7. Harms Due to Anticoagulants

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Introduction

Anticoagulants are a critical therapy in the prevention and treatment of various types of thromboembolic disorders. Key indications for anticoagulants include the prevention of stroke among patients with chronic atrial fibrillation, and prevention and treatment of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. Anticoagulants include vitamin K antagonists (e.g., warfarin); heparin (unfractionated and low-molecular weight heparin); and novel oral anticoagulants (NOACs), such as direct thrombin inhibitors (e.g., argatroban and dabigatran) and factor Xa inhibitors (e.g., apixaban, rivaroxaban).

Anticoagulants have been consistently identified as the most common cause of adverse drug events (ADEs) in health care settings, such that an entire chapter of the National Action Plan for ADE Prevention is devoted to anticoagulants.[1] Bleeding is the primary ADE of concern for anticoagulants, but they require "a careful balance between thrombotic and hemorrhagic risks" (National Action Plan for ADE Prevention).[1]

Methods for Selecting Anticoagulant PSPs

The following three patient safety practices (PSPs) specific to addressing the potential harms of anticoagulants, particularly bleeding and thromboembolic events, were selected. They were among the list of nine specific PSPs that were compiled from various sources, particularly the National Action Plan for ADE Prevention, on recommended practices and potential gaps. Practices relevant to inpatient, ambulatory and long-term care settings were considered. Based on the survey of the Technical Expert Panel described in the methods section, the following PSPs were selected:

- PSP 1: Anticoagulation management service in the ambulatory setting
- PSP 2: Use of dosing protocols or nomograms for NOACs
- PSP 3: Interventions to support safe transitions and continuation of patients' anticoagulants post-discharge from a hospital or emergency department

What's New/Different Since the Last Report

In the Making Health Care Safer II report, a few chapters examined anticoagulants for specific thromboembolic disorders. It examined PSPs for intravenous anticoagulants and reviewed prevention of VTE.

References for Introduction

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7.1 Patient Safety Practice 1: Anticoagulation Management Service in the Ambulatory Setting

Reviewer: Scott Winiecki, M.D.

7.1.1 Practice Description

An anticoagulation management service is a systematic and coordinated approach to anticoagulation care delivery by a single provider following a physician-approved protocol. For example, these may be pharmacist- or nurse-led "anticoagulant clinics," in which patients are seen in an ambulatory setting on a regular basis to closely monitor bleeding and clotting laboratory values and adjust medications accordingly.

Note that many of the systematic reviews and studies compared different models of anticoagulation management services in terms of which professional provided the service as well as the specific model aims and mode (e.g., telephone) or how the model compared with usual care, which was not always described.

Key Findings:

- A range of models for anticoagulation management services are examined in the literature. Most are pharmacist led, but some are led by nurse practitioners, physician assistants, nurses, or pharmacy technicians.
- Some models examined different modes of providing anticoagulation management services (e.g., telephone).
- Overall quality of individual studies and studies within the systematic reviews is moderate to high, given the number of randomized controlled trials and non-randomized controlled trials with comparison groups or pre/post designs.
- There have been several recent systematic reviews of pharmacist-led anticoagulation management services compared with usual care or other models.
- Evidence shows that the effect of anticoagulant management services on time to therapeutic range is moderately positive, but evidence is low or mixed on bleeding events and thromboembolic events.

7.1.2 Methods

The question of interest for this review is, "What is the effect of an anticoagulant management service in the ambulatory setting on bleeding events and thrombotic events compared with usual care or different models of anticoagulant management service?"

Two databases (CINAHL® and MEDLINE®) were searched for articles published during the past 10 years using a combination of (1) terms related to anticoagulant and (2) pharmacist, nurse, nurse practitioner, or physician assistant, and (3) the outcomes of interest (bleeding or hemorrhage or patient safety, generally). Detailed search terms are provided in Appendix C.

Studies were included if they were empirical studies (or systematic reviews) of a systematic and coordinated anticoagulation care delivery service by a single clinician following a physician-approved protocol in an ambulatory setting. Studies were included if they used experimental, quasi-experimental, or observational study designs, examining anticoagulation management services pre/post, compared with usual care or different service models. Key findings for this review are located in the box above.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

7.1.3 Review of Evidence

Six systematic reviews and five single studies met the inclusion criteria and are characterized in terms of their setting, specific clinician and mode of delivery, and key outcomes in Appendix B. A synthesis of the evidence by outcome is shown below.

The majority of studies examined anticoagulation management services provided by pharmacists, although a few examined other professionals, including a nurse practitioner, nurse-pharmacist-dietician model, and a pharmacy technician versus a pharmacist-led model. Five of the systematic reviews examined the pharmacist-led model of anticoagulation service. The review by the Canadian Agency for Drugs and Technologies in Health (2011) also examined what they called "specialized anticoagulation services," defined as "tertiary or community hospital-based anticoagulation clinics, primary care settings, point-of-care (POC) testing and dose adjustment by community pharmacies, and patient self-testing and patient self-management."[1] These models were provided by pharmacists, other professionals, and patients themselves (i.e., patient self-testing).

The studies of anticoagulation management services were provided across a range of settings, including within an integrated health care delivery system; academic medical center; and safety-net, primary care, or ambulatory clinics; as well as for home-bound patients. Three studies specifically examined telephone-based models of anticoagulation management services—managed by nurse practitioner, clinical pharmacist, and patient self-testing, with various comparators.

The single studies examined the anticoagulation management services pre/post or compared with usual care or other models. Overall strength of the evidence is moderate to high given the inclusion of six recent systematic reviews, although few single studies had significant findings.

7.1.3.1 Clinical Outcomes

The clinical outcomes examined in the studies included time to therapeutic range (TTR), bleeding, and thrombotic events. The studies also examined patient-reported outcomes (satisfaction, quality of life), utilization and cost, and mortality. The findings for each of these are synthesized below.

7.1.3.1.1 Time to Therapeutic Range

TTR or percentage of time in therapeutic range were commonly reported in the studies and reviews.

Systematic reviews of pharmacist-led anticoagulation management services compared with usual care or other models found mixed results for significant differences in TTR. Entezari-Maleki et al. and Hou et al. found significant differences across observational studies in pharmacist models versus comparators (72.1% vs. 56.7%; p=0.013 for Entezari-Maleki et al.), although not for randomized controlled trials (RCTs).[2,3] However, Zhou et al.'s meta-analysis and Manzoor's review reported significantly higher percentages of anticoagulants within the therapeutic range as compared with all other models.[4,5] For "specialized anticoagulation services," which could include pharmacist-led models as well as other models such as patient self-testing, their review found significantly more favorable TTR compared with usual care.[1]

In the Duran-Parrondo et al. study of a pharmacist-involved model with patient education, compared with the control group, the intervention group improved its proportion of individuals' international normalized ratio (INR) results by 25 percent (relative risk [RR]=0.75; 95% confidence level [CI], 0.69 to 0.82) for those within 0.5 units of the target range and by 26 percent (RR=0.74; 95% CI, 0.67 to 0.81 for those within 0.75 units of the target range).[6]

Hawkins et al. examined the difference between a pharmacist-led versus a pharmacy technician-led model of anticoagulation management. They found that the technician-led group had a higher percentage of in-range INRs (mean difference=6.8%; 95% CI, 5.0% to 8.7%) and patients with 100-

percent TTR (mean difference, 10.5%; 95% CI, 7.0% to 14.0%) during followup. They also found that the propensity-weighted 6-month followup mean TTR was 83.3 percent (95% CI, 82.4% to 84.2%) in the technician group and 77.7 percent (95% CI, 76.4% to 78.9%) in the usual care (pharmacist-managed) group, resulting in a mean difference in the followup mean TTR of 5.7 percent (95% CI, 4.1% to 7.2%).[7]

Three studies examined the use of telephone-based anticoagulation management services and found few differences from other models.[8-10] Lee et al. found that face-to-face management resulted in significantly greater INR TTR than did distance management using local laboratory testing (69.0% vs. 60.5%, p=0.0032). This study also found no difference in INR TTR between face-to-face management and patient self-testing (69.0% vs. 68.0%, p=0.25).[8] The Philip et al. study examined a telephone-based clinical pharmacist model to augment the clinical pharmacy service that was in high demand; the authors found no difference between the two groups in percentage of INR values in the therapeutic range.[9] Hassan et al. reported the percentage of INR values in therapeutic range (58.39%) and the mean TTR (62.75%) for homebound patients receiving telephone-based anticoagulation management but did not have a comparison group.[10]

7.1.3.1.2 Bleeding

Systematic reviews of pharmacist-managed anticoagulation service compared with other models or usual care found somewhat positive results on the number of bleeding events. Entezari-Maleki et al., Hou et al., and Zhou et al. found no significant differences in RCTs but observed significantly fewer bleeding events in non-RCTs (0.6% vs. 1.7%, p<0.001)[2] and a significantly lower risk of hemorrhage.[2,3,4] Manzoor et al. noted that 10 of the 12 studies that reported on bleeding found that the pharmacist-managed group had lower or equal risk of major bleeding as compared with usual care.[5] Saokaew et al. found that in RCTs, pharmacist-led management was significantly associated with substantial reductions in total and major bleedings (29% reduction in total bleedings, RR, 0.71; 95% CI, 0.52 to 0.96; p=0.028; 51% reduction in major bleedings, RR, 0.49; 95% CI, 0.26 to 0.93; p=0.030).[11] The Canadian review of specialized anticoagulation services did not find a reduction in bleeding or hemorrhage compared with usual care.[1]

In terms of the single studies, Duran-Parrondo et al. found that patients receiving followup by a pharmacist had a 75-percent reduction in bleeding (hazard ratio [HR]=0.25; 95% CI, 0.18 to 0.36).[6] When comparing a prior clinical pharmacist model with a telephone-based service led by a clinical pharmacist, bleedings were not significantly different, indicating comparable quality of anticoagulation management with either mode of delivery.[9] Hawkins et al. found that bleeding (HR=0.60; 95% CI, 0.39 to 0.94; p=0.026) was lower in the pharmacy-technician group during followup compared with the pharmacist-led model.[7]

7.1.3.1.3 Thromboembolic Events

Systematic reviews of pharmacist-managed anticoagulation service compared with other models or usual care found limited positive results in terms of the effect on thromboembolic events. Three reviews found no significant differences in RCTs,[2-4] although the review by Saokaew et al. found that the risk ratio for pharmacist-led anticoagulation versus usual care on thromboembolic events was 0.79 (95% CI, 0.33 to 1.93; p=0.610).[11] Three reviews found significantly fewer thromboembolic events in the non-RCT studies versus usual care.[2,3,11] Manzoor et al. found that in 9 of 10 studies that reported on the outcome, the pharmacist-managed group had lower or equal risk of thromboembolic events as compared with

usual care.[5] The Canadian review of specialized anticoagulation services found significant differences in the occurrence of thromboembolism.[1]

Of the four single studies that examined thromboembolic events, none observed a significant difference from the comparators—either usual care or different models.

7.1.3.2 Patient-Reported Outcomes

Some reviews examined patient-reported outcomes, including patient satisfaction and quality of life. In a pooled meta-analysis, Zhou et al. found that pharmacist-led models had significantly higher patient satisfaction as compared with all other models.[4] One study in the Entezari-Maleki et al. systematic review found no significant difference in quality of life between pharmacist-managed and usual care.[2]

7.1.3.3 Utilization and Cost

7.1.3.3.1 Utilization

The review by Entezari-Maleki et al. found significant differences in emergency department (ED) visits compared with usual care (7.9% vs. 23.9%; $p<0.0001$) and instances of hospitalization (3% vs, 10%; $p<0.001$) in non-RCTs, but no significant differences in RCTs.[2] Similarly, Manzoor et al. found decreased rates of hospitalization, shorter length of hospital stay, and fewer ED visits as compared with usual care in their review.[5]

Specialized anticoagulation services were not found to affect use.[1]

Duran-Parrondo et al. found that the intervention group had an - percent reduction (odds ratio=0.92; 95% CI, 0.88 to 0.96) in the number of medical consultations required to maintain individual patients' INR within the correct range.[6] Philip et al. did not find significant differences between the telephone-based clinical pharmacist service and previous in-person service in terms of percentage of clinical pharmacy visits for anticoagulation management, elapsed time to the third available clinic appointment (a measure of access to care), and number of clinical pharmacy visits for anticoagulation management, or pharmacist work hours per prescription volume.[9]

7.1.3.3.2 Cost

Three reviews reported a cost savings with a pharmacist-managed model.[2,3,5] The study by Hassan et al. of a telephone-based service for homebound patients led by a nurse practitioner determined the costs per visit to be $82, as compared with $300 for standard in-person visits to the hospital-based anticoagulation clinic.[10]

7.1.3.4 Mortality

Five systematic reviews that synthesized the evidence on mortality found no significant differences in RCTs or non-RCTs. The single study by Hawkins et al. examining a pharmacy technician model found that all-cause mortality (HR=0.44; 95% CI, 0.25 to 0.77; $p=0.004$) was lower in the technician group than in the pharmacist-managed group during followup.[7]

7.1.4 Implementation

No studies formally evaluated effective approaches for implementing anticoagulation management services.

7.1.5 Gaps and Future Directions

There is rather substantial literature on the effects of anticoagulation management services, in particular pharmacist-led services, as indicated by the six systematic reviews and five studies described above. Many of the studies and reviews examined the comparative effectiveness of different models, potentially exploring perhaps more cost-effective models (e.g., pharmacy technician model or telephone provided) with comparable quality and safety. There are still opportunities to expand the evidence and improve the safety of anticoagulants. An et al. (2017) is an example of expanding the evidence on anticoagulation management services beyond comparisons with usual care to quality improvement efforts within a management service, assessing the associations between management patterns and clinical outcomes.[12] Additional studies could expand the evidence looking at mixed models, especially to reach rural populations. For example, Hodge et al. (2008) studied a rural county in Australia, where a program "incorporated an anticoagulation clinic, point of care INR testing in remote centers, development of anticoagulation dosing protocol for GP use, and a comprehensive patient education program over 3 years."[13] With the NOACs, there are likely to be more therapeutic options with less direct management; however, they may also pose other challenges.

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7.2 Patient Safety Practice 2: Use of Dosing Protocols or Nomograms for Newer Oral Anticoagulants

Reviewers: Katharine Witgert, M.P.H., and Scott Winiecki, M.D.

Anticoagulants have consistently been identified as the most common causes of ADEs in healthcare settings.[1] While bleeding is the primary ADE of concern, anticoagulants require "a careful balance between thrombotic and hemorrhagic risks."[1] The introduction of NOACs, including the direct thrombin inhibitors (DTIs) (e.g., dabigatran, argatroban) and factor Xa inhibitors (e.g., rivaroxaban, apixaban), may be associated with lower rates of some bleeding events compared with warfarin;[2-5] however, the direct thrombin inhibitors are associated with a higher risk of major bleeding when used for management of heparin-induced thrombocytopenia.[6] While NOACs may offer different risks and benefits from older oral anticoagulants, careful dosing to balance the risks of thrombotic and hemorrhagic adverse events is required for NOACs, just as it is for older drugs. The Joint Commission National Patient Safety Goal (NPSG) 03.05.01[7] and the Institute for Safe Medication Practices (ISMP) Pathways for Medication Safety toolkit identify standardized anticoagulation dosing protocols as a potentially helpful PSP. This review focused on examining the use of dosing protocols and nomograms for NOACs.

7.2.1 Practice Description

A protocol or nomogram is a dosing tool that specifies the proper amount of drug (e.g., dose, infusion rate) to be given to a patient based on specific criteria (e.g., patient characteristics such as weight, kidney or liver function, laboratory results). The goal of a dosing protocol or nomogram is "to rapidly achieve and maintain a therapeutic range while guiding dosage adjustments and minimizing subtherapeutic or supratherapeutic concentrations."[8] The use of dosing nomograms has been shown to improve the safety and effectiveness of older anticoagulants, particularly heparin therapy.[9-13] Dosing protocols or nomograms are used for many drugs with a narrow window between their effective doses and doses at which they produce adverse effects; examples include several antibiotics (e.g., gentamicin, vancomycin) as well as anticoagulants (e.g., warfarin, heparin). Dosing protocols or nomograms may reflect different patient characteristics, such as kidney or liver function, depending on how a drug is metabolized. This PSP review was focused on the use of dosing protocols or nomograms for NOACs.

7.2.2 Methods

The question of interest for this review is, "What is the effect of dosing protocols or nomograms for NOACs on bleeding events?"

Two databases (CINAHL® and MEDLINE®) were searched for articles published during the past 10 years using a combination of (i) specific NOAC drug classes and drug names and (ii) terms for protocols or nomograms, and (iii) the outcomes of interest (bleeding or hemorrhage or patient safety, generally).

Key Findings:

- There is a paucity of studies on the use of dosing protocols or nomograms for the NOACs.
- The few empirical studies that examine the effectiveness of protocols or nomograms for NOACs are observational, non-randomized studies without control groups or tests of significance and with very small sample sizes.
- At present, there is insufficient evidence to indicate the effectiveness of using dosing protocols/nomograms for NOACs to prevent bleeding.

Studies were included if they were empirical studies of the use of nomograms or protocols for dosing NOACs, regardless of the specific clinical aim or target of the protocols. Studies were included if they used experimental, quasi-experimental, or observational study designs. This review also includes studies

without a test of significance, since there were few relevant, more rigorous studies identified in the literature. Key findings are located in the box above.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

7.2.3 Review of Evidence

The four studies that met the inclusion criteria are characterized in terms of their setting, the specific anticoagulant(s) targeted, the aim of the nomogram or protocol, and key outcomes. A summary of the study characteristics and key outcomes is provided in Table 1, with a detailed overview of each study provided in the Evidence Table in Appendix B.

Three of the four studies examined the use of protocols or nomograms for various NOACs to treat heparin-induced thrombocytopenia (HIT) within hospitals.[8,14,15] HIT is a "dangerous, potentially lethal, immunologically-mediated adverse drug reaction to unfractionated heparin or, less commonly, low molecular weight heparin. HIT can be associated with thrombosis formation in the more serious forms."[16] While somewhat rare (0.1%–5% prevalence in patients receiving heparin), of those who have HIT, 35 to 50 percent develop thrombosis (Salter et al., 2016).[16] Cessation of heparin therapy is paramount in HIT; other management or treatment considerations are alternative anticoagulants.

The fourth study examined adherence to a protocol for NOAC prescribing in an outpatient setting and whether there were differences between patients enrolled in an anticoagulation service and those who were not.[17]

The overall strength of the evidence on the effect of dosing nomograms or protocols for NOACs on bleeding is extremely low.

Table 1: Summary of Study Setting, Indication, Anticoagulant, Protocol Tested, and Outcomes

Author, Year	Setting, Study Design, Sample Size	Indication, Anticoagulant(s)	Protocol or Nomogram Tested	Outcomes
Ansara, et al., 2009[8]	• Community hospital • Observational, retrospective • N=51 patients	• Treat heparin-induced thrombocytopenia (HIT) • Argatroban	• Weight-based standard dosing nomogram • Hepatic/critically ill nomogram	• 16.25 hours mean time to activated partial thromboplastin time (aPTT) stabilization(standard) • 27.05 hours mean time to aPTT stabilization (hepatic) • 0 cases of major bleeding (standard) • 3 cases of major bleeding (hepatic), although not all attributable to drug • 0 thrombotic events after initiation of argatroban
Burcham et al., 2013[14]	• One academic medical center intensive care unit • Observational, retrospective • N=65 patients	• Treat HIT • Bivalirudin	• Dosing nomogram with fixed adjustments based on aPTT for use by nurses for intravenous bivalirudin	• 11.00 hours median time to steady state (range, 5.0–31.8 hours) • 53.7% of the aPTT values were in the target range • Bleeding occurred in 20 (30.8%) patients: 7 (10.8%) major bleed and 13 (20%) minor bleed. • All-cause mortality was 41.5%, and the median hospital length of stay was 28 days (range, 2–104 days).

Author, Year	Setting, Study Design, Sample Size	Indication, Anticoagulant(s)	Protocol or Nomogram Tested	Outcomes
Draper et al., 2017[17]	• One large multicenter, multispecialty group practice • Observational, retrospective cohort study • n=1,518 prescriptions	• Use of novel oral anticoagulants • Apixaban • Dabigatran • Rivaroxaban	• Anticoagulation service to encourage protocol NOAC adherence	Overall, the following percentages were prescribed per protocol: • 72% of apixaban • 52% of dabigatran • 70% of rivaroxaban Enrollment in the anticoagulation service was not associated with increased adherence to protocols.
Smythe et al., 2012[15]	• One academic medical center • Pre-/post-evaluation • N=49 patients	• Treat HIT • Argatroban • Lepirudin	• HIT recognition and management protocol	Correct dose per direct thrombin inhibitors protocol for initial dose ordered for 100% of patients post implementation vs. 31% pre implementation.

7.2.3.1 Clinical Outcomes

The clinical outcomes examined in the studies included measures of coagulation (activated partial thromboplastin time, aPTT), bleeding, and thrombotic events. The findings for each of these outcomes is synthesized below. The studies reported that clinical outcomes were not compared with usual care or a control group, so whether the time to coagulation and occurrence of bleeding and thrombotic events should be considered high or low for this patient population is unknown. The following are the descriptive findings on the reported outcomes.

7.2.3.1.1 Activated Partial Thromboplastin Time

Two studies evaluated the effect of the nomograms on the time to aPTT stabilization, a measure of the coagulation of blood.[8,14] Of the 51 patients in the study by Ansara et al. (2009), the *mean* time to aPTT was 16.25 hours and 27.05 hours for patients with the standard and hepatic/critically ill nomogram, respectively. Burcham et al. (2013) found a *median* aPTT of 11.00 hours (range, 5.0–31.8 hours) for intravenous bivalirudin with the use of a dosing nomogram in the intensive care unit.[14]

7.2.3.1.2 Bleeding

Two studies examined the occurrence of bleeding events with use of the nomograms or protocols.[8,14] With the standard nomogram, Ansara et al. (2009) observed no bleeding events. They observed three cases of major bleeding for the hepatic/critically ill nomogram, but the authors asserted these were not attributable to the argatroban.[8] In the study by Burcham et al., bleeding occurred in 20 (30.8%) patients, 7 (10.8%) meeting the criteria for a major bleed and 13 (20%) meeting the criteria for a minor bleed.[14]

7.2.3.1.3 Thrombotic Events

Ansara et al. (2009) reported no thrombotic events for patients after initiation of argatroban and during the hospital stay.[8]

7.2.3.2 Process Outcomes

The primary process outcome examined was adherence to the nomograms or protocols.

At a large multicenter, multispecialty group practice, Draper et al. (2017) examined prescribing adherence overall and whether enrollment of a patient in an anticoagulation service, specifically, would improve adherence to a protocol for direct acting oral anticoagulants (DOACs), including apixaban,

dabigatran, and rivaroxaban. Of 1,518 DOAC prescriptions, 72 percent of apixaban, 52 percent of dabigatran, and 70 percent of rivaroxaban prescriptions were per protocol. Therefore, 24 to 45 percent of prescriptions were not per protocol, with some variance in reasons for classifying as not per protocol (e.g., off-label indication, renal impairment, hepatic impairment, dose too low, dose too high, or advanced age) across the different DOACs. Enrollment in the anticoagulation service was low (22% to 27% across the DOACs). Enrollment in the anticoagulation service was not associated with improved adherence to the DOAC protocols based on tests of significance.[17]

Smythe et al. (2012) found that after implementation of a dosing nomogram, 100 percent of patients' initial doses for DTIs were concordant with the protocol, as compared with only 31 percent before the protocol was implemented.[15]

7.2.4 Implementation

No studies formally evaluated effective approaches for implementing nomograms; however, Smythe et al. (2012) describe in detail their quality initiative for improving DTI prescribing as part of a protocol for recognizing and managing HIT. They describe the establishment of a multidisciplinary HIT working group led by the pharmacy department of an academic medical center that conducted a needs assessment, developed and revised dosing protocols, optimized HIT documentation in the electronic health record, expanded pharmacists' role in HIT, and provided education across disciplines on the protocols.[15]

7.2.5 Gaps and Future Directions

There are very few rigorous studies of the use of nomograms or protocols for NOACs in the literature, despite their expanding use and the remaining complexities of balancing between the risks of thrombotic and hemorrhagic adverse events with these newer agents and with the older anticoagulants (i.e., warfarin, heparin). There are many opportunities to expand the evidence, particularly in understanding whether and how use of nomograms or protocols improve aPTT and bleeding outcomes compared with normal care, and for what specific indications and/or patient populations.

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7.3 Patient Safety Practice 3: Interventions To Support Safe Transitions and Continuation of Patients' Anticoagulants Post Discharge

Reviewer: Scott Winiecki, M.D.

Transitioning patients from one setting to another is a particularly vulnerable time when safety lapses can result in negative clinical outcomes,[1-4] preventable adverse events,[5-9] and avoidable hospital readmissions.[10,11] The Joint Commission describes transitions of care as "the movement of patients between healthcare practitioners, settings, and home, as their conditions and care needs change."[12] Care transitions can also be cause for concern with anticoagulants, given they are the most common causes of ADEs in healthcare settings.[13] While bleeding is the primary ADE of concern, anticoagulants require "a careful balance between thrombotic and hemorrhagic risks."[13] Anticoagulants vary in their complexity, dosing, and requirements for transitioning to home from a hospital or ED.

7.3.1 Practice Description

Any intervention, service, or program that focuses on the safe transition and continuation of a patient's anticoagulant medications after discharge from a hospital or ED.

Key Findings:

- There is a paucity of literature and strong evidence on interventions, services, or programs for the safe transition of patients receiving anticoagulants after discharge from hospital or ED.
- Three studies of education and pill packs for rivaroxaban on dose transition (transitioning to daily at Day 22) found no significant improvements or differences.
- Two studies of low to moderate rigor examined a home-based service and a multi-component model for an ED.

7.3.2 Methods

The question of interest for this review is, "What is the effect of interventions to support care transitions for patients on anticoagulants discharged from emergency departments or hospitals?"

Two databases (CINAHL® and MEDLINE®) were searched for articles published in the past 10 years using a combination of (i) terms for anticoagulant and (ii) medication reconciliation and various terms for discharge, transfer, or handoff, and (iii) the outcomes of interest (bleeding or hemorrhage or patient safety, generally). Detailed search terms are provided in Appendix C.

Studies were included if they were empirical studies of an intervention specific to anticoagulants of any class for any indication upon discharge from an ED or hospital. Studies were included if they used experimental, quasi-experimental, or observational study designs with tests of significance. Key findings are located in the box above.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

7.3.3 Review of Evidence

The five studies that met the inclusion criteria are characterized in terms of their setting, study design, sample size, indication, anticoagulant(s), intervention, and outcomes in Table 2 and the findings synthesized below. A detailed overview of each study is provided in the Evidence Table in Appendix B.

Table 2: Summary of Study Setting, Indication, Anticoagulant, Intervention Tested, and Outcomes

Author, Year	Setting, Study Design, Sample Size	Indication Anticoagulant(s)	Intervention Description	Outcomes
Barbic et al., 2018[17]	• Emergency department (ED) discharge (Canada) • Pre/post • N=301 (n=129 pre; n=172 post)	• Atrial fibrillation (AF) or atrial flutter • Anticoagulants	• A coordinated, evidence-based ED AF pathway consisting of a care map, decision aids, medication orders, management suggestions, and electronic consultation or referral documents, all embedded into the electronic health record.	• Rates of new anticoagulation discharge for patients incorrectly not on anticoagulants upon ED admission significantly increased. • Median ED length of stay decreased from 262 to 218 minutes (44 minutes [p <0.03; 36.2–51.8]). • The 30-day ED revisit rate for congestive heart failure decreased from 13.2% (pre) to 2.3% (post) (absolute difference of 10.9%; p <0.01[(95% confidence interval, -8.1% to -13.7%]). • No significant differences between pre and post on: 30-day ED revisit for stroke, major bleeding, or atrial fibrillation; death within 30 days; outpatient clinic referral.
Castelli et al., 2017[14]	• Hospital discharge • Randomized controlled trial • N=25 patients	• Venous thromboembolism (VTE) • Rivaroxaban	• Rivaroxaban Patient Assistance Kit (R-PAK) is a novel discharge tool that includes reminder card stating dates of dose transition and a customizable pill box. Patients were also taught by a pharmacist how to use the pill box. • Control group received pharmacist education alone.	• No significant difference between the two groups on any outcomes: adherence, proper transition to daily administration on Day 22, percentage of patients who stopped rivaroxaban for any reason, patient understanding of correct timing and dose of medication, overall patient satisfaction, self-reported side effects, recurrent VTE, death.
Chu and Limberg, 2017[15]	• ED discharge • Retrospective cohort • N=41	• VTE • Rivaroxaban	• Patients discharged were counseled and provided a blister pack with dose instructions for the first 30 days • Control: usual care	• No statistically significant differences were found between the two groups on: adherence beyond the first month after discharge, 90-day readmission for recurrent VTE due to nonadherence or treatment failure, 90-day readmission due to bleeding or adverse event.
DiRenzo et al., 2018[16]	• ED discharge • Prospective cohort • N=17	• VTE • Rivaroxaban	• Intervention: outpatient VTE pharmacist-managed clinic under a collaborative practice agreement with a physician • Control: primary care provider management	• There were no significant differences 6 months following diagnosis between groups in major bleeding, recurrent thromboembolism, fatal event due to either bleeding or thromboembolism, number of hospitalizations after diagnosis, adverse events, or Morisky medication adherence score.

Author, Year	Setting, Study Design, Sample Size	Indication Anticoagulant(s)	Intervention Description	Outcomes
Stafford et al., 2011[18]	• Hospital discharge (Australia) • Prospective cohort • n= 236 patients (n=108 intervention)	• Newly initiated on warfarin, or continuing preadmission therapy with indication of at least 3 months of therapy • Warfarin	• Intervention: Collaborative, home-based post-discharge service. First visit within 2–3 days post discharge, subsequent visits based on risk assessment • Control: Usual care of the patient's community health care providers	• Persistence with warfarin improved (95.4% vs. 83.6%; p=0.004). • Significant decrease in major and minor hemorrhagic events at 90 days post discharge (5.3% vs. 14.7%; p=0.03) and at 8-day followup (0.9% vs. 7.2%; p=0.01). • Rate of combined hemorrhagic and thrombotic events at 90 days post discharge decreased (6.4% vs. 19.0%; p=0.008).

7.3.3.1 Outcomes

Three studies examined the effect of an intervention targeted at patients discharged on rivaroxaban for VTE from the hospital[14,15] or ED.[16] These three studies were observational and had quasi-experimental designs, had very small sample sizes (25, 41, and 17 intervention patients) and reflect a very low strength of evidence. The studies found no significant differences in bleeding, thromboembolic events, readmission, mortality, adherence, or dosing transition.

Barbic et al.'s multicomponent intervention of a coordinated ED approach for atrial fibrillation (pathway) significantly improved the rates of new anticoagulation for patients incorrectly not on anticoagulants upon ED admission. The median length of stay decreased significantly, as did the 30-day ED revisit rate for congestive heart failure. The study found no significant differences between pre and post intervention on: 30-day ED revisit for stroke, major bleeding, or AF; death within 30 days; or outpatient clinic referral.[17]

Stafford et al.'s collaborative, home-based post-discharge service significantly improved warfarin persistence/adherence (95.4% vs 83.6%; p=0.004), significantly decreased major and minor bleeding at 8-day followup (0.9% vs. 7.2%; p=.0.01) and 90 days post discharge (5.3% vs. 14.7%; p=0.03); and decreased the rate of combined hemorrhagic and thrombotic events at 90 days post discharge (6.4% vs. 19.0%; p=0.008).[18]

7.3.4 Implementation

No studies formally evaluated effective approaches for implementing anticoagulation management services.

7.3.5 Gaps and Future Directions

The available studies on safety practices for discharging patients on anticoagulants from hospitals and EDs are extremely few and reflect poor-quality evidence. Additional research is warranted to further understand the evidence-based approaches for successfully transitioning patients upon discharge to safely continue their anticoagulants and monitor appropriately for the specific anticoagulant. However, the paucity of studies may be a function of most care transition programs focusing on all of a patients' medications, not just anticoagulants.

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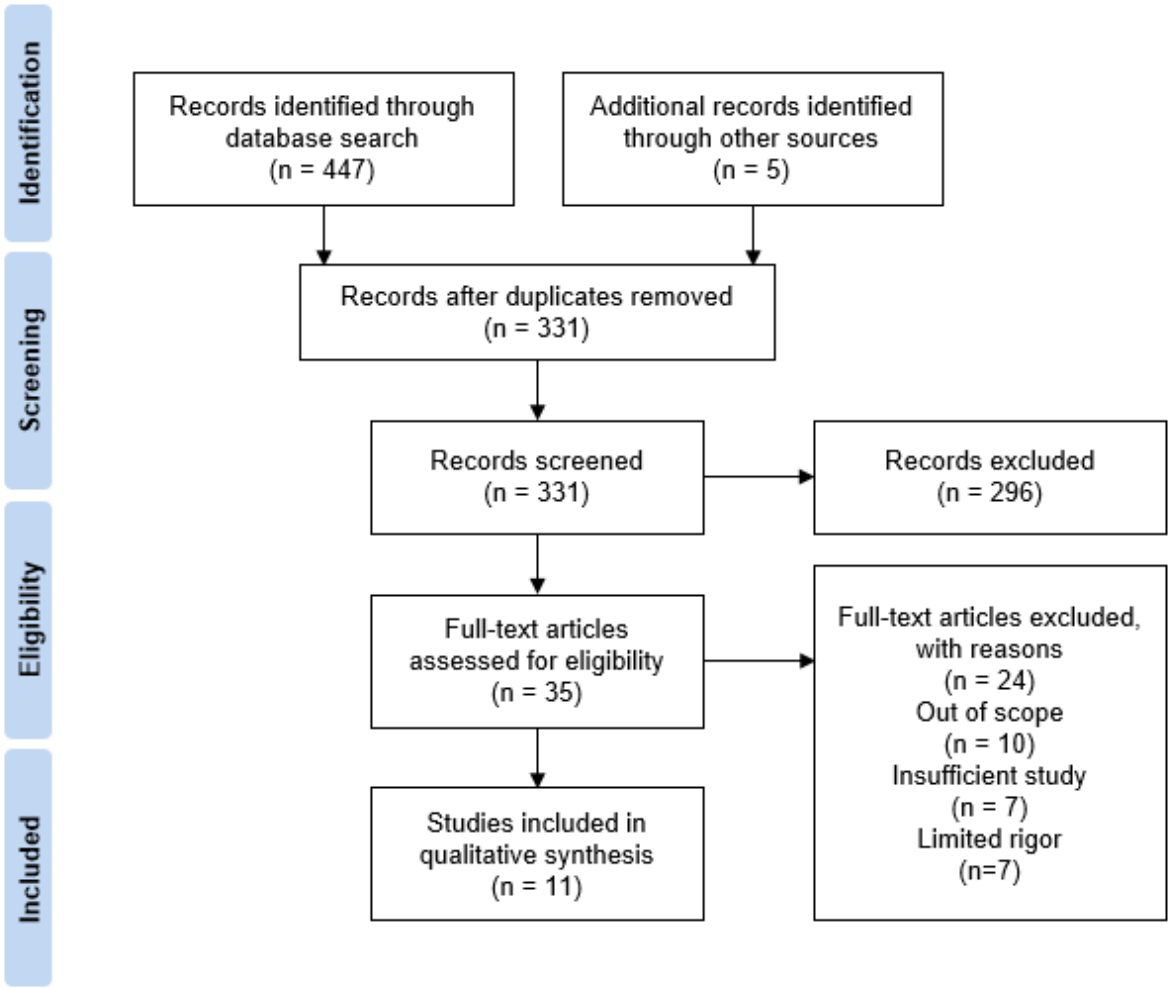
Conclusion

Evidence was sought on patient safety strategies to mitigate against bleeding and other adverse events associated with anticoagulants. There appears to be moderate evidence of pharmacist-provided anticoagulation management services, as well as some, albeit limited, evidence of different models being as effective, as described in Section 7.1. The studies of dosing protocols for the NOACs are largely observational, non-RCT studies without control groups or tests of significance, and with very small sample sizes. Thus, there is insufficient evidence to indicate the effectiveness of using dosing protocols/nomograms for NOACs to prevent bleeding. There is a paucity of literature and strong evidence on interventions, services, and programs for the safe transition of anticoagulant therapy post discharge from the hospital or ED. While this review may expand what we know and do not know about some patient safety practices to address the harms associated with anticoagulants, there are still many opportunities to improve the evidence base.

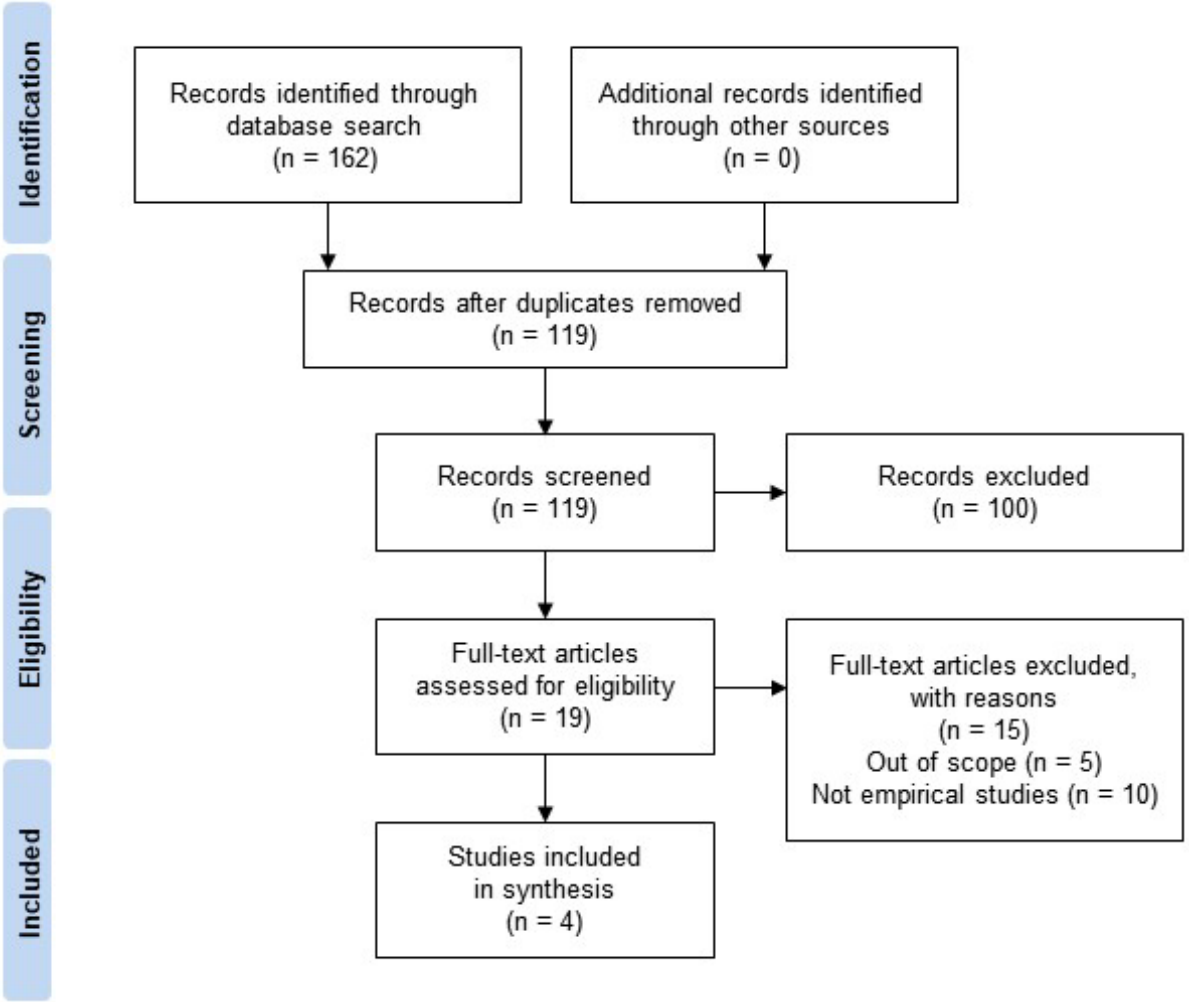
Appendix A. Harms Due to Anticoagulants PRISMA Diagrams

Figure A.1: Anticoagulants, Management Service, Ambulatory Setting—Study Selection for Review



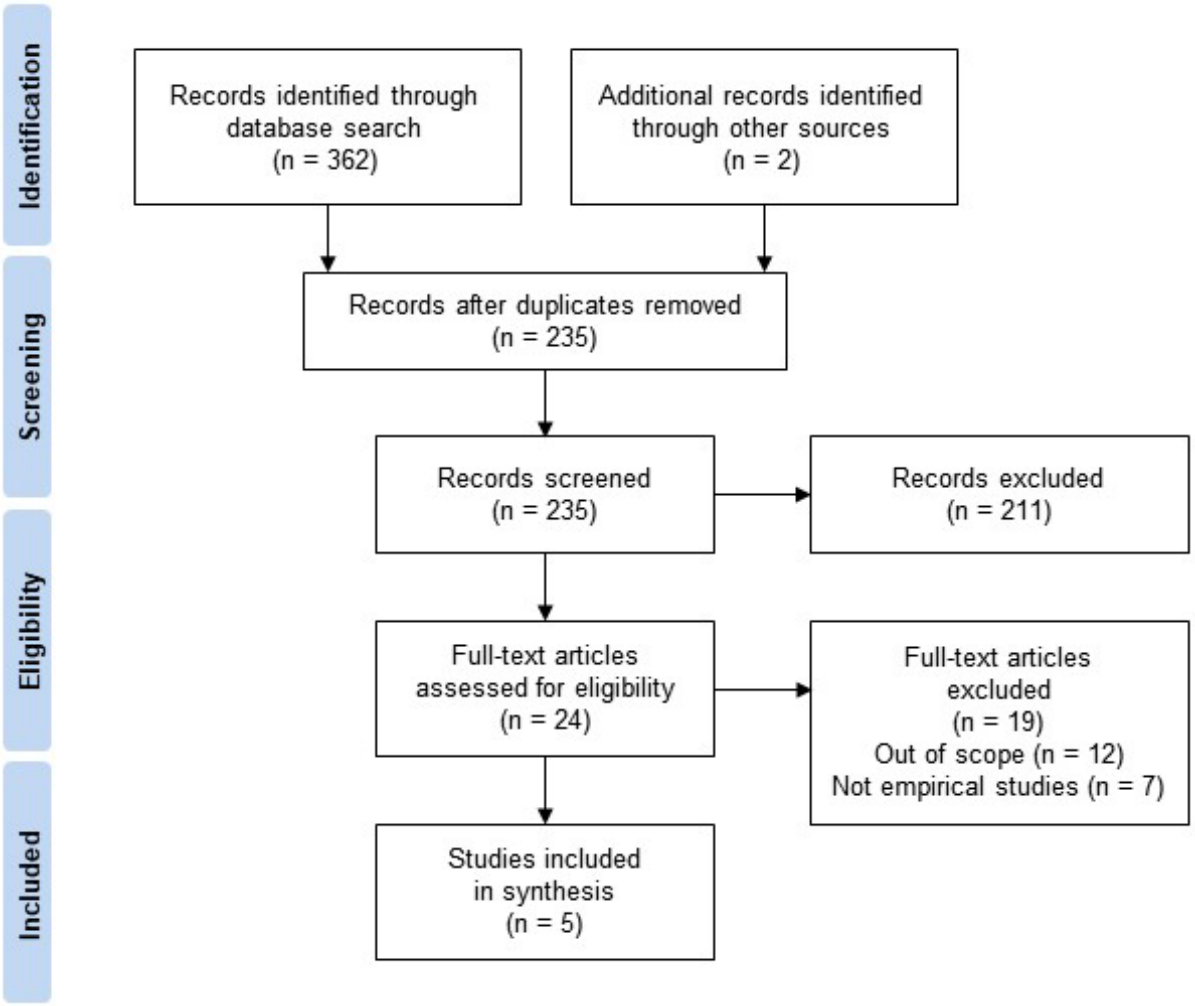
PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.2: Anticoagulants, Protocols for Newer Oral Anticoagulants—Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.3: Anticoagulants, Transitions Between Hospital or Emergency Department and Home—Study Selection for Review



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Appendix B. Harms Due to Anticoagulants Evidence Tables

Table B.1: Anticoagulants, Ambulatory Setting–Systematic Reviews

Note: Full references are located in the Section 7.1 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/ Findings	Notes
Canadian Agency for Drugs and Technologies in Health, 2011[1]	Specialized anticoagulation services that include patient self-testing or self-management, as compared with other specialized anticoagulation services or usual care (defined as dose adjustment managed by a non-hematologist physician who also treats other medical problems)	Adult patients receiving long-term warfarin treatment, most for atrial fibrillation but also including some patients with thromboembolism	One health technology assessment, 8 systematic reviews or meta-analyses, 6 randomized controlled trials (RCTs), and 12 non-RCT studies were included. Specialized anticoagulation services had significantly more favorable time to therapeutic range (TTR) compared with usual care. Improved TTR did not correlate with reduction in hemorrhage, thromboembolism, or need for additional medical care. Patient self-testing or patient self-management had mixed results, with some studies finding improved TTR and others finding no difference as compared with usual care. In most studies, patient self-testing/self-management resulted in lower mortality rates and reduced incidence of thromboembolism, but rate of bleeding events did not differ between specialized and usual care. Some evidence suggests that patient self-testing/self-management may improve quality of life.	Not provided	None

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/ Findings	Notes
Entezari-Maleki et al., 2016[2]	Pharmacist-managed warfarin therapy, usually in a primary care clinic using a protocol approved by physician specialists	Outpatient settings comparing pharmacist-managed warfarin therapy with "usual medical care"	Of 24 included studies, 4 were RCTs and 20 were observational studies. A total patient population of 11,607 was included. In non-RCT studies, pharmacist-managed patients had a significantly higher percentage of time in the therapeutic range (72.1% vs. 56.7%; p=0.013) and significantly fewer major bleeding events (0.6% vs. 1.7%, p<0.001), thromboembolic events (0.6% vs. 2.9%; p<0.001), instances of hospitalization (3% vs. 10%; p<0.001), and emergency department (ED) visits (7.9% vs. 23.9%; p<0.0001), as compared with patients managed with usual medical care. No cases of mortality were noted among the non-RCT studies. In RCT studies, pharmacist-managed and usual care groups did not significantly differ in the following outcomes: percentage of time in therapeutic range, major bleeding events, mortality, instances of hospitalization, and ED visits. No thromboembolic events were observed in the four included RCTs. One report on health-related quality of life did not find significant differences between pharmacist-managed and usual care. With the exception of one RCT, included studies indicated cost savings in the pharmacist-managed service as compared with usual care.	Not provided	None
Hou et al., 2017[3]	Pharmacist-managed warfarin therapy	Studies comparing pharmacist management of warfarin and any other model, e.g., physician-managed, nurse-managed	Of 17 included studies, 8 were RCTs and 9 were observational cohort studies. A total of 9,919 patients were included. Overall study quality was reported to be high, as evaluated by two independent reviewers using GRADE. In pooled results of the RCTs, the following outcomes were not significantly different between groups: TTR, hemorrhage events, thrombosis events, and mortality. In pooled results of the observational studies, TTR was significantly higher in the pharmacist-managed group, and risks of hemorrhage and thrombosis events were significantly lower in the pharmacist-managed group. Two included studies that reported on cost found that pharmacist management resulted in a significant decrease in cost.	Not provided	None

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/ Findings	Notes
Manzoor et al., 2017[5]	Pharmacist-managed outpatient warfarin clinics	Outpatient settings; patients receiving warfarin therapy for any reason	Of 25 included studies, 3 were RCTs and 22 were observational studies that included a comparison group of some kind. A total of 12,252 participants were included. In the majority of studies (23 out of 25), the pharmacist-managed group showed better quality of anticoagulation control as compared with regular medical care, as indicated by TTR. In 10 of 12 studies that reported on the outcome, the pharmacist-managed group also had lower or equal risk of major bleeding as compared with usual care. In 9 of 10 studies that reported on the outcome, the pharmacist-managed group had lower or equal risk of thromboembolic events as compared with usual care. In 9 of 9 studies that reported on the outcome, the pharmacist-managed group had decreased rates of hospitalization, shorter length of hospital stay, and fewer ED visits as compared with usual care. In 6 of 6 studies that reported on cost, the pharmacist-managed group had cost savings as compared with usual care.	Not provided	None
Satokaew et al., 2010[11]	Pharmacist-participated warfarin therapy management (PWTM)—may include dosage adjustment, medication/drug interaction review, and/or providing patient or provider education	Various—both acute and ambulatory; Three studies included only surgical patients; others included all patient groups	Of 24 included studies, 5 were RCTs, 9 were quasi-experimental studies, and 10 were cohort studies. A total of 728,377 patients were included in the meta-analysis. In RCTs, PWTM was significantly associated with a 49% reduction in total bleedings (relative risk [RR], 0.51; 95% confidence interval [CI], 0.28 to 0.94) compared with usual care without heterogeneity. In 19 non-RCTs, PWTM was significantly associated with a 29% reduction in total bleedings (RR, 0.71; 95% CI, 0.52 to 0.96; p=0.028) when compared to usual care. For major bleeding (4 RCTs), the RR for PWTM vs. usual care was 0.64 (95% CI, 0.81 to 2.36; p=0.507) without heterogeneity. In 11 non-RCTs, PWTM was significantly associated with a 51% reduction in major bleedings (RR, 0.49; 95% CI, 0.26 to 0.93; p=0.030). Out of four RCTs, the RR for PWTM vs. usual care on thromboembolic events was 0.79 (95% CI, 0.33 to 1.93; p=0.610) without heterogeneity. In 15 non-RCTs, PWTM was significantly associated with a 63% reduction in thromboembolic events (RR, 0.37; 95% CI, 0.26 to 0.53; p<0.001) without heterogeneity. There was no significant difference in mortality between PWTM and usual care in either RCTs or non-RCTs.	Not provided	None

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/ Findings	Notes
Zhou et al., 2016[4]	Pharmacist-managed warfarin therapy as compared with other models	Various	Eight randomized controlled trials with a total of 1,493 patients were included. In the pooled meta-analysis, pharmacist-managed models had significantly higher patient satisfaction and a higher percentage of time within the standard therapeutic range as compared with all other models. The models did not significantly differ on time within the expanded therapeutic range, mortality, and incidence of bleeding and thromboembolic events.	Not provided	None

Table B.2: Anticoagulants, Ambulatory Settings —Single Studies

Note: Full references are available in the Section 7.1 reference list.

Author, Year	Description of PSP	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Risk of Bias (High, Moderate, Low)
Duran-Parrondo et al., 2011[5]	Followup by a pharmacist within primary care, who provided patient education for 12 months—providers in primary care setting did not provide management of anticoagulation, only patient education	Controlled trial; 272 patients followed by pharmacist, 460 controls; patients receiving oral anticoagulation therapy under the care of a hematologist	Four primary care clinics in northwest Spain	Compared with the control group, the intervention group improved its proportion of individuals with international normalized ratio (INR) results within 0.5 units of the target range by 25% (relative risk [RR]=0.75; 95% confidence interval [CI] 0.69 to 0.82) and by 26% (RR=0.74; 95% CI, 0.67 to 0.81) for those within 0.75 units of the target range. Patients belonging to the intervention group additionally had a 75% reduction in bleeding (hazard ratio [HR]=0.25; 95% CI, 0.18 to 0.36). The intervention group had an 8% reduction (odds ratio 0.92; 95% CI, 0.88 to 0.96) in the number of medical consultations required to maintain individual patients' INR within the correct range. Additionally, the intervention group had a fivefold reduction (HR=0.20; 95% CI 0.13 to 0.32) in the need to use rescue medications. There was no significant difference between the two groups in incidence of thromboembolic events or in the number of times that the dose needed to be adjusted to maintain the correct range.	Low: not randomized
Hassan et al., 2013[9]	Telephone-based warfarin management by nurse practitioner—phlebotomist visited patients' homes to draw blood samples, and the nurse practitioner called the patient to communicate results and direct dosage adjustment	Observational; 448 homebound patients receiving warfarin therapy for at least 3 months from 2000 to 2011	Patients' homes	The mean percentage of INR values in range was 58.39%. The mean time of the INR in therapeutic range (TTR) was 62.75%. The percent of patients who were therapeutically controlled decreased as the number of medications increased. The complication rate was 4% per patient year, with an equal distribution between bleeding and clotting. The cost per visit at the anticoagulation clinic was found to be approximately $300, compared with $82 when using the homebound service.	Moderate: no control group

Author, Year	Description of PSP	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Risk of Bias (High, Moderate, Low)
Hawkins et al., 2018[6]	Management of stable, in-range warfarin by pharmacy technicians as opposed to pharmacists	Retrospective cohort; 2,956 patients—1,840 managed by pharmacy technicians and 1,116 receiving usual care (pharmacist-managed); patients receiving chronic warfarin therapy with INR within therapeutic range 100% of the time during the 3 months prior to the index date	One integrated healthcare delivery system with a centralized pharmacy team that provides anticoagulation management for > 10,000 patients	The technician group had a higher percentage of in-range INRs (mean difference=6.8%; 95% CI, 5.0% to 8.7%) and patients with 100% TTR (mean difference=10.5%; 95% CI, 7.0% to 14.0%) during followup. The propensity-weighted 6-month followup mean TTR was 83.3% (95% CI, 82.4% to 84.2%) in the technician group and 77.7% (95% CI, 76.4% to 78.9%) in the usual care group, with a mean difference of 5.7% (95% CI, 4.1% to 7.2%. The mean difference did not cross the noninferiority margin of -2.5%, indicating that technician management was noninferior to usual care. There was no significant difference between groups in incidence of thromboembolic events. Bleeding (HR=0.60; 95% CI, 0.39 to 0.94; p=0.026) and all-cause mortality (HR=0.44; 95% CI, 0.25 to 0.77; p=0.004) were lower in the technician group during followup.	Low-to-moderate: no random assignment, single health care system—findings may not be generalizable
Lee et al., 2018[7]	Telephone-based warfarin management using either local laboratory testing or patient self-testing, as compared with face-to-face management by a pharmacist	Retrospective cohort; 336 patients on established warfarin therapy, with those not living within a given proximity of the clinic eligible for either local laboratory or self-testing	Academic medical center providing outpatient care in both rural and urban settings across a single U.S. State	INR TTR for face-to-face management was significantly greater than for distance management using local laboratory testing (69.0% vs 60.5%, p=0.0032). No difference was observed between face-to-face management and patient self-testing (69.0% vs 68.0%, p=0.25). No significant difference in bleeding or thromboses was observed. Although increased clinician time was used during face-to-face encounters compared with telephone encounters (8.7-minute face-to-face, 5.5-minute local laboratory, and 5.4-minute patient self-testing), face-to-face encounters tended to be billable at lower levels, whereas telephone-based encounters were billable at higher levels.	Moderate: no random assignment; relatively small sample size; single health care system—findings may not be generalizable

Author, Year	Description of PSP	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Risk of Bias (High, Moderate, Low)
Philip et al., 2015[8]	Telephone-based anticoagulation management by clinical pharmacists	Quasi-experimental; 502 patients (301 pre-intervention and 201 post-intervention); randomly selected patients who had not been hospitalized in the past 12 months and had at least three consecutive INR readings within the target therapeutic range	Four ambulatory care centers within one health system	The mean number of visits per month for the clinical pharmacy service significantly differed between the pre-intervention group and the post-intervention group (270 vs. 313; p=0.011). The following outcomes were not significantly different between the two groups: percentage of clinical pharmacy visits for anticoagulation management, elapsed time to the third available clinic appointment, number of clinical pharmacy visits for anticoagulation management, percentage of INR values in the therapeutic range, proportion of hospitalizations due to thromboembolic or bleeding events, pharmacist work hours per prescription volume.	Moderate: no true control group; single health care system—findings may not be generalizable

Table B.3: Anticoagulants, Protocols for Newer Oral Anticoagulants—Single Studies

Note: Full references are located in the Section 7.2 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Ansara et al., 2009[8]	Weight-based dosing nomogram for argatroban to treat Heparin-induced thrombocytopenia (HIT)—one nomogram for standard and one for hepatic/ critically ill	Observational, retrospective study; N=51 patients prospectively treated for suspected or documented HIT: n=34 patients treated with the standard nomogram, n=17 with the hepatic/critically ill nomogram	One community hospital	Mean time to activated partial thromboplastin time (aPTT) stabilization was 16.25 hours with the standard nomogram and 27.05 hours with the hepatic/critically ill nomogram. The percentages of patients with aPTTs within the therapeutic range at 6, 12, 24, 48, 72, and 96 hours were 82.4%, 82.4%, 88.2%, 96.4%, 100%, and 100% with the standard nomogram and 58.8%, 82.4%, 76.5%, 93.3%, 100%, and 90.9% with the hepatic/critically ill nomogram. No statistical significance examined.	Three cases of major bleeding occurred in patients dosed on hepatic/critically ill nomogram, although the authors asserted they were not attributable to argatroban. No bleeding events in the standard nomogram patients. There were no thrombotic events after the initiation of argatroban during hospital stay. One patient died during the observation, although this was attributed to other factors.	Not provided	High: no control group, small sample size, one health system—not generalizable

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Burcham et al., 2013[14]	Simplified dosing nomogram for nurses to administer intravenous bivalirudin for heparin-induced thrombocytopenia, which specifies fixed adjustments (0.005 or 0.01 mg/kg/hr) according to the current aPTT value relative to aPTT goals	Observational, retrospective study n=65 patients who received continuous infusion of bivalirudin for suspected or confirmed HIT during 3-year period	One academic medical center intensive care unit	Mean time to aPTT stabilization was 11.0 hours (range, 5.0–31.8 hours). Nurse adherence to the nomogram was 100%, and no dosing errors occurred during a total of 487 dosage changes. Overall, 53.7% of the aPTT values were in the target range (30.5% of values were above target, and 15.8% were below target). The median bivalirudin dosage for all patients at steady state was 0.04 mg/kg/hr (range, 0.02–0.07 mg/kg/hr), the median length of bivalirudin treatment was 49 hours (range, 29.0–190.5 hours), and the median number of dosing changes per patient was 4.0 (range, 1.5–8.5 changes), with a median of 1.2 dosing changes per day. After the pilot study, the nomogram was adjusted for patients with creatinine clearance values of >30 mL/min. Provided more direction for initial dosing, too.	Bleeding occurred in 20 (30.8%) of the evaluated patients, with 7 (10.8%) meeting the criteria for a major bleed and 13 (20%) having a minor bleed. All-cause mortality was 41.5%, and the median hospital length of stay was 28 days (range, 2–104 days).	Not provided	High: no control group, small sample size, one health system—not generalizable

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Draper et al., 2017[17]	Anticoagulation service to encourage adherence to novel oral anticoagulant prescribing protocols	Observational, retrospective study; N=1,518 total prescriptions; all initial prescriptions of apixaban, dabigatran, and rivaroxaban to adults 18 and older over 4-year period; 1,518 total initial prescriptions were issued: 247 for apixaban (16%), 537 for dabigatran (36%), and 734 for rivaroxaban (48%)	One large multicenter, multispecialty group practice	Seventy-two percent of apixaban, 52% of dabigatran, and 70% of rivaroxaban prescriptions were per protocol. Therefore, 24–45% of prescriptions were potentially inappropriately prescribed. The most common reasons for nonadherence to protocol for apixaban and rivaroxaban were off-label indications (11% and 13%, respectively) and dosage too low (11% and 11%, respectively). Age greater than 75 years (35%) and off-label indication (5%) were the most common reasons for not per protocol dabigatran prescriptions. A minority of patients enrolled in the anticoagulation service: 24% of patients receiving apixaban, 22% receiving dabigatran, and 27% receiving rivaroxaban. Enrollment in anticoagulation service was low across the direct acting oral anticoagulants (22–27%). Based on a test of significance, enrollment in the anticoagulation service was not associated with increased adherence to protocols.	Not provided	Not provided	Moderate-to-high: patients not randomly assigned to participate in anticoagulation service, one health system—not generalizable

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)
Smythe et al., 2012[15]	HIT recognition and management protocol	Pre-post evaluation; N=49 patients started on direct thrombin inhibitors (DTI) post-protocol implementation; 4-month period before implementation compared with 4-month period after implementation	One academic medical center	Correct protocol-directed initial DTI dose ordered for 100% of patients, compared with only 31% of patients during the pre-implementation period. Prior to protocol implementation, the appropriate documentation of HIT in the medical record was lacking in >15% of cases. During the post-implementation period, documentation of HIT was found in the electronic medical record of 100% of patients with suspected or confirmed HIT at the time of discharge.	Not provided	The authors describe the establishment of a multidisciplinary HIT working group that conducted a needs assessment, developed and revised protocols, and conducted education on the protocols.	High, no control group, small sample size, one health system

Table B.4: Anticoagulants, Transitions Between Hospital or Emergency Department and Home —Single Studies

Note: Full references are located in the Section 7.3 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Risk of Bias (High, Moderate, Low)
Barbic et al., 2018[17]	Atrial fibrillation and flutter (AFF) pathway developed at the study site by emergency physicians, cardiologists, and pharmacists. The pathway consists of a care map, decision aids, medication orders, management suggestions, and electronic consultation or referral documents, all embedded into the computerized physician order entry and integrated electronic medical record program.	Pre-post; 301 (129 pre-pathway and 172 post-pathway); patients presenting in the emergency department (ED) with final diagnosis of AFF	Two EDs—one academic inner-city medical center, one community hospital; Vancouver, BC	The rates of new anticoagulation on discharge from the ED for patients who were incorrectly not on anticoagulation at ED arrival were 51/105 (48.6%, 95% confidence interval [CI] 42.1% to 55.1%) in the pre group and 97/138 (70.2%, 95% CI, 62.1% to 78.3%) in the post group, for an absolute difference of 20.6% (95% CI, 15.1% to 26.3%). The 30-day ED revisit rate for congestive heart failure decreased from 13.2% (pre) to 2.3% (post) (absolute difference of 10.9%; p<0.01 [95% CI, -8.1% to -13.7%]). Median ED length of stay decreased from 262 to 218 minutes (44 minutes [p<0.03; 36.2–51.8]). There were no significant differences between pre and post groups on the following outcomes: 30-day ED revisit for stroke, major bleeding, or AFF; death within 30 days; outpatient clinic referral.	Moderate-to-high: small sample size, no comparison group
Castelli et al., 2017[14]	Rivaroxaban Patient Assistance Kit (R-PAK)	Randomized controlled trial—patients randomized to receive either education by a pharmacist plus the R-PAK or education by pharmacist alone; 25 patients; patients newly diagnosed with acute venous thromboembolism(s) (VTE) and treated with rivaroxaban	Hospital discharge from one community teaching hospital	No difference in the baseline assessment of health literacy status was noted (p=1.00). Proper transition to daily administration on Day 22 was no different between the groups (p=0.891). Adherence was reported in 99.8% of R-PAK patients and 97.65% of control patients (p=0.074). There was no significant difference between the two groups on any of the following outcomes: percentage of patients who stopped rivaroxaban for any reason, patient understanding of correct timing and dose of medication, overall patient satisfaction, self-reported side effects, recurrent VTE, death.	High: very small sample; single site

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Risk of Bias (High, Moderate, Low)
Chu and Limberg, 2017[15]	Commercially available medication dose pack with counseling by ED pharmacist	Retrospective cohort; 75 patients (41 received intervention, 34 received usual care); patients discharged from ED on rivaroxaban with a discharge diagnosis of VTE	Discharge from ED in one urban community hospital	No statistically significant differences were found between the two groups on the following outcomes: medication adherence beyond the first month after discharge, 90-day readmission for recurrent VTE due to nonadherence or treatment failure, 90-day readmission due to bleeding or adverse event.	High: very small sample; single site
DiRenzo et al., 2018[16]	Pharmacist management of rivaroxaban, as compared with management by primary care provider	Prospective cohort; pharmacist-managed patients (n=17) were seen for low-risk VTE in the ED over a 5-month period in 2015; Comparison group (n=17) was selected from the outpatient pharmacy records and matched to patients in intervention group on month and year of rivaroxban initiation, age, and sex	One academic, safety-net medical center in a metropolitan city	There were no significant differences between groups 6 months after diagnosis in major bleeding, recurrent thromboembolism, fatal event due to either bleeding or thromboembolism, number of hospitalizations after diagnosis, adverse events, or Morisky medication adherence score. Only one complication (recurrent thromboembolism) occurred in each group. Only eight patients in the pharmacist group were assessed for medication adherence, compared with no patients in the comparison group.	Moderate-to-high: small sample size; no random assignment; one health system—not generalizable
Stafford et al., 2011[18]	Home-based post-discharge warfarin management service adapted from the Australian Home Medicines Review program—includes home visits for patients with INR monitoring and a summary of the patient's inpatient warfarin therapy sent to the patient's general practitioner, from which the general practitioner may make adjustments	Prospective cohort; 268 patients (129 intervention, 139 controls); adults being discharged from the hospital with an indication for ongoing warfarin therapy for at least 3 months	Eight hospitals across five metropolitan, rural, and remote regions of Australia	The intervention was associated with significantly decreased major and minor hemorrhagic events at 90-day followup post discharge (5.3% vs. 14.7%; p=0.03) and at 8-day followup (0.9% vs. 7.2%; p=0.01) as compared with usual care. The rate of combined hemorrhagic and thrombotic events at Day 90 also decreased (6.4% vs. 19.0%; p=0.008) and persistence with warfarin therapy improved (95.4% vs. 83.6%; p=0.004). No significant differences in readmission and death rates or time to therapeutic range or international normalized ratio control were demonstrated.	Low-to-moderate: moderately small sample size

Appendix C. Harms Due to Anticoagulants Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study	Single Provider	(((MH "Anticoagulants") OR (AB Anticoagulant*)) AND ((MH Nurses OR Pharmacists OR "Physician Assistants" OR "Nurse Practitioners") OR (AB Nurse OR Pharmacist OR "Physician Assistant*" OR "Nurse Practitioner*")) AND (AB “Warfarin Clinic” or “Anticoagulation Clinic” or “Coumadin Clinic") AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety") OR (AB "Patient Safety" OR "Safety Management")))	(((MH "Anticoagulants") OR (AB Anticoagulant*)) AND ((MH Nurses OR Pharmacists OR "Physician Assistants" OR "Nurse Practitioners") OR (AB Nurse OR Pharmacist OR "Physician Assistant*" OR "Nurse Practitioner*")) AND (AB “Warfarin Clinic” or “Anticoagulation Clinic” or "Coumadin Clinic”) AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety" OR "Safety Management") OR (AB "Patient Safety" OR "Safety Management")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review			

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article	Nomograms	(((MH "Dabigatran Etexilate" OR Bivalirudin OR "Argatroban") OR (AB "Thrombin Inhibitors" OR Dabigatran OR Bivalirudin OR Argatroban)) AND ((MH Rivaroxaban OR "Fondaparinux Sodium") OR (AB "Factor Xa Inhibitors" OR Rivaroxaban OR Apixaban OR Edoxaban OR Fondaparinux)) AND (AB "New Oral Anticoagulants") AND ((MH "Medical Orders" OR Protocols OR Algorithms) OR (AB Protocol* OR "Medication Orders" OR "Order Sets" OR Algorithm* OR "Dosing Nomograms" OR Nomograms))	(((MH Dabigatran) OR (AB "Thrombin Inhibitors" OR Dabigatran OR Bivalirudin OR Argatroban)) AND ((MH "Factor Xa Inhibitors" OR Rivaroxaban OR Fondaparinux) OR (AB "Factor Xa Inhibitors" OR Rivaroxaban OR Apixaban OR Edoxaban OR Fondaparinux)) AND (AB "New Oral Anticoagulants") AND ((MH "Medication Order Entry Systems" OR Algorithms OR Nomograms) OR (AB Protocols OR "Medication Orders" OR "Order Sets" OR Algorithm* OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial		AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety") OR (AB "Patient Safety" OR "Safety Management")))	“Dosing Nomograms” OR Nomograms)) AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety" OR MH "Safety Management") OR (AB "Patient Safety" OR "Safety Management")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article	Medication Reconciliation and Handoff	(((MH Anticoagulants) OR (AB Anticoagulant*)) AND ((MH "Medication Reconciliation") OR (AB "Medication Reconciliation")) AND ((MH "Patient Discharge" OR "Patient Handoff") OR (AB "Discharge Planning" OR "Patient Discharge" OR "Patient Transfer" OR "Patient Handoff" OR "Hospital Discharge")) AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety") OR (AB "Patient Safety" OR "Safety Management")))	(((MH Anticoagulants) OR (AB Anticoagulant*)) AND ((MH "Medication Reconciliation") OR (AB "Medication Reconciliation")) AND ((MH "Patient Discharge" OR "Patient Handoff") OR (AB "Discharge Planning" OR "Patient Discharge" OR "Patient Transfer" OR "Patient Handoff" OR "Hospital Discharge")) AND ((MH Hemorrhage) OR (AB Bleeding OR Hemorrhage OR Haemorrhage)) AND ((MH "Patient Safety" OR MH "Safety Management") OR (AB "Patient Safety" OR "Safety Management")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial			

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Research Review • Systematic Review			