and after implementation of a hospital-based multidisciplinary antithrombotic team focusing on: (1) education of hospital physicians, nurses, and pharmacists; (2) daily structured medication reviews by pharmacists; (3) drafting and updating antithrombotic therapy guidelines; (4) daily patient counseling; and (5) medication reconciliation at admission (preadmission data from patient's thrombosis service were provided to the responsible physician) and discharge (advice from the team was provided to the thrombosis service, general practitioner and community pharmacist). There was no statistically significant change from pre-implementation to postimplementation in the proportion of patients who experienced a composite end point consisting of one or more bleeding or thrombotic events in the three months post-discharge (odds ratio = 1.00, 95% CI = [0.70 to 1.42]).

Shields 2019³³ compared outcomes before and after implementation of a multidisciplinary anticoagulation task force including: (1) an electronic module that stores lab results, displays data trends, and offers providers recommendations for warfarin management, including best practice alerts and a calendar for followups and timely lab draws; (2) information for primary care providers on how to use the electronic module, monitor their patients' INRs, and educate patients about warfarin use; (3) a hyperlink to American College of Cardiology dosing protocols; and (4) a calendar and after-visit summary for patients containing previous INR values, upcoming appointments, and warfarin dosing. There was no statistically significant change in the time in therapeutic range (percentage of days INR was in therapeutic range out of the total number of days all patients were treated with warfarin) over the five-year study period for patients prescribed warfarin either by primary care providers (60.6% to 62.5%, $p = 0.191$) or by cardiologists (68.2% to 68.8%, $p = 0.182$). However, a statistically significant decrease occurred in the rate of severe adverse drug reactions (ADRs) attributed to warfarin following hospital discharge (the ratio of the number of severe warfarin ADRs to the total number of warfarin prescriptions), from 3.8 percent at baseline in 2013 to 1.8 percent, 2.4 percent, 1.2 percent, and 1.0 percent in 2014, 2015, 2016, and 2017, respectively ($p < 0.0001$).

Table 1. Overview of the included studies for PSP 1

Author, Year	Clinical Setting	Patients	PSP(s) and Comparator(s)	Risk of Bias*
Study Design	Country			
Manzato, 2021 ²⁸ RCT	Two teaching hospitals Brazil	52 adults initiating warfarin (25% for DVT, 25% for acute PE, 13% for cerebral VT, 11% AF, 25% other)	During hospitalization, both groups received education (illustrated powerpoint slides and a booklet) about warfarin, including signs and symptoms of complications. Intervention: 5 post-discharge telephone calls, reinforcing the education Comparator: No calls	High
Kapoor, 2020 ²⁹ RCT	Multihospital healthcare system United States	162 adults with a new episode of venous thromboembolism and prescribed anticoagulation (45% for DVT only, 36% for PE, and 19% for both DVT and PE)	Intervention: Home visit by a pharmacist within 7 days after discharge, and a follow-up call by an anticoagulation expert 8-30 days later Comparator: No intervention	High
Liang, 2020 ³⁰ RCT	Tertiary hospital China	152 adults initiated on warfarin (about 50% for AF, another 20% for DVT)	Intervention: Before discharge, 15 minutes of one-on-one warfarin education with a pharmacist, and a booklet. Two pharmacist follow-up telephone calls at 30 and 90 days after discharge, for reinforcement Comparator: Usual care. At discharge, education from their physicians. To control for contact time, study staff contacted patients at 30 and 90 days (no education provided).	High

Author, Year Study Design	Clinical Setting Country	Patients	PSP(s) and Comparator(s)	Risk of Bias*
Wu, 2022 ³¹ NRS with comparison	Tertiary hospital Taiwan	72 patients >20 years of age who were admitted for mechanical valve replacement with newly started warfarin therapy	<p>Intervention: Pharmacist- managed warfarin therapy including (1) suggesting initial dose and dose adjustment, (2) developing a monitoring plan for INR and adverse reactions, (3) documenting and managing drug-drug and drug-food interactions, (4) identifying causes of supratherapeutic INR and providing suggestions for management, and (5) providing education to patients and their caregivers</p> <p>Comparator: Conventional care (in the period prior to implementation of the intervention, initial dose and dose adjustment were managed by attending physicians based on clinical experience, and patients received education from a nurse or pharmacist with an instruction leaflet)</p>	Critical

Author, Year	Clinical Setting	Patients	PSP(s) and Comparator(s)	Risk of Bias*
Study Design	Country			
<p>Dreijer, 2020³²</p> <p>NRS with comparison</p>	<p>Two hospitals</p> <p>Netherlands</p>	<p>1,886 hospitalized patients treated with anticoagulant therapy</p>	<p>Intervention: Hospital-based multidisciplinary antithrombotic team focusing on: (1) education of hospital physicians, nurses, and pharmacists; (2) daily structured medication reviews by pharmacists; (3) drafting and updating antithrombotic therapy guidelines; (4) daily patient counseling; and (5) medication reconciliation at admission (pre-admission data from patient's thrombosis service were provided to the responsible physician) and discharge (advice from the team was provided to the thrombosis service, general practitioner and community pharmacist)</p> <p>Comparator: Usual care. Patients received standard automated medication surveillance at admission, limited or no patient counseling, and medication reconciliation at discharge without involvement of the hospital pharmacy</p>	<p>Critical</p>

Author, Year	Clinical Setting	Patients	PSP(s) and Comparator(s)	Risk of Bias*
Study Design	Country			
Shields, 2019 ³³ NRS with comparison	Healthcare system (the intervention appears to have been designed primarily for use by PCPs in the system) United States	4,311 patients prescribed warfarin at hospital discharge during the 5-year study period (patients discharged more than once during the period may be counted more than once in this total)	Intervention: Multidisciplinary anticoagulation task force including: (1) an electronic module that stores lab results, displays data trends, and offers providers recommendations for warfarin management, including best practice alerts and a calendar for follow-ups and timely lab draws; (2) information for PCPs on how to use the electronic module, monitor their patients' INRs, and educate patients about warfarin use; (3) hyperlink to American College of Cardiology dosing protocols; and (4) a calendar and after-visit summary for patients containing previous INR values, upcoming appointments, and warfarin dosing Comparator: Conventional care (prior to implementation of the intervention), not described	Critical

AF = atrial fibrillation; DVT = deep venous thrombosis; INR = international normalized ratio; NRS = nonrandomized study; PCP = primary care physician; PE = pulmonary embolism; RCT = randomized controlled trial; VT = venous thromboembolism

*For RCTs, we used a Cochrane Collaboration tool for assessing the risk of bias of RCTs,¹² and for NRS, we used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.¹³

Evidence Summary for PSP 2: Anticoagulation Management in Ambulatory Settings

We included eight systematic reviews that evaluated interventions for anticoagulation management in ambulatory settings (Table 2). Four SRs examined various telemedicine interventions or a combination of telemedicine and self-testing. Two SRs evaluated educational programs, with one of the two SRs focusing exclusively on educational programs delivered via mobile health applications. One SR examined the use of remote monitoring devices for management of anticoagulation therapy. The remaining SR focused on anti-Xa monitoring for management of anticoagulation therapy with low-molecular weight heparin. More details of the eight SRs appear in Table C-2, Appendix C.

Three SRs were rated as High risk of bias due to limitations of the studies included in the SRs. Two of these SRs included predominantly retrospective comparative studies or a mix of RCTs, comparative observational studies and single-arm pre-post studies; the third SR included 25 RCTs with many rated as High risk (11 RCTs) or unclear risk of bias (11 RCTs) by the authors of that SR. The remaining SRs were rated as Moderate risk of bias based on the average risk of bias of the RCTs included in those SRs.

Braga Ferreira 2023²³ included 25 RCTs that randomized a total of 25,476 participants to receive telemedicine-based management of oral anticoagulation therapy or usual care; the specific telemedicine interventions were categorized as computer-assisted dosing, laboratory testing with remote adjustment, self-testing, and multitasking application. Most of the included studies enrolled patients on VKAs; 2 studies included patients on DOACs. The authors performed meta-analyses for several outcomes. Overall, telemedicine increased the time in therapeutic range (TTR) compared to usual care and was associated with lower rates of thromboembolic events, although the latter between-group difference reached statistical significance only in the multitasking application subgroup of studies. Telemedicine and usual care showed similar rates of major bleeding and mortality.

Huang 2023²⁰ included eight RCTs that randomized a total of 3,853 participants on VKAs to receive a combination of telemedicine and self-testing (with portable coagulometers) or usual anticoagulation management. The authors performed meta-analyses for several outcomes. Like Braga Ferreira, Huang et al. found that combined telemedicine and self-testing statistically significantly improved TTR compared to usual care; while it also reduced thromboembolic events, the between-group difference did not reach statistical significance. Compared to usual care, telemedicine plus self-testing did not reduce major bleeding, rehospitalization, or mortality.

Tran 2021²⁵ included 11 studies (1 RCT and 10 retrospective controlled cohort studies) that enrolled 8,395 participants who received either a telepharmacy intervention (telephone, video, or online anticoagulation management by a pharmacist) or face-to-face management by a pharmacist or physician. The authors performed meta-analyses for several outcomes. Telepharmacy had a statistically significantly lower rate of any bleeding and any hospitalization than face-to-face management. It

also showed lower rates of thromboembolic events and major bleeding, but the between-group differences were not statistically significant. The mean TTR was identical in both groups.

Dai 2020²⁴ included 15 RCTs that randomized 2,218 participants on warfarin to receive telemedicine (delivered via telephone, internet, or software) for anticoagulation monitoring or usual care. The authors performed meta-analyses for several outcomes. The TTR was statistically significantly higher in the telemedicine group than the control group. The telemedicine group had lower mortality and fewer thromboembolic events than the control group, but the between-group differences were not statistically significant. The two groups did not differ significantly in the number of major or minor bleeding events or hospitalizations.

Jang 2021²² included 12 studies (5 RCTs, 4 controlled cohort studies, 3 single-group pre-post studies) that enrolled 18,812 participants who received mobile health application educational programs; in controlled studies this was compared to usual care. The SR did not perform quantitative synthesis of data and provided a minimal and somewhat insufficient narrative summary of study findings. Quality of life was more improved in the mobile apps group than the control group in most of the included studies. Clinical indicators of INR maintenance, mortality, and readmission also showed improvement with mobile apps.

Lo 2022²¹ included 9 studies (8 RCTs and 1 controlled clinical trial) that enrolled 1,335 participants on warfarin who received educational programs on anticoagulation management or usual care. The SR authors performed a narrative synthesis of findings. Results were mixed with some studies showing significantly higher TTR in the education groups and other studies showing no significant between-group difference. Similarly, two studies showed significantly lower rates of minor bleeding (one also showed significantly fewer major bleeding events), while four other studies showed either no significant differences (two studies) or no bleeding events in either group (two studies). No studies reported significant between-group differences in thromboembolic events. All studies that demonstrated positive effects on any outcome included multiple educational strategies (lecture, question and answer, written material, video, slides and/or telephone).

Jang 2020²⁶ included three RCTs that randomized 2,837 participants to receive either remote monitoring for guiding anticoagulation therapy or conventional anticoagulation therapy. Patients in one study received DOACs, in another study patients received NOACs, and anticoagulants used in the third study were not reported. Remote monitoring devices included ICDs, CRT defibrillators (CRT-D), pacemakers (PM), or iphones. The results were narratively summarized. For patients with paroxysmal atrial fibrillation, 1 of 2 studies showed gastrointestinal bleeding was more frequent with conventional anticoagulation therapy than with RM-guided anticoagulation therapy (16% vs. 0%; $P=0.047$). However, another study reported 1 case of fatal bleeding in the RM-guided anticoagulation therapy group and no major bleeding in the control group. In the remaining study, patients were included without existing arrhythmia and patients were divided into RM-guided anticoagulation therapy

and conventional anticoagulation therapy. The rate of major bleeding was similar in the two groups.

Wu 2020²⁷ included 6 studies (2 RCTs and 4 controlled cohort studies) that enrolled 1,617 participants who received either anti-Xa monitoring of low-molecular weight heparin (LMWH, with variable dosing based on provider monitoring of LMWH via anti-Xa assay [the gold standard of LMWH monitoring]) or a fixed dose of LMWH with no monitoring (control group). No details were reported on the types of providers who performed anti-Xa monitoring, and the only specific LMWHs used in the studies were enoxaparin and dalteparin. A meta-analysis found that the Anti-Xa monitoring group had a significantly lower incidence of venous thromboembolism events than the control group. A subgroup analysis found that the incidence of venous thromboembolism events in the anti-Xa monitoring group was lower than that in the control group when the anti-Xa trough level was monitored but not when the anti-Xa peak level was monitored. A meta-analysis comparing bleeding events found no statistically significant between-group difference.

Table 2. Overview of the included reviews for PSP 2

Author, Year	Clinical Setting	Number of Participants	PSP(s)	Risk of Bias*
Study Design	Country			
Braga Ferreira, 2023 ²³ Systematic review (SR)	Home setting (telemedicine) SR conducted in Brazil; included studies were from several countries	25,476 participants in 25 RCTs	Computer-assisted dosing Laboratory testing with remote adjustment Self-testing Multitasking application	High
Huang, 2023 ²³ SR	Home setting (telemedicine) SR conducted in China; included studies were from several countries	3,853 participants in 8 RCTs	Combines telemedicine and self-testing (with portable coagulometers)	Moderate
Lo, 2022 ²¹ SR	Outpatient hospital, clinic, or community pharmacy SR conducted in Hong Kong; included studies were from several countries	1,335 participants in 9 studies (8 RCTs and 1 CCT)	Educational programs on how to manage anticoagulants (most studies used a mix of multiple educational strategies: lecture, question and answer, written material, video, slides and/or telephone). Outcomes included bleeding rates, thromboembolic events, and TTR.	Moderate

Author, Year	Clinical Setting	Number of Participants	PSP(s)	Risk of Bias*
Study Design	Country			
Jang, 2021 ²² SR	Outpatient hospital SR conducted in Korea; included studies were from several countries	18,812 participants in 12 studies (5 RCTs, 4 controlled cohort studies, 3 single-group pre-post studies)	Mobile Health apps educational program	High
Tran, 2021 ²⁵ SR	Home or laboratory (telepharmacy) SR conducted in USA; 10 of 11 included studies were from USA	8,395 participants in 11 studies (1 RCT and 10 retrospective controlled cohort studies)	Telephone, video or online anticoagulation management by pharmacist compared with face-to-face management by pharmacist or physician	High
Jang, 2020 ²⁶ SR	Home or other non-hospital setting SR conducted in Taiwan; included studies conducted in other countries	2,837 participants in 3 RCTs	Remote monitoring (ICD, CRT-D, PM, or iphone) for guiding anticoagulation therapy vs. conventional anticoagulation therapy	Moderate
Wu, 2020 ²⁷ SR	Ambulatory setting (not specified) SR conducted in China; included studies conducted in several countries	1,617 participants in 6 studies (2 RCTs and 4 controlled cohort studies)	Anti-Xa monitoring of low-molecular weight heparin	Moderate
Dai, 2020 ²⁴ SR	Home setting (telemedicine) SR conducted in China; included studies conducted in several countries	2,218 participants in 15 RCTs	Telemedicine (telephone, internet, or software) for anticoagulation monitoring	Moderate

CCT = controlled clinical trial; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardiac defibrillator; PM = pacemaker; PSP = patient safety practice; RCT = randomized controlled trial; SR = systematic review; TTR = time in therapeutic range

3.2.6 Question 6. What Are the Common Barriers and Facilitators to Implementing These PSPs?

Egunsola 2021³⁴ conducted a qualitative systematic review summarizing some barriers to one particular type of anticoagulation PSP, namely community pharmacist-led anticoagulation management services (CPAMS). These provide point-of-care INR testing and warfarin dose adjustment. The review included 17 studies, conducted in New Zealand (9 studies), Canada (4 studies), the United Kingdom (3 studies), and Australia (1 study). The reviewers reported 5 barriers to implementation:

- *Patients' perceived quality of care.* Some patients were skeptical that they would receive sufficient care, either due to doubts about the pharmacists'

- expertise, or their perceived reliance on dose recommendations from a computer.
- *Resistance from clinicians.* This was due to not being initially approached by a general-practitioner organization, or concern about who would be responsible if something went wrong, or a lack of belief that pharmacists were necessary for anticoagulation management, or concerns about warfarin doses recommended by the computer.
 - *Concerns about the funding model.* Funding was based on number of patients rather than number of consultations, and some pharmacists felt that this did not account for complicated patients who required multiple consultations. Some patients said they would rather pay their regular doctor than the service and were concerned about high cost.
 - *Capping.* One program set a limit on the number of patients enrolled per pharmacy, or the number of pharmacies providing the service, which reduced access.
 - *Organizational limits.* In some implementations, the CPAMS services demanded time that required juggling staff, or building physical layout limitations that made CPAMS harder to implement.

Egunsola 2021³⁴ noted some reported advantages of CPAMS that reviewers called “facilitators,” but they were not PSP facilitators as relevant to this Review Question, which would be specific aspects that assist PSP implementation (e.g., CPAMS work better when aspect X is present or when aspect Y is absent). The advantages listed were convenience, accessibility, efficiency, clinical outcomes, scalability, professional satisfaction, and enhanced collaboration. While such advantages are not unique to CPAMSs (e.g., many telehealth interventions), the authors did discuss them in the context of CPAMS.

Huang 2023²⁰ considered the popularity of portable coagulometers to be a facilitator of self-testing and self-management of anticoagulation therapy. The authors also considered telemedicine via telephone or internet to be a facilitator of drug monitoring, including anticoagulation therapy.

Braga Ferreira 2023²³ mentioned cost and reimbursement as limiting factors to telemedicine services in general, which includes telemedicine interventions for anticoagulation management.

3.2.7 Question 7. What Resources (e.g., Cost, Staff, Time) Are Required for the Implementation of These PSPs?

In this section, we discuss five publications that describe the resources necessary for the implementation of either PSP 1 or PSP 2. We only discuss studies addressing potential costs in countries categorized as those with “very high” human development index (HDI), because costs in other countries would not apply to the United States.

Jones 2022³⁵ performed a systematic review on economic aspects of service interventions. Two studies of the relative cost of anticoagulation clinics (one in the United States and one in the Netherlands) each found that the clinics were cost-saving (by \$2,100 over 10 years in the U.S. study and 735 euros per patient per year in the Dutch study). Neither review detailed the precise factors contributing to the lower costs in those two studies. A third study compared two types of anticoagulation clinics in the United Kingdom: those in primary care versus those in secondary care (the meaning of this comparison was not explicitly stated by the review authors). Primary care clinics had higher National Health Service costs (by 28 pounds) but lower patient costs (by 34 pounds), and the overall cost did not statistically significantly differ between primary and secondary care.

Garay 2022³⁶ presented cost-utility models of anticoagulation clinics (AC) and point-of-care (POC) monitoring devices (e.g., CoaguCheck, which can be administered either by nurses/clinicians in a clinic or by patients in their home) in Argentina (using various years of modeled data). There were four modeled interventions: (1) neither AC nor POC, (2) AC but not POC, (3) POC but no AC, and (4) both AC and POC. The per-patient lifetime discounted costs for these four simulated groups (using Argentinian pesos) were \$377,625 in group 1, \$374,683 in group 2, \$368,370 in group 3, and \$365,416 in group 4. These numbers indicate cost savings for both AC (about \$9000 per-patient lifetime) and POC (about \$3000 per-patient lifetime). Using the study's exchange rate of 143 Argentine pesos per dollar, these savings correspond to about \$63 USD for AC and \$21 USD for POC (again, per-patient lifetime).

Huang 2022²⁰ performed a systematic review that summarized two RCTs on costs (one in 2003-2008 in the United States, and one in 2002-2004 in Hong Kong). The intervention in both studies involved giving patients portable coagulometers and utilizing telemedicine (e.g., telephone, internet) for important reminders and education regarding anticoagulation medications, and the control groups received ordinary anticoagulation management. The U.S. study of about 3,000 patients at VA medical centers found an average two-year cost of \$25,754 for the intervention group and \$24,505 for the control group, for a difference of \$1,249 over 2 years (not statistically significant from zero). The Hong Kong study of 138 patients found a per-patient-per-month cost of \$76 for the intervention group and \$98 for the control group, for a difference of \$22 (not statistically significant from zero).

Dreijer 2020³² conducted a prospective comparative study in the Netherlands in 2015-2017. The intervention group received care from a “multidisciplinary antithrombotic team focusing on education, medication reviews by pharmacists, implementing of local anticoagulant therapy guidelines based on national guidelines, patient counselling and medication reconciliation at admission and discharge.” Note that the intervention group did not receive any post-discharge intervention, but because the intent was to improve post-discharge anticoagulation safety (i.e., at home), and data were collected up to three months after discharge, it is relevant to PSP 1. The usual care group received “the normal procedures of medication surveillance, patient counselling and medication reconciliation at admission and discharge.” The mean cost

per patient admission for staff labor was slightly higher in the intervention group in both hospitals (by 70–90 euros). However, other costs were much higher in the usual care group in both hospitals, most prominently the costs for hospitalization days (by 400–780 euros, average difference of 1.5 hospital days). This resulted in an overall cost savings of the intervention in both hospitals (by 518–842 euros).

Bobade 2019³⁷ conducted a cost study about a warfarin management clinic at the Mayo Clinic in 2014–2015. They considered the overall cost of clinic care for three types of patients: the average patient (those who required one-to-three patient care visits per month, 33% of the population, average \$1,458 per year), the stable patient (those who required one patient care visit per month, 48%, \$960 per year), and the unstable patient (those who required three or more patient care visits per month, 19 percent, \$3,145 per year). The actual program cost (excluding other costs such as warfarin cost, bridging medication, POC INR testing, and lab INR testing) contributed 60–88 percent of the overall cost depending on the type of patient as well as whether the patient was tested using venipuncture with telephone followup or in-person POC testing.

3.2.8 Question 8. What Toolkits Are Available To Support the Implementation of the PSPs?

For this question, we identified two relevant toolkits from AHRQ’s Patient Safety Network (PSNet). The first, *Medications at Transitions and Clinical Handoffs (MATCH) Toolkit for Medication Reconciliation* (August 2012)³⁸ is relevant to PSP 1 of this report. While primarily focused on transitions within healthcare settings (see Figure 1 of the report for a visual overview of the inpatient process), it does also provide some guidance for transition to home (Figure 2 of the report). The toolkit comprises seven chapters ranging from how to gain leadership support within the healthcare organization developing the reconciliation process to training staff and measuring success. Each chapter contains lists of questions to consider when addressing various components of managing medication transitions.

The other toolkit, *Improving Medication Safety in High Risk Medicare Beneficiaries Toolkit* (July 2012),³⁹ is relevant to PSP 2 of this report, and provided nine tools, six for the delivery or provision of a medication treatment management program, and three for assessing the effect of such a program. An example of the first type of tool is the Modified Pharmaceutical Care Network Europe (PCNE) Drug Assessment Form (Appendix E of the toolkit). This form is completed separately for each medication a patient is taking, and asks healthcare staff questions about whether an ADE is occurring, whether there is a problem with the specific medication or its dose, whether the patient is having difficulty taking the drug, and whether the patient is at risk of either an ADE or drug-drug interaction. An example of a tool in the second category is the Office, Emergency Department, and Hospital Visit Assessment Survey Form (Appendix H of the toolkit). This patient-completed form asks the patient about any visits to the emergency room or hospital or doctor’s offices in the past 3 months, and which of those visits were due to medication side effects.

An additional related tool, published by AHRQ in 2015 in both English and Spanish, helps educate patients about blood thinners and safe usage. See <https://www.ahrq.gov/sites/default/files/wysiwyg/patients-consumers/diagnosis-treatment/treatments/btpills/btpills.pdf>.



4. Discussion

4.1 Interpretation of Findings

For PSP 1 on care transitions, we included three RCTs and three nonrandomized comparative studies. Considering the three RCTs together, we saw evidence of no clinical benefit of PSPs that target the immediate post-discharge period, despite patients' vulnerability to bleeding during that time. Of the three NRSs, two found no statistically significant impact of the PSP. The third had mixed effects, finding that even though there was no impact on time-in-therapeutic INR range, adverse drug reactions related to warfarin decreased statistically significantly from 3.8 percent in the year prior to implementation to 1–2.4 percent in the 4 years after implementation. One notable difference between this study and the other two NRSs is that the PSP was instituted by a healthcare system and was primarily aimed at medical care providers in ambulatory settings, whereas in the other two studies, the PSPs were instituted by hospitals and were primarily aimed at hospital staff, although they included provision of information, education, and/or advice to patients and post-hospitalization caregivers. One cannot determine the precise reason(s) for why this study found an impact on adverse events but other studies did not.

Across the six studies, the balance of evidence suggests that PSPs targeting care transitions do not influence adverse event rates related to anticoagulation. In two of the three RCTs (all except Kapoor 2020),²⁹ patients in the control groups had received some anticoagulation education before discharge. The same was true in two of the three NRSs (the third NRS, Shields,³³ did not report what level of pre-discharge education they gave to the control group). Possibly, brief patient education before discharge is sufficient to prevent most major bleeding, at least in the short-term.

In the longer term ambulatory care setting (PSP 2), patients may gradually lapse in their medication adherence and consistent INR testing, providing a clear need for a PSP. We included 8 systematic reviews covering various telemedicine-related interventions, educational programs, remote monitoring, and anti-Xa monitoring. Most telemedicine interventions improved TTR relative to usual care, which theoretically should reduce the risk of more serious events (e.g., thromboembolic events and major bleeding). Telepharmacy was the only telemedicine intervention shown to significantly reduce the risk of any bleeding and any hospitalization. Other telemedicine interventions showed statistically–non-significant reductions in major bleeding and thromboembolic events. Given the relatively low frequency of these events, the meta-analyses may have lacked adequate statistical power to detect a between-group difference. The evidence evaluating the impact of educational programs on clinical outcomes is mixed and given that the studies could not be combined in meta-analyses the clinical benefits therefore remain unclear. Remote monitoring studies showed mixed findings regarding the impact of remote monitoring on rates of major bleeding; more studies are necessary to clarify the potential benefit of these devices for anticoagulation management. These devices would only be

applicable to patients with specific indications, not all conditions for which one might receive anti-coagulation. Anti-Xa monitoring appears to provide clinical benefit in the ambulatory setting, as it did lower the rate of thromboembolic events in patients receiving LMWH for venous thromboembolism, while major bleeding rates did not differ between the monitoring and control groups.

Three publications described possible facilitators and barriers of implanting PSPs related to safe anticoagulation. Facilitators included portability for coagulometers, and telephones/internet for monitoring and reminders. Barriers included financial concerns, skepticism from both patients and general practitioners, and organizational limits such as staff assignments and building configurations.

4.2 Limitations

Confidence intervals around effects allow one to categorize statistically non-significant effects as “no benefit” or, alternatively, “inconclusive.” However, studies on care transitions did not generally report confidence intervals. This meant that when a study on a PSP for care transitions found a statistically non-significant effect, we could not determine whether a conclusion of no-benefit was statistically justified.

For the studies of care transitions, many interventions had multiple components, some of which were not focused on the safety of anticoagulation, but still could theoretically influence rates of adverse events. The study designs did not allow one to isolate the contributions of specific components.

For risk of bias of the evidence included in the eight systematic reviews on ambulatory care, we relied on the authors’ assessments. Different authors used different scales for assessing risk of bias; therefore, the same study may have been rated differently by different reviews.

4.3 Implications and Conclusions

Many patient safety practices exist to help prevent bleeding episodes due to anticoagulation medications. The time period immediately after discharge is particularly important, but evidence on PSPs that target this period generally did not find that PSPs reduce the risk of adverse events. For general ambulatory care (e.g., monitoring), several systematic reviews have found benefits of telemedicine interventions or anti-Xa monitoring in increasing patients’ time in therapeutic range or reducing rates of bleeding, hospitalization, and thromboembolic events. Because the majority of patients in the evidence base were receiving warfarin, but not DOACs, future research should address the effectiveness of PSPs for reducing the risk of bleeding and other adverse events in patients receiving DOACs. Also, future research should attempt to determine which components of telemedicine for ambulatory care (e.g., better dose monitoring, better patient education, better caregiver education) are most critical to help reduce adverse events related to anticoagulation.



5. References

1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019 Jul;140(2):e125-e51. doi: 10.1161/CIR.0000000000000665. PMID: 30686041.
2. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016 Oct;17(10):e452-e66. doi: 10.1016/S1470-2045(16)30369-2. PMID: 27733271.
3. Kakkar AK, Cimminiello C, Goldhaber SZ, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N Engl J Med*. 2011 Dec;365(26):2463-72. doi: 10.1056/NEJMoa1111288. PMID: 22204723.
4. Wang C, Chi C, Guo L, et al. Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis. *Crit Care*. 2014 Oct;18(5):563. doi: 10.1186/s13054-014-0563-4. PMID: 25318353.
5. Giossi R, Menichelli D, Pani A, et al. A systematic review and a meta-analysis comparing prophylactic and therapeutic low molecular weight heparins for mortality reduction in 32,688 COVID-19 patients. *Front Pharmacol*. 2021;12:698008. doi: 10.3389/fphar.2021.698008. PMID: 34539396.
6. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: Focus on new anticoagulant agents. *Blood*. 2008 May;111(10):4871-9. doi: 10.1182/blood-2007-10-120543. PMID: 18309033.
7. Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016 Nov;316(20):2115-25. doi: 10.1001/jama.2016.16201. PMID: 27893129.
8. Harris Y, Hu DJ, Lee C, et al. Advancing medication safety: establishing a national action plan for adverse drug event prevention. *Jt Comm J Qual Patient Saf*. 2015 Aug;41(8):351-60. doi: 10.1016/s1553-7250(15)41046-3. PMID: 26215524.
9. Hall KK, Shoemaker-Hunt S, Hoffman L, et al. Making healthcare safer III: a critical analysis of existing and emerging patient safety practices. (Prepared by Abt Associates Inc., under Contract No. 233-2015-00013-I) AHRQ Publication No. 20-0029-EF. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2020 Mar. <https://www.ahrq.gov/research/findings/making-healthcare-safer/mhs3/index.html>.
10. Holbrook A, Benipal H, Paterson JM, et al. Adverse event rates associated with oral anticoagulant treatment early versus later after hospital discharge in older adults: a retrospective population-based cohort study. *CMAJ Open*. 2021 Apr-Jun;9(2):E364-E75. doi: 10.9778/cmajo.20200138. PMID: 33863794.
11. Evidence-based Practice Centers. Rockville (MD): Agency for Healthcare Research and Quality; 2023 May. <https://effectivehealthcare.ahrq.gov/about/epc>. Accessed on July 28, 2023.
12. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(7829). doi: 10.1136/bmj.d5928. PMID: 22008217.
13. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.

14. Kahwati LC, Asher GN, Kadro ZO, et al. Screening for atrial fibrillation: Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2022 Jan;327(4):368-83. doi: 10.1001/jama.2021.21811. PMID: 35076660.
15. Fong KY, Chan YH, Yeo C, et al. Systematic review and meta-analysis of direct oral anticoagulants versus warfarin in atrial fibrillation with low stroke risk. *Am J Cardiol*. 2023 Oct;204:366-76. doi: 10.1016/j.amjcard.2023.07.108. PMID: 37573616.
16. Geller AI, Shehab N, Lovegrove MC, et al. Bleeding related to oral anticoagulants: Trends in US emergency department visits, 2016-2020. *Thromb Res*. 2023 May;225:110-5. doi: 10.1016/j.thromres.2023.03.010. PMID: 37062120.
17. Alonso A, MacLehose RF, Chen LY, et al. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. *Heart*. 2017 Jun;103(11):834-9. doi: 10.1136/heartjnl-2016-310586. PMID: 28057799.
18. Zareh M, Davis A, Henderson S. Reversal of warfarin-induced hemorrhage in the emergency department. *West J Emerg Med*. 2011 Nov;12(4):386-92. doi: 10.5811/westjem.2011.3.2051. PMID: 22224125.
19. Pourdeyhimi N, Bullard Z. Warfarin-induced skin necrosis. *Hosp Pharm*. 2014;49(11):1044-8. doi: 10.1310/hpj4911-1044. PMID: 25673894.
20. Huang Y, Xie Y, Huang L, et al. The value of anticoagulation management combining telemedicine and self-testing in cardiovascular diseases: A meta-analysis of randomized controlled trials. *Ther Clin Risk Manag*. 2023 Aug;19:279-90. doi: 10.2147/TCRM.S395578. PMID: 36941980.
21. Lo FMW, Wong EML, Hong FKW. The effects of educational programs on knowledge, international normalized ratio, warfarin adherence, and warfarin-related complications in patients receiving warfarin therapy: An integrative review. *J Cardiovasc Nurs*. 2022 May-Jun;37(3):E32-E46. doi: 10.1097/JCN.0000000000000790. PMID: 33657063.
22. Jang I. A systematic review on mobile health applications' education program for patients taking oral anticoagulants. *Int J Environ Res Public Health*. 2021 Aug;18(17):8902. doi: 10.3390/ijerph18178902. PMID: 34501492.
23. Braga Ferreira L, Lanna de Almeida R, Arantes A, et al. Telemedicine-based management of oral anticoagulation therapy: Systematic review and meta-analysis. *J Med Internet Res*. 2023 Jul;25:e45922. doi: 10.2196/45922. PMID: 37428532.
24. Zheng C, Dai H, Lin C, et al. Technology-based interventions in oral anticoagulation management: Meta-analysis of randomized controlled trials. *J Med Internet Res*. 2020 Jul;22(7):e18386. doi: 10.2196/18386. PMID: 32673227.
25. Tran RJC, Yamzon J, Stewart TL, et al. Effectiveness of telepharmacy versus face-to-face anticoagulation services in the ambulatory care setting: A systematic review and meta-analysis. *Ann Pharmacother*. 2021 Sep;55(9):1084-95. doi: 10.1177/1060028020983539. PMID: 33384017.
26. Jang JP, Lin HT, Chen YJ, et al. Role of remote monitoring in detection of atrial arrhythmia, stroke reduction, and use of anticoagulation therapy - a systematic review and meta-analysis. *Circ J*. 2020 Oct;84(11):1922-30. doi: 10.1253/circj.CJ-20-0633. PMID: 33012748.
27. Wu T, Xia X, Chen W, et al. The effect of anti-Xa monitoring on the safety and efficacy of low-molecular-weight heparin anticoagulation therapy: A systematic review and meta-analysis. *J Clin Pharm Ther*. 2020 Aug;45(4):602-8. doi: 10.1111/jcpt.13169. PMID: 32449992.

28. Manzato RO, Ciol MA, Bolela F, et al. The effect of reinforcing an educational programme using telephone follow-up on health-related quality of life of individuals using warfarin: A randomised controlled trial. *J Clin Nurs*. 2021 Oct;30(19-20):3011-22. doi: 10.1111/jocn.15811. PMID: 33893673.
29. Kapoor A, Landyn V, Wagner J, et al. Supplying pharmacist home visit and anticoagulation professional consultation during transition of care for patients with venous thromboembolism. *J Patient Saf*. 2020 Dec;16(4):e367-e75. doi: 10.1097/PTS.0000000000000571. PMID: 30702452.
30. Liang JB, Lao CK, Tian L, et al. Impact of a pharmacist-led education and follow-up service on anticoagulation control and safety outcomes at a tertiary hospital in China: A randomised controlled trial. *Int J Pharm Pract*. 2020 Feb;28(1):97-106. doi: 10.1111/ijpp.12584. PMID: 31576625.
31. Wu CW, Wu CC, Chen CH, et al. The impact of pharmacist-managed service on warfarin therapy in patients after mechanical valve replacement. *Int J Clin Pract*. 2022 Mar;2022:1617135. doi: 10.1155/2022/1617135. PMID: 35685594.
32. Dreijer AR, Kruip M, Diepstraten J, et al. Effect of antithrombotic stewardship on the efficacy and safety of antithrombotic therapy during and after hospitalization. *PLoS ONE*. 2020 Jun;15(6):e0235048. doi: 10.1371/journal.pone.0235048. PMID: 32584857.
33. Shields LBE, Fowler P, Siemens DM, et al. Standardized warfarin monitoring decreases adverse drug reactions. *BMC Fam Pract*. 2019 Nov;20(1):151. doi: 10.1186/s12875-019-1041-5. PMID: 31699045.
34. Egunsola O, Li JW, Mastikhina L, et al. A qualitative systematic review of facilitators of and barriers to community pharmacists-led anticoagulation management service. *Ann Pharmacother*. 2022 Jun;56(6):704-15. doi: 10.1177/10600280211045075. PMID: 34510918.
35. Jones NR, Crawford W, Yang Y, et al. A systematic review of economic aspects of service interventions to increase anticoagulation use in atrial fibrillation. *Thromb Haemost*. 2022 Mar;122(3):394-405. doi: 10.1055/a-1515-9428. PMID: 34020487.
36. Garay OU, Guiñazú G, Adamczuk YP, et al. Cost-utility and budget impact analysis of implementing anticoagulation clinics and point-of-care monitoring devices in anticoagulated patients in Argentina. *Pharmacoecoon Open*. 2022 Sep;6(5):657-68. doi: 10.1007/s41669-022-00352-4. PMID: 35835938.
37. Bobade RA, Helmers RA, Jaeger TM, et al. Time-driven activity-based cost analysis for outpatient anticoagulation therapy: Direct costs in a primary care setting with optimal performance. *J Med Econ*. 2019 May;22(5):471-7. doi: 10.1080/13696998.2019.1582058. PMID: 30744455.
38. Medications at Transitions and Clinical Handoffs (MATCH) toolkit for medication reconciliation [internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2012. <https://www.ahrq.gov/patient-safety/settings/hospital/match/index.html>. Accessed on September 22, 2023.
39. Touchette DR, Stubbings J, Schumock G. Improving medication safety in high risk Medicare beneficiaries toolkit. (Prepared by the Duke University DEcIDE Center, under Contract No. 290-05-0032, the RTI International DEcIDE Center, under Contract No. 290-05-0036, and the University of Illinois at Chicago (UIC)/Chicago-Area DEcIDE Center, under Contract No. 290 05-0038). Effective healthcare research report. Rockville (MD): Agency for Healthcare Research and Quality; 2012 Jul:61. http://www.effectivehealthcare.ahrq.gov/ehc/products/33/1186/DEcIDE38_Toolkit_2012071.pdf.

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Disclaimers

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Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program is developing a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe. AHRQ recognizes that people are struggling with urgent questions on how to make healthcare safer. AHRQ is using this rapid format for the fourth edition of its Making Healthcare Safer series of reports, produced by the EPC Program and the General Patient Safety Program. To shorten timelines, reviewers make strategic choices about which processes to abridge. However, the adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used and the resulting limitations of the evidence synthesis are extremely important.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to AHRQ. If you have comments related to this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to MHS@ahrq.hhs.gov.

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Appendixes

Appendix A. Methods: Search Strategy for Published Literature

Table A-1. Interventions to support safe transitions and continuation of anticoagulants post-discharge

Line #	Description	String
#1	General Anticoagulants	"Anticoagulants"[Majr] OR "anti coagula*"[ti] OR anticoagula*[ti] OR "anti thromb*"[ti] OR antithromb*[ti] OR "indirect thrombin inhibitor*"[ti]
#2	Heparin	"Heparin"[Majr] OR clexane*[ti] OR dalteparin*[ti] OR enoxaparin*[ti] OR fragmin*[ti] OR fraxiparin*[ti] OR heparin*[ti] OR innohep*[ti] OR liquaemin*[ti] OR lovenox*[ti] OR nadroparin*[ti] OR tedelparin*[ti] OR tinzaparin*[ti]
#3	Warfarin	"Vitamin K/antagonists and inhibitors"[Majr] OR "Warfarin"[Majr] OR aldocumar*[ti] OR coumadin*[ti] OR marevan*[ti] OR tedicumar*[ti] OR warfant*[ti] OR warfarin*[ti]
#4	Direct Thrombin Inhibitors	"Antithrombins"[Majr] OR "argatroban" [Supplementary Concept] OR "bivalirudin" [Supplementary Concept] OR "Dabigatran"[Majr] OR "desirudin" [Supplementary Concept] OR "direct thrombin inhibitor*"[ti] OR acova*[ti] OR angiomax*[ti] OR argatroban*[ti] OR bivalirudin*[ti] OR dabigatran*[ti] OR desirudin*[ti] OR desulfatohirudin*[ti] OR desulphatohirudin*[ti] OR hirulog*[ti] OR Iprivask*[ti] OR novastan*[ti] OR pradaxa*[ti] OR revasc[ti]
#5	Factor Xa Inhibitors	"Factor Xa Inhibitors"[Majr] OR "antistasin" [Supplementary Concept] OR "apixaban" [Supplementary Concept] OR "betrixaban" [Supplementary Concept] OR "Dabigatran"[Majr] OR "edoxaban" [Supplementary Concept] OR "Fidexaban" [Supplementary Concept] OR "Fondaparinux"[Majr] OR "lefaxin" [Supplementary Concept] OR "otamixaban" [Supplementary Concept] OR "razaxaban" [Supplementary Concept] OR "Rivaroxaban"[Majr] OR "factor xa inhibit*"[ti] OR antistasin*[ti] OR apixaban*[ti] OR arixtra*[ti] OR betrixaban*[ti] OR bevyxxa*[ti] OR dabigatran*[ti] OR doac[ti] OR doacs[ti] OR edoxaban*[ti] OR eliquis*[ti] OR eribaxaban*[ti] OR fidexaban*[ti] OR fondaparinux*[ti] OR lefaxin*[ti] OR letaxaban*[ti] OR lixiana*[ti] OR noac[ti] OR noacs[ti] OR otamixaban*[ti] OR pradaxa*[ti] OR quixidar*[ti] OR razaxaban*[ti] OR rivaroxaban*[ti] OR savaysa*[ti] OR tanogitran*[ti] OR xarelto*[ti] OR yagin*[ti]
#6	Combine Population Strings	#1 OR #2 OR #3 OR #4 OR #5
#7	Care Transitions	"Continuity of Patient Care"[Mesh] OR "Health Transition"[Mesh] OR "after treatment"[tiab] OR "care continu*"[tiab] OR "care retention"[tiab] OR "continuity of care*"[tiab] OR "follow up care*"[tiab] OR "hospital to home*"[tiab] OR "transitional care*"[tiab] OR discharg*[tiab] OR handoff*[tiab] OR transfer*[tiab] OR transition*[tiab]
#8	Combine Populations & Interventions	#6 AND #7
#9	Identify SRs	((meta-analysis[pt] OR "systematic review"[pt] OR "cochrane database syst rev"[ta] OR systematic*[ti] OR cochrane*[tiab] OR "meta analy*"[tiab] OR metaanaly*[tiab] OR (search*[tiab] AND (cinahl*[tiab] OR databases[tiab] OR ebSCO*[tiab] OR embase*[tiab] OR psychinfo*[tiab] OR psycinfo*[tiab] OR "science direct*"[tiab] OR sciencedirect*[tiab] OR scopus*[tiab] OR systematic*[tiab] OR "web of knowledge*"[tiab] OR "web of science*"[tiab])) OR ((rapid[tiab] OR systematic*[tiab] AND review*[tiab])))

Line #	Description	String
#10	Identify RCTs	(random allocation[mh] OR "randomized controlled trial"[pt] OR "phase 3"[tiab] OR "phase iii"[tiab] OR random*[tiab] OR RCT[tiab])
#11	Identify non-randomized studies	(clinical trial[pt] OR compar*[ti] OR comparative study[pt] OR versus[ti] OR vs[ti] OR "comparative effectiveness research"[Mesh] OR (control[tw] AND study[tw]) OR program[tw] OR epidemiologic studies[mh]) NOT((animals[mh:noexp] NOT humans[mh:noexp]) OR comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])
#12	Limit study types	#8 AND (#9 OR #10 OR #11)
#13	Remove Animal Studies	#12 NOT (((Animals[Mesh:NoExp] OR "Models, Animal"[Mesh:NoExp] OR "Disease Models, Animal"[Mesh:NoExp]) NOT Humans[Mesh:NoExp]) OR ((animal[Title] OR animals[Title] OR canine*[Title] OR dog[Title] OR dogs[Title] OR feline[Title] OR hamster*[Title] OR lamb[Title] OR lambs[Title] OR mice[Title] OR monkey[Title] OR monkeys[Title] OR mouse[Title] OR murine[Title] OR pig[Title] OR piglet*[Title] OR pigs[Title] OR porcine[Title] OR primate*[Title] OR rabbit*[Title] OR rat[Title] OR rats[Title] OR rodent*[Title] OR sheep*[Title] OR swine[Title] OR veterinar*[Title] OR (vitro[Title] NOT vivo[Title])) NOT (human*[Title] OR patient*[Title])))
#14	Remove Pediatric Studies	#13 NOT ((adolescen*[ti] OR babies[ti] OR baby[ti] OR boy[ti] OR boys[ti] OR child*[ti] OR girl*[ti] OR infancy[ti] OR infant*[ti] OR juvenile*[ti] OR neonat*[ti] OR newborn*[ti] OR nurser*[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR "school age"[ti] OR schoolchildren*[ti] OR teen*[ti] OR toddler*[ti] OR youth*[ti]) NOT (adult*[tiab] OR father*[ti] OR matern*[tiab] OR men[tiab] OR mother*[ti] OR parent*[ti] OR patern*[tiab] OR women[tiab]))
#15	Remove Undesired Publication Types	#14 NOT (bookdocs[Filter] OR "case reports"[pt] OR comment[pt] OR congress[pt] OR editorial[pt] OR letter[pt] OR "case report"[ti] OR comment*[ti] OR editorial[ti] OR letter[ti] OR news[ti])
#16	Limit to English language	#15 AND (english[Filter])
#17	Limit results by date	#16 AND ((2019:2023[pdat]) AND ("1900/01/01"[Date - Create] : "2023/08/22"[Date - Create]))
#18	Identify retractions	#17 AND (retraction of publication[pt] OR retracted publication[pt] OR retracted[ti] OR retraction[ti] OR withdrawn[ti])
#19	Remove retracted items	#17 NOT (33122529 OR 33477158 OR 33835990 OR 34745306 OR 35231905 OR 36387358 OR 37388012 OR 37501878)

Table A-2. Anticoagulation management services in ambulatory settings, limited to SRs only

Line #	Description	String
#1	General Anticoagulants	"Anticoagulants"[Majr] OR "anti coagula*[ti] OR anticoagula*[ti] OR "anti thromb*[ti] OR antithromb*[ti] OR "indirect thrombin inhibitor*[ti]
#2	Heparin	"Heparin"[Majr] OR clexane*[ti] OR dalteparin*[ti] OR enoxaparin*[ti] OR fragmin*[ti] OR fraxiparin*[ti] OR heparin*[ti] OR innohep*[ti] OR liquaemin*[ti] OR lovenox*[ti] OR nadroparin*[ti] OR tedelparin*[ti] OR tinzaparin*[ti]
#3	Warfarin	"Vitamin K/antagonists and inhibitors"[Majr] OR "Warfarin"[Majr] OR aldocumar*[ti] OR coumadin*[ti] OR marevan*[ti] OR tedicumar*[ti] OR warfant*[ti] OR warfarin*[ti]
#4	Direct Thrombin Inhibitors	"Antithrombins"[Majr] OR "argatroban" [Supplementary Concept] OR "bivalirudin" [Supplementary Concept] OR "Dabigatran"[Majr] OR "desirudin" [Supplementary Concept] OR "direct thrombin inhibitor*[ti] OR acova*[ti] OR angiomas*[ti] OR argatroban*[ti] OR bivalirudin*[ti] OR dabigatran*[ti] OR desirudin*[ti] OR desulfathirudin*[ti] OR desulphathohirudin*[ti] OR hirulog*[ti] OR lprivask*[ti] OR novastan*[ti] OR pradaxa*[ti] OR revasc*[ti]

Line #	Description	String
#5	Factor Xa Inhibitors	"Factor Xa Inhibitors"[Majr] OR "antistasin" [Supplementary Concept] OR "apixaban" [Supplementary Concept] OR "betrixaban" [Supplementary Concept] OR "Dabigatran"[Majr] OR "edoxaban" [Supplementary Concept] OR "Fidexaban" [Supplementary Concept] OR "Fondaparinux"[Majr] OR "lefaxin" [Supplementary Concept] OR "otamixaban" [Supplementary Concept] OR "razaxaban" [Supplementary Concept] OR "Rivaroxaban"[Majr] OR "factor xa inhibit"[ti] OR antistasin*[ti] OR apixaban*[ti] OR arixtra*[ti] OR betrixaban*[ti] OR bevyxxa*[ti] OR dabigatran*[ti] OR doac[ti] OR doacs[ti] OR edoxaban*[ti] OR eliquis*[ti] OR eribaxaban*[ti] OR fidexaban*[ti] OR fondaparinux*[ti] OR lefaxin*[ti] OR letaxaban*[ti] OR lixiana*[ti] OR noac[ti] OR noacs[ti] OR otamixaban*[ti] OR pradaxa*[ti] OR quixidar*[ti] OR razaxaban*[ti] OR rivaroxaban*[ti] OR savaysa*[ti] OR tanogitran*[ti] OR xarelto*[ti] OR yagin*[ti]
#6	Combine Population Strings	#1 OR #2 OR #3 OR #4 OR #5
#7	Management Services	"Monitoring, Physiologic"[Majr] OR "anti coagulant clinic"[tiab] OR "anti coagulant service"[tiab] OR "anti coagulation clinic"[tiab] OR "anti coagulation service"[tiab] OR "anticoagulant clinic"[tiab] OR "anticoagulant service"[tiab] OR "anticoagulation clinic"[tiab] OR "anticoagulation service"[tiab] OR "coumadin clinic"[tiab] OR "coumadin service"[tiab] OR "doac clinic"[tiab] OR "doac service"[tiab] OR "hematology clinic"[tiab] OR "hematology service"[tiab] OR "management program"[tiab] OR "monitoring clinic"[tiab] OR "monitoring service"[tiab] OR "risk reduction center"[tiab] OR "risk reduction clinic"[tiab] OR "risk reduction service"[tiab] OR "self monitor"[tiab] OR "therapy center"[tiab] OR "thrombosis clinic"[tiab] OR "thrombosis service"[tiab] OR clinic[ti] OR clinics[ti] OR manag*[ti] OR monitor*[ti] OR nurse*[tiab] OR pharmacist*[tiab] OR service[ti] OR services[ti] OR toolkit*[tiab] OR "tool kit"[tiab]
#8	Combine Populations & Interventions	#6 AND #7
#9	Limit to SRs	#8 AND ((meta-analysis[pt] OR "systematic review"[pt] OR "cochrane database syst rev"[ta] OR systematic*[ti] OR cochrane*[tiab] OR "meta analy"[tiab] OR metaanaly*[tiab] OR (search*[tiab] AND (cinahl*[tiab] OR databases[tiab] OR ebco*[tiab] OR embase*[tiab] OR psychinfo*[tiab] OR psycinfo*[tiab] OR "science direct"[tiab] OR sciencedirect*[tiab] OR scopus*[tiab] OR systematic*[tiab] OR "web of knowledge"[tiab] OR "web of science"[tiab])) OR ((rapid[tiab] OR systematic*[tiab] AND review*[tiab])))
#10	Remove Animal Studies	#9 NOT (((Animals[Mesh:NoExp] OR "Models, Animal"[Mesh:NoExp] OR "Disease Models, Animal"[Mesh:NoExp]) NOT Humans[Mesh:NoExp]) OR ((animal[Title] OR animals[Title] OR canine*[Title] OR dog[Title] OR dogs[Title] OR feline[Title] OR hamster*[Title] OR lamb[Title] OR lambs[Title] OR mice[Title] OR monkey[Title] OR monkeys[Title] OR mouse[Title] OR murine[Title] OR pig[Title] OR piglet*[Title] OR pigs[Title] OR porcine[Title] OR primate*[Title] OR rabbit*[Title] OR rat[Title] OR rats[Title] OR rodent*[Title] OR sheep*[Title] OR swine[Title] OR veterinar*[Title] OR (vivo[Title] NOT vivo[Title])) NOT (human*[Title] OR patient*[Title])))
#11	Remove Pediatric Studies	#10 NOT ((adolescen*[ti] OR babies[ti] OR baby[ti] OR boy[ti] OR boys[ti] OR child*[ti] OR girl*[ti] OR infancy[ti] OR infant*[ti] OR juvenile*[ti] OR neonat*[ti] OR newborn*[ti] OR nurser*[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR "school age"[ti] OR schoolchildren*[ti] OR teen*[ti] OR toddler*[ti] OR youth*[ti]) NOT (adult*[tiab] OR father*[ti] OR matern*[tiab] OR men[tiab] OR mother*[ti] OR parent*[ti] OR patern*[tiab] OR women[tiab]))
#12	Remove Undesired Publication Types	#11 NOT (bookdocs[Filter] OR "case reports"[pt] OR comment[pt] OR congress[pt] OR editorial[pt] OR letter[pt] OR "case report"[ti] OR comment*[ti] OR editorial[ti] OR letter[ti] OR news[ti])

Line #	Description	String
#13	Limit to English language	#12 AND (english[Filter])
#14	Limit results by date	#13 AND ((2019:2023[pdat]) AND ("1900/01/01"[Date - Create] : "2023/08/22"[Date - Create]))

Appendix B. List of Excluded Studies Upon Full-Text Review

1. Antoniazzi S, Ardoino I, Proietti M, Monzani V, Mannucci PM, Nobili A, Franchi C. Appropriateness of prescription of oral anticoagulant therapy in acutely hospitalized older people with atrial fibrillation. Secondary analysis of the SIM-AF cluster randomized clinical trial. *British Journal Of Clinical Pharmacology*, 2019, 85(9):2134-2142. **No outcomes of interest.**
2. Bauman ME, Hellinger A, Pluym CV, Bhat R, Simpson E, Mehegan M, Knox P, Massicotte MP. Online KidClot education for patients and families initiating warfarin therapy: The eKITE study. *Thrombosis Research*, 2022, 215:14-18. **No comparison group or before-after comparison.**
3. Bautista M, Muskus M, Tafur D, Bonilla G, Llinás A, Monsalvo D. Thromboprophylaxis for Hip Revision Arthroplasty: Can We Use the Recommendations for Primary Hip Surgery? A Cohort Study. *Clinical And Applied Thrombosis/Hemostasis: Official Journal Of The International Academy Of Clinical And Applied Thrombosis/Hemostasis*, 2019, 25:1076029618820167. **Not an intervention of interest.**
4. Chaturvedi S, Kelly AG, Prabhakaran S, Saposnik G, Lee L, Malik A, Boerman C, Serlin G, Mantero AM. Electronic Decision support for Improvement of Contemporary Therapy for Stroke Prevention. *Journal Of Stroke And Cerebrovascular Diseases: The Official Journal Of National Stroke Association*, 2019, 28(3):569-573. **No outcomes of interest.**
5. Dhipayom T, Rattanachaisit N, Jhunsom S, Dilokthornsakul P, Chaiyakunapruk N, Devine B. Comparative effects of telemedicine and face-to-face warfarin management: A systematic review and network meta-analysis. *Journal Of The American Pharmacists Association : JAPhA*, 2020, 60(2003):880-891.e9. **Superseded by a more recent systematic review.**
6. Dorsch MP, Chen CS, Allen AL, Sales AE, Seagull FJ, Spoutz P, Sussman JB, Barnes GD. Nationwide Implementation of a Population Management Dashboard for Monitoring Direct Oral Anticoagulants: Insights From the Veterans Affairs Health System. *Circulation. Cardiovascular Quality And Outcomes*, 2023, 16(2):e009256. **Not an intervention of interest.**
7. Gebreyohannes EA, Mill D, Salter S, Chalmers L, Bereznicki L, Lee K. Strategies for improving guideline adherence of anticoagulants for patients with atrial fibrillation in primary healthcare: A systematic review. *Thrombosis Research*, 2021, 205:128-136. **No outcomes of interest.**
8. Jiritano F, Fina D, Lorusso R, ten Cate H, Kowalewski M, Matteucci M, Serra R, Mastroberto P, Serraino GF. Systematic review and meta-analysis of the clinical effectiveness of point-of-care testing for anticoagulation management during ECMO. *Journal Of Clinical Anesthesia*, 2021. **Not a setting of interest.**
9. Khouja C, Brunton G, Richardson M, Stokes G, Blanchard L, Burchett H, Khatwa M, Walker R, Wright K, Sowden A, Thomas J. Oral anticoagulants: a systematic overview of reviews on efficacy and safety, genotyping, self-monitoring, and stakeholder experiences. *Systematic Reviews*, 2022, 11(1):232. **Not an intervention of interest.**

10. Kim K, Duarte JD, Galanter WL, Han J, Lee JC, Cavallari LH, Nutescu EA. Pharmacist-guided pharmacogenetic service lowered warfarin-related hospitalizations. *Pharmacogenomics*, 2023, 24(6):303-314. **Not an intervention of interest.**
11. Kuhrau S, Masic D, Mancl E, Brailovsky Y, Porcaro K, Morris S, Haines J, Charo K, Fareed J, Darki A. Impact of Pulmonary Embolism Response Team on Anticoagulation Prescribing Patterns in Patients With Acute Pulmonary Embolism. *Journal Of Pharmacy Practice*, 2022, 35(1):38-43. **No comparison group or before-after comparison.**
12. Lee LC, Farwig P, Kirk L, Mitchell VD, Sabatino JA, Barnes KD. Impact of pharmacist intervention on anticoagulation management and risk for potential COVID-19 exposure during the COVID-19 pandemic. *Thrombosis Research*, 2022, 217:52-56. **No outcomes of interest.**
13. Lim MS, Indran T, Cummins A, Bennett A, Wood E, Brown S, McQuilten Z, Tran H, Epi MC, Chan NC, Chunilal S. Utility of a Nurse-Led Pathway for Patients with Acute Venous Thromboembolism Discharged on Rivaroxaban: A Prospective Cohort Study. *Seminars In Thrombosis And Hemostasis*, 2019, 45(2):187-195. **No comparison group or before-after comparison.**
14. Mangrum JS, Saunders JA, Chaiyakunapruk N, Witt DM, King JB. A scoping review of direct oral anticoagulant ambulatory management practices. *Journal Of Thrombosis And Thrombolysis*, 2023, 55(4):700-709. **Not an intervention of interest.**
15. Naderi Haji M, Moghaddasi H, Sharif-Kashani B, Kazemi A, Rahimi F. Characteristics of software used in self-management of vitamin K antagonist therapy: A systematic review. *European Journal Of Cardiovascular Nursing*, 2019, 18(5):358-365. **Not an intervention of interest.**
16. Quiros Ambel H, Crespo-Robledo P, Arribalzaga Juaristi K, Plo-Seco I, Martínez Simón JJ, Pérez Fernández E, Perez Encinas M. Effectiveness of antithrombotic prophylaxis in hospitalised patients with SARS-CoV-2 infection. *European Journal Of Hospital Pharmacy: Science And Practice*, 2023, 30(5):264-267. **No comparison group or before-after comparison.**
17. Rajsic S, Breitkopf R, Treml B, Jadzic D, Oberleitner C, Oezpeker UC, Innerhofer N, Bukumiric Z. Association of aPTT-Guided Anticoagulation Monitoring with Thromboembolic Events in Patients Receiving V-A ECMO Support: A Systematic Review and Meta-Analysis. *Journal Of Clinical Medicine*, 2023, 12(9):3224. **Not a setting of interest.**
18. Rajsic S, Treml B, Jadzic D, Breitkopf R, Oberleitner C, Bachler M, Bösch J, Bukumiric Z. aPTT-guided anticoagulation monitoring during ECMO support: A systematic review and meta-analysis. *Journal Of Critical Care*, 2023, 77:154332. **Not a setting of interest.**
19. Roseau C, Richard C, Renet S, Kowal C, Eliahou L, Rieutord A, Chaumais MC. Evaluation of a program of pharmaceutical counseling for French patients on oral anticoagulant therapy. *International Journal Of Clinical Pharmacy*, 2020, 42(2):685-694. **No outcomes of interest.**

20. Ruell J, Smith A, Perera T, Carter J. The role of a specialist bridging service. A New Zealand prospective study of 600 patients. *Journal of Thrombosis and Haemostasis*, 2019, 17:1756-1761. **No comparison group or before-after comparison.**
21. Sakunrag I, Danwilai K, Dilokthornsakul P, Chaiyakunapruk N, Dhippayom T. Clinical Outcomes of Telephone Service for Patients on Warfarin: A Systematic Review and Meta-Analysis. *Telemedicine Journal And E-Health: The Official Journal Of The American Telemedicine Association*, 2020, 26(12):1507-1521. **Superseded by a more recent systematic review.**
22. Schwab K, Smith R, Wager E, Kaur S, Alvarez L, Wagner J, Leung H. Identification and early anticoagulation in patients with atrial fibrillation in the emergency department. *The American Journal Of Emergency Medicine*, 2021, 44:315-322. **Not a setting of interest.**
23. Succar L, Sulaica EM, Donahue KR, Wanat MA. Management of Anticoagulation with Impella® Percutaneous Ventricular Assist Devices and Review of New Literature. *Journal Of Thrombosis And Thrombolysis*, 2019, 48(2):284-291. **Not a setting of interest.**
24. Sun J, Ma Y, Su W, Miao H, Guo Z, Chen Q, Zhang Y, Ma X, Chen S, Ding R. Comparison of anticoagulation monitoring strategies for adults supported on extracorporeal membrane oxygenation: A systematic review. *Heart & Lung: The Journal Of Critical Care*, 2023, 61:72-83. **Not a setting of interest.**
25. Wang L, Yao W. A Cohort Study on the Safety and Efficacy of Warfarin and Rivaroxaban in Anticoagulant Therapy in Patients with Atrial Fibrillation Study. *Biomed Research International*, 2022, 2022:4611383. **No comparison group or before-after comparison.**
26. Wilson AS, Triller DM, Allen A, Burnett A, Gouveia-Pisano JA, Brenner A, Pritchard B, Medico C, Vazquez SR, Witt DM, Barnes GD. Digital dashboards for oral anticoagulation management: a literature scoping review. *Journal Of Thrombosis And Thrombolysis*, 2023, **Not an intervention of interest.**
27. Wittig-Wells D, Higgins M, Carter J, et al. Impact of a smartphone app reminder on adherence to aspirin prescribed as antithrombotic therapy. *Orthop Nurs*. 2020 Nov-Dec;39(6):395-401. doi: 10.1097/NOR.0000000000000711. PMID: 33234910. **Not an intervention of interest.**
28. Yuan X, Chen Y, Zhuang Y, Qin W, Lin Y. Effect of continuity of care on anticoagulant therapy and quality of life after heart valve replacement: a systematic review and meta-analysis. *Annals Of Palliative Medicine*, 2021, 10(5):5568-5579. **SR with majority of studies not from very high HDI countries.**
29. Zado ES, Pammer M, Parham T, Lin D, Frankel DS, Dixit S, Marchlinski FE. “As Needed” nonvitamin K antagonist oral anticoagulants for infrequent atrial fibrillation episodes following atrial fibrillation ablation guided by diligent pulse monitoring: A feasibility study. *Journal Of Cardiovascular Electrophysiology*, 2019, 30(5):631-638. **Not an intervention of interest.**
30. Zhang H, Dong Y, Ao X, Zhu D, Dong L. Optimal oral anticoagulant therapy in Chinese patients with mechanical heart valves. *European Journal Of Pharmaceutical Sciences*:

Official Journal Of The European Federation For Pharmaceutical Sciences, 2020,
144:105202. **No comparison group or before-after comparison.**

Appendix C. Data Tables

Table C-1. Overview of the studies of PSP 1 on care transitions

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants , n	Funding	PSP	Main Findings
Manzato, 2021 ²⁸	RCT	“Evaluate the effect of reinforcing an educational programme through telephone follow-up on health-related quality of life and anxiety and depression symptoms in individuals starting warfarin therapy”	2015-2017	Two teaching hospitals Brazil	52	Coordination for the Improvement of Higher Education Personnel (Finance Code 001) and National Council for Scientific and Technological Development	5 post-discharge telephone calls, reinforcing the education	<ul style="list-style-type: none"> • No between-group difference in the amount of time in therapeutic range • Only 1 of 12 quality of life comparisons showed a statistically significant impact of the intervention (there were 6 metrics at each of 2 timepoints, 3 months and 6 months post-discharge). At 6 months, the intervention group had better scores on psychological impact • None of 4 anxiety/depression comparisons showed a statistically significant impact of the intervention

Kapoor, 2020 ²⁹	RCT	"Assess the feasibility, satisfaction, and effectiveness, of a care transition intervention with pharmacist home visit and subsequent anticoagulation expert consultation for patients with new episode of venous thromboembolism"	2016-2018	Multihospital healthcare system United States	162	Pfizer Independent Grants for Learning and Change Initiative, and the National Center for Advancing Translational Sciences	One home visit within 7 days of discharge by a pharmacist, consisting of three parts. First a medication self-management simulation that builds on the "show me" paradigm advocated by experts. Second, a series of open-ended questions to assess patient understanding of medications and VTE condition to ensure understanding of lab work and adverse effects. Third, a medication review including color illustrations. A nurse practitioner (expert in anticoagulation) telephoned the patient 8-30 days later,	<ul style="list-style-type: none"> • Patient-rated quality of care transition did not differ statistically significantly between groups • The clinicaltrials.gov record indicated that other outcomes were collected but not reported (recurrence of venous thromboembolism, major hemorrhage, readmission to hospital)
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Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants , n	Funding	PSP	Main Findings
							providing additional consultation	
Liang, 2020 ³⁰	RCT	"Evaluate the impact of a pharmacist-led anticoagulation service on international normalised ratio (INR) control and other outcomes among patients receiving warfarin therapy"	2014-2017	Tertiary hospital China	152	Macao Polytechnic Institute	Before discharge, intervention patients received one-on-one warfarin education with a pharmacist, and a booklet. Two pharmacist follow-up telephone calls at 30 and 90 days after discharge, for reinforcement	<ul style="list-style-type: none"> • No statistically significant difference in anticoagulation control in 3 of 4 metrics. The exception was % of time within the expanded range, 54% vs 42% in favor of the intervention. The other 3 were the percentage of time in therapeutic range for INR, the percentage of time with INR less than or equal to 1.5, and the percentage of time with INR less than or equal to 5 • No statistically significant difference in anticoagulation-related complications (4 metrics)

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Wu, 2022 ³¹	NRS with comparison	"To evaluate the impact of pharmacist interventions on international normalized ratio (INR) control during the warfarin initiation phase after mechanical valve replacement"	2015-2019	Tertiary hospital Taiwan	72	Research grants from the National Taiwan University Hospital (110-S5003, 111-X0007, and 111-S0087)	Pharmacist-managed warfarin therapy including (1) suggesting initial dose and dose adjustment, (2) developing a monitoring plan for INR and adverse reactions, (3) documenting and managing drug-drug and drug-food interactions, (4) identifying causes of supratherapeutic INR and providing suggestions for management, and (5) providing education to patients and their caregivers	<ul style="list-style-type: none"> There was no statistically significant difference between patients who were admitted after the implementation of the PSP and patients who had been admitted pre-implementation in terms of the proportion who had an INR in the therapeutic range at their first return appointment post-discharge (71.0% vs. 62.9%)

Dreijer, 2020 ³²	NRS with comparison	"To study the effect of implementation of a hospital-based multidisciplinary antithrombotic team on the efficacy and safety of antithrombotic therapy during and after hospitalization"	2015-2017	Two hospitals Netherlands	1,886	Unrestricted grants from Stichting Phoenix Schiedam, Daiichi Sankyo, Boehringer Ingelheim, Bayer, Pfizer, and the Scientific Committee Reinier de Graaf Gasthuis	Hospital-based multidisciplinary antithrombotic team focusing on: (1) education of hospital physicians, nurses, and pharmacists; (2) daily structured medication reviews by pharmacists; (3) drafting and updating antithrombotic therapy guidelines; (4) daily patient counseling; and (5) medication reconciliation at admission (pre-admission data from patient's thrombosis service were provided to the responsible physician) and discharge (advice from the team was provided to the thrombosis service, general practitioner and community pharmacist)	<ul style="list-style-type: none"> The proportion of patients who experienced a composite end point consisting of one or more bleeding or thrombotic events in the three months post-discharge did not statistically significantly differ across the periods before and after the PSP was implemented (OR = 1.00, 95% CI = (0.70 to 1.42)).
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Shields, 2019 ³³	NRS with comparison	“To decrease the number of severe warfarin ADRs” and to assess “whether the establishment of [an] anticoagulation task force had a positive effect on TTR and severe ADRs”	2013-2017	Healthcare system (the PSP appears to have been designed primarily for use by PCPs in the system) United States	4,311 patients prescribed warfarin at hospital discharge during the 5-year study period (patients discharged more than once during the period may be counted more than once in this total)	None	Multidisciplinary anticoagulation task force established at the start of year 2 (2014), including: (1) an electronic module that stores lab results, displays data trends, and offers providers recommendations for warfarin management, including best practice alerts and a calendar for follow-ups and timely lab draws; (2) information for PCPs on how to use the electronic module, monitor their patients’ INRs, and educate patients about warfarin use; (3) hyperlink to American College of Cardiology dosing protocols; and (4) a calendar and after-visit	<ul style="list-style-type: none"> • Time in therapeutic range (percentage of days INR was in therapeutic range out of the total number of days all patients were treated with warfarin) did not statistically significantly change over the five-year study period either for PCPs (60.6% to 62.5%, $p = 0.191$) or for cardiologists (68.2% to 68.8%, $p = 0.182$). • There was a statistically significant decrease in the rate of severe ADRs attributed to warfarin following hospital discharge (the ratio of the number of severe warfarin ADRs to the total number of warfarin prescriptions) over the five-year study period, from 3.8% at baseline in 2013 to 1.8%, 2.4%, 1.2%, and 1.0% in 2014, 2015, 2016, and 2017, respectively ($p < 0.0001$).
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Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants , n	Funding	PSP	Main Findings
							summary for patients containing previous INR values, upcoming appointments, and warfarin dosing.	

Table C-2. Overview of the systematic reviews of PSP 2 on ambulatory care

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Braga Ferreira, 2023 ²³	Systematic review	“To systematically review the evidence on the impact of telemedicine-based oral anticoagulation management compared to usual care on thromboembolic and bleeding events.”	Literature search end date September 2021	Home setting (telemedicine) SR conducted in Brazil; included studies were from several countries	25,476 participants in 25 RCTs	National Council for Scientific and Technological Development, National Institute of Science and Technology for Health Technology Assessment, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, and Brazilian Ministry of Education. Grants from CNPq and Federal University of Minas Gerais.	Computer-assisted dosing Laboratory testing with remote adjustment Self-testing Multitasking application	<ul style="list-style-type: none"> • Telemedicine resulted in lower rates of thromboembolic events, though not statistically significant (n=13 studies, RR 0.75, 95% CI 0.53-1.07; I² =42%) • Telemedicine resulted in similar rates of major bleeding (n=11 studies, RR 0.94, 95% CI 0.82-1.07; I² =0%) • Telemedicine resulted in similar rates of mortality (n=12 studies, RR 0.96, 95% CI 0.78-1.20; I² =11%) • Telemedicine increased time in therapeutic range (n=16 studies, MD 3.38, 95% CI 1.12-5.65; I² =90%) • In the multitasking application subgroup, telemedicine led to a substantial reduction of thromboembolic events (RR 0.20, 95% CI 0.08-0.48)

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Huang, 2023 ²³	Systematic review	“This study used meta-analysis to provide high-level evidence on the effectiveness and safety of the management model combining portable coagulometers and telemedicine with VKA therapy.”	Literature search end date May 1, 2022	Home setting (telemedicine) SR conducted in China; included studies were from several countries	3,853 participants in 8 RCTs	None	Combines telemedicine and self-testing (with portable coagulometers)	<ul style="list-style-type: none"> • Combined telemedicine and self-testing significantly improved time in therapeutic range (MD 9.50%; 95% CI, 3.16–15.85; I² = 87%; P < 0.01) • The combined intervention reduced thromboembolic events, but the difference was not statistically significant (RR 0.72; 95% CI, 0.51–1.01; I² = 0%; P = 0.05) • The combined intervention did not significantly differ from ordinary outpatient anticoagulation management in the following outcomes: major bleeding (RR 0.96; 95% CI, 0.78–1.18; I² = 0%; P = 0.68), rehospitalization (RR 1.39; 95% CI, 0.56–3.46; I² = 0%; P = 0.48), and mortality (RR 0.94; 95% CI, 0.77–1.14; I² = 0%; P = 0.53)

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Lo, 2022 ²¹	Systematic review	“To explore the effects of educational programs on patients prescribed warfarin for the aforementioned cardiovascular diseases and to identify the components of effective programs.”	Literature search end date August 2020	Outpatient hospital, clinic, or community pharmacy SR conducted in Hong Kong; included studies were from several countries	1,335 participants in 9 studies (8 RCTs and 1 CCT)	None	Educational programs	<ul style="list-style-type: none"> ● Results were mixed with some studies showing significantly higher TTR in the education groups and other studies showing no significant between-group difference. ● Similarly, two studies showed significantly lower rates of minor bleeding (one also showed significantly fewer major bleeding events), while four other studies showed either no significant differences (two studies) or no bleeding events in either group (two studies). ● No studies reported significant between-group differences in thromboembolic events.

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Jang, 2021 ²²	Systematic review	“This study evaluated the elements and effectiveness of interventions using mHealth applications on outcomes such as patient knowledge of his or her disease and treatment, treatment guidelines and drug use adherence, prothrombin time levels control, and satisfaction with treatment received.”	Literature search end date May 2020	Outpatient hospital SR conducted in Korea; included studies were from several countries .	18,812 participants in 12 studies (5 RCTs, 4 controlled cohort studies, 3 single-group pre-post studies)	National Research Foundation of Korea	Mobile Health apps educational program	<ul style="list-style-type: none"> • Quality of life was more improved in the mobile apps group than the control group in most studies. However, in one study, quality of life did not show improvement with mobile apps. • Clinical indicators of INR maintenance and mortality and readmission also showed improvement with mobile apps.

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Tran, 2021 ²⁵	Systematic review	“This systematic review and meta-analysis compares the effectiveness of TP anticoagulation services to face-to-face (FTF) anticoagulation services in the ambulatory care setting.”	Literature search end date November 18, 2020	Home or laboratory (telepharmacy) SR conducted in USA; 10 of 11 included studies were from USA	8,395 participants in 11 studies (1 RCT and 10 retrospective controlled cohort studies)	None	Telephone, video or online anticoagulation management by pharmacist compared to face-to-face management by pharmacist or physician	<ul style="list-style-type: none"> • Telepharmacy had a lower rate of thromboembolic events (RR 0.69, 95% CI 0.33 to 1.44) and major bleeding (RR 0.84, 95% CI 0.53 to 1.32) than face-to-face management, but the differences were not statistically significant • Telepharmacy had a significantly lower rate of any bleeding (RR 0.65, 95% CI 0.47 to 0.90) and any hospitalization (RR 0.59, 95% CI 0.39 to 0.87) than face-to-face management • Time in therapeutic range was similar between groups (WMD 0.0, 95% CI -5.3 to 5.3).

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Dai, 2020 ²⁴	Systematic review	"To comprehensively evaluate the role of technology-based interventions in the management of oral anticoagulants."	Literature search end date November 1, 2019	Home setting (telemedicine) SR conducted in China; included studies conducted in several countries	2,218 participants in 15 RCTs	Fuzhou Science and Technology Project and the Startup Fund for Scientific Research, Fujian Medical University	Telemedicine (telephone, internet, or software) for anticoagulation monitoring	<ul style="list-style-type: none"> • The telemedicine group had fewer thromboembolism events than the control group, but the difference did not reach statistical significance (RR 0.71; 95% CI 0.49-1.01; I² =0%; P=0.06). • There was no between-group difference in major bleeding events (RR 1.02; 95% CI 0.78-1.32; I² =0%; P=0.90) or minor bleeding events (RR 1.06, 95% CI 0.77-1.44; I² =41%; P=0.73). • The time in therapeutic range of the telemedicine group was significantly higher than that of the control group (MD 6.07; 95% CI 0.84-11.30; I² =72%; P=0.02). • Mortality was lower in the telemedicine group but the difference was not statistically significant (RR 0.61, 95% CI 0.26 to 1.41). • Hospitalization did not differ between groups (RR 1.02, 95% CI 0.85 to 1.23).

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Jang, 2020 ²⁶	Systematic review	"To evaluate the role of RM in atrial arrhythmia detection, stroke reduction and anticoagulation therapeutic intervention."	Literature search end date February 29, 2020	Home or other non-hospital setting SR conducted in Taiwan; included studies conducted in other countries	2,837 participants in 3 RCTs	Taipei Medical University grant	Remote monitoring (ICD, CRT-D, PM, or iphone) for guiding anticoagulation therapy vs. Conventional anticoagulation therapy	<ul style="list-style-type: none"> • For patients with paroxysmal AF, 1 of 2 studies showed gastrointestinal bleeding was more frequent with conventional anticoagulation therapy than with RM-guided anticoagulation therapy (16% vs. 0%; P=0.047). However, another study reported 1 case of fatal bleeding in the RM-guided anticoagulation therapy group and no major bleeding in the control group. • In another study of anticoagulation therapy, 18 patients were included without existing arrhythmia and patients were divided into RM-guided anticoagulation therapy and conventional anticoagulation therapy if atrial tachyarrhythmia was noted. Major bleeding (HR, 1.39; 95% CI, 0.89–2.17) was similar in the 2 groups.

Author, Year	Study Design	Objectives	Study Years	Clinical Setting Country	Number of Participants, n	Funding	PSP	Main Findings
Wu, 2020 ²⁷	Systematic review	"To explore the effect of anti-Xa monitoring on the safety and efficacy of LMWH anticoagulant therapy."	Literature search end date May 27, 2019	Ambulatory setting (not specified) SR conducted in China; included studies conducted in several countries	1,617 participants in 6 studies (2 RCTs and 4 controlled cohort studies)	NR	Anti-Xa monitoring of low-molecular weight heparin	<ul style="list-style-type: none"> • Anti-Xa monitoring group had a significantly lower incidence of venous thromboembolism events than the control group (OR 0.44, 95% CI 0.29-0.68, P = 0.0002, I² = 49%) • Subgroup analysis found that the incidence of venous thromboembolism events in the anti-Xa monitoring group was lower than that in the control group when the anti-Xa trough level was monitored (OR 0.40, 95% CI 0.25-0.63, P < 0.0001, I² = 45%) but not when the anti-Xa peak level was monitored (OR 1.59, 95% CI 0.31-8.08, P = 0.57) • A meta-analysis comparing bleeding events found no statistically significant between-group difference (OR 1.22, 95% CI 0.26-5.71, P = 0.80)

AF = atrial fibrillation; CCT = controlled clinical trial; CI = confidence interval; CRT-D = cardiac resynchronization therapy defibrillator; HR = hazard ratio; ICD = implantable cardiac defibrillator; INR = international normalized ratio; LMWH = low molecular weight heparin; MD = mean difference; NR = not reported; OR = odds ratio; PM = pacemaker; PSP = patient safety practice; RCT = randomized controlled trial; RM = remote monitoring; RR = risk ratio; SR = systematic review; TTR = time in therapeutic range; WMD = weighted mean difference

Table C-3. Risk of bias assessment for RCTs*

Author, Year	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Assessment
Manzato, 2021 ²⁸	Low	High	High	Low	Unclear	Low	High
Kapoor, 2020 ²⁹	Unclear	High	High	High	High	Low	High
Liang, 2020 ³⁰	Low	High	High	Low	Unclear	Low	High

* Cochrane Collaboration’s 2011 tool for assessing the risk of bias of randomized controlled trials (RCTs)¹²

Table C-4. Risk of bias assessment for nonrandomized studies*

Author, Year	Confounding	Patient Selection	Classifying Interventions	Deviations From Intended Interventions	Missing Data	Measurement Outcomes	Selection of Reported Results	Overall Assessment
Wu, 2022 ³¹	Critical	Moderate	Low	Low	Moderate	Low	Low	Critical
Dreijer, 2020 ³²	Critical	Low	Low	Low	Low	Low	Low	Critical
Shields, 2019 ³³	Critical	Moderate	Low	Moderate	Low	Low	Low	Critical

*Based on the Cochrane Collaboration’s 2016 tool Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I).¹³