SECTION 5

Anticoagulants

Magnitude of the Problem

Anticoagulants are the mainstay of therapy for the acute and long-term prevention and treatment of numerous types of thromboembolic disorders. The prevention of thromboembolic stroke among patients with chronic atrial fibrillation (AF) is one of the primary indications for oral anticoagulation therapy. The current U.S. prevalence estimate of AF is approximately 2.6 million persons, and it is predicted to reach 12 million persons by the year 2050 [1]. In addition, anticoagulants are indicated in, and are increasingly prescribed for the prevention and treatment of, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that more than 900,000 incident or recurrent, fatal and nonfatal VTE events occur in the United States annually [2]. Total annual direct medical costs and indirect costs (including lost earnings from premature mortality) of VTE are estimated to be $13 to $27 billion (USD 2011) [3]. Vitamin K antagonists (e.g., warfarin), unfractionated heparin (UFH, low-molecular-weight heparin [LMWH, e.g., enoxaparin and dalteparin]), direct thrombin inhibitors (e.g., argatroban and dabigatran), and factor Xa inhibitors (e.g., apixaban, fondaparinux, and rivaroxaban) are critical for the treatment and prevention of these disorders [4]. More than 30 million prescriptions for warfarin are written annually [5], more than two-thirds of Medicare beneficiaries with AF use warfarin [6], and total direct expenditures on warfarin have been estimated to be around $158 million per quarter (USD 2010) [7]. Prescriptions of new oral anticoagulants (NOACs), such as dabigatran and rivaroxaban, are also increasing [7].

Bleeding is the primary ADE of concern associated with the use of anticoagulants [4, 5, 8, 9]. Thus, anticoagulation requires a careful balance between thrombotic and hemorrhagic risks and is easily influenced by a multitude of factors, such as patient age, co-morbidities, concomitant medications, and for warfarin especially, diet and pharmacogenetics. Bleeding rates associated with anticoagulants vary depending on the types of anticoagulant agents, dosing strategies, prophylactic versus therapeutic indications, durations of therapy, and patient populations. For warfarin, bleeding frequency has been estimated to be 15 percent to 20 percent per year, and life-threatening or fatal bleeding rates are

estimated at 1 percent to 3 percent per year [10]. Bleeding frequency while on warfarin is approximately five times that observed without warfarin therapy [11]. In recent clinical trials, NOACs (e.g., dabigatran and rivaroxaban) were associated with statistically significant lower rates of intracranial bleeding but higher rates of gastrointestinal bleeding relative to warfarin [12, 13, 14, 15]. Among patients with AF, studies indicate that NOACs were associated with statistically significant reductions in hemorrhagic strokes relative to warfarin [12, 13, 14, 15, 16]. In most studies to date of patients with VTE or PE, NOACs were associated with statistically significant reductions in major or clinically relevant bleeding, as compared with warfarin [17, 18, 19, 20, 21]. The bleeding risks associated with the use of NOACs outside of clinical trials and in populations who are especially vulnerable to ADEs (e.g., elderly patients and patients with renal impairment) require further postmarketing experience [22]. Data on the economic impact of anticoagulant-related harms are scarce. Among older adults (age ≥ 65 years), a population shown to be especially vulnerable to ADEs, the annual cost of hospitalizations for warfarin-related bleeding has been estimated to be hundreds of millions of dollars [9, 23].

Among hospitalized patients (i.e., inpatient settings), significant challenges to optimal anticoagulation management persist despite advancements in health care delivery models and health information technology (health IT) resources (e.g., computerized physician order entry, electronic medication administration records, clinical decision support) [24, 25, 26, 27]. These challenges may result from clinicians having to rely on a wide range of anticoagulants with differing pharmacodynamic and pharmacokinetic profiles, the acuity and complexity of hospitalized patient populations, unique inpatient dosing considerations (e.g., rapidly changing renal function and extremes of weight), dietary inconsistency (e.g., changing or reduced dietary intake while hospitalized), the need for interruption of anticoagulation in preparation for invasive procedures, and transitions between parenterally and orally administered agents (e.g., in preparation for surgery or at time of hospital discharge). Care transitions from one unit to another (e.g., intensive care to step-down unit) and at discharge from the hospital to postacute or ambulatory care settings can also pose significant challenges to optimal anticoagulant management [28, 29].

Among nonhospitalized patients (i.e., outpatient settings), requirements for frequent monitoring, dose adjustments, and regular provider–patient contact can often render management of warfarin—the most commonly utilized oral anticoagulant in the outpatient setting [30]—labor-intensive and complex [31, 32]. However, patient interaction with coordinated anticoagulation management services [29, 33] and exposure to anticoagulant education [34] have been correlated with positive outcomes, as measured by

reductions in emergency department visits and hospitalizations and associated health care costs for thromboembolic and hemorrhagic events [35, 36, 37].

The introduction of NOACs to the market may attenuate some of the health care system burdens associated with outpatient warfarin management. The cost-effectiveness and postmarketing safety of these agents relative to warfarin is currently being evaluated [38, 39, 40]. Nevertheless, outpatient coordinated anticoagulation management services will likely continue to be heavily relied on to manage patient populations for whom NOACs are not prescribed. In addition, several of the critical elements of warfarin patient education will continue to be relevant for the NOACs, including such elements as patient recognition and understanding of signs and symptoms of thromboembolism/bleeding, appropriate dosing/administration instructions, and potential for drug-drug and drug-herbal interactions. Other important areas in which coordinated outpatient anticoagulation management may play a role for the NOACs are discussed below under the subheading "Evidence-Based Prevention Tools."

Anticoagulants have been consistently identified as the most common causes of ADEs across health care settings.

Inpatient Settings

In a nationally representative sample of inpatient stays, anticoagulants caused an estimated 10 percent of drug-related adverse outcomes [41], and in a nationally representative sample of hospitalized Medicare beneficiaries, anticoagulants comprised one-third of identified ADEs (12 of 40 events) [42]. Data from inpatient settings suggest that anticoagulant ADEs most commonly result from medication errors, a large proportion are amenable to prevention, and they incur significant costs to the health care system, largely because of increased nursing and pharmacy costs [25, 27, 43, 44].

Outpatient Settings

On the basis of national public health surveillance data, anticoagulants have been shown to be among the most frequently implicated drug classes in ADEs that contribute to emergency department visits and hospital admissions [9, 45, 46, 47, 48, 49, 50]. Among older adults, warfarin was implicated in an estimated 17 percent of emergency department visits and 33 percent of emergent hospitalizations for ADEs annually [9, 50]. An estimated two-thirds of all warfarin-related emergent hospitalizations were because of unintentional overdose, as indicated by "warfarin overdose" in the clinician diagnosis, or supratherapeutic effects, as indicated by such factors as prolonged international normalized ratio (INR)

and/or hemorrhagic events [9]. Data for ADEs as causes of hospital readmissions are scarce; however, the few studies that are available also have found anticoagulant-related harms to be among the most common reasons for ADE-related readmissions [48, 51].

Long-Term Care (LTC) Settings

Data for anticoagulant-related harms in institutional LTC settings are more limited than for inpatient and other outpatient settings but also suggest that anticoagulant ADEs are common causes of preventable harms [52, 53]. As an example, it is estimated that there may be as many as 34,000 fatal, life-threatening, or serious warfarin-related ADEs per year in nursing home settings—many of which may be preventable [54]. In one cohort of nursing home residents, an estimated 29 percent of warfarin-related ADEs and 57 percent of serious, life-threatening, or fatal warfarin-related ADEs were deemed to be preventable [55]. In a retrospective cohort study within five VA nursing homes, even though INR-monitoring frequency was judged to be adequate, INRs were in therapeutic range for only 55 percent of the person-days, with a greater portion of person-time spent in the subtherapeutic (35 percent) compared with supratherapeutic range (11 percent) [56]. A similar study in LTC facilities found that residents spent only half of the time in therapeutic range, 36 percent of the time below the therapeutic range, and 13 percent of the time above therapeutic range [57].

Anticoagulation therapy is underutilized in the patient populations for whom it is most beneficial. Future public health initiatives will need to foster a comprehensive approach that addresses both anticoagulant effectiveness and safety.

AF, the most common arrhythmia encountered in clinical practice [58], is associated with a fourfold to fivefold increased risk of ischemic stroke. As an example of the importance of oral anticoagulation therapy in this patient population, warfarin has been shown to reduce the relative risk of ischemic stroke by approximately 64 percent and of death by approximately 25 percent [58]. The effectiveness of oral anticoagulation therapy for the prevention or treatment of VTE varies with indication; anticoagulation prophylaxis is associated with a 59 percent reduction in fatal pulmonary embolisms (PEs) and a 53 percent reduction in symptomatic DVT among acutely ill, hospitalized medical patients [59]. In medical patients at highest risk, anticoagulation reduces the risk of PE by approximately 40 percent to 60percent [60]. Warfarin reduces the risk of symptomatic VTE by approximately 80 percent among patients undergoing hip or knee arthroplasty or hip fracture surgery [60].

However, despite this well-established role for anticoagulation in prevention and treatment of thromboembolism, U.S. studies have consistently reported underuse of anticoagulants for these

indications [61, 62]. Underuse of anticoagulation when indicated can contribute to higher health care costs associated with strokes and VTE that otherwise would be prevented by effective anticoagulation therapy [63, 64]. In two studies involving a large, commercially insured patient population, less than one-half of high-risk stroke patients with AF received warfarin and more than three-quarters of high-risk VTE patients were considered noncompliant with warfarin therapy [65, 66]. A study conducted in a convenience sample of 21 community-based LTC facilities in a single State found that only 55 percent of ideal candidates for warfarin therapy were receiving it [57].

The factors underlying underuse of anticoagulants have not been explored extensively, but may include clinician and patient concerns regarding supratherapeutic INRs/bleeding risks [67] and lack of patient understanding of the importance of and indications for anticoagulation [68, 69]. Patients residing in rural or remote regions may especially be at increased risk of both undertreatment with anticoagulants and anticoagulant ADEs because of challenges in access to health care providers and anticoagulation management services. For example, studies have found that, despite having similar high-risk profiles, elderly, rural patients with chronic AF receive warfarin less frequently than urban patients [61, 70]. Providers caring for rural-dwelling patients may be reluctant to prescribe warfarin because of difficulties in followup and monitoring, which may contribute to underuse of anticoagulants in this population [61]. A better understanding of the extent of, and contributors to, undertreatment with anticoagulants is needed for those residing in rural areas and other patient populations who may be especially vulnerable to ADEs on the basis of race/ethnicity, socioeconomic status, educational attainment, low health literacy, physical disability, and physical distance from providers.

The ADE Action Plan is intended to address harms associated with exposure to anticoagulants; it does not address adverse events resulting from lack of treatment or undertreatment with anticoagulants (i.e., thromboembolic events, such as stroke or VTE). However, it is fully acknowledged that, in order to optimize health system and provider efforts in the area of anticoagulation management, future public health strategies will be needed to address both the effectiveness and safety of anticoagulation. Addressing the effectiveness of anticoagulation management requires a far more detailed approach than can be afforded by the ADE Action Plan alone. This includes considerations of effectiveness as it varies across indications for anticoagulation therapy (e.g., prophylactic vs. treatment indications) and consideration of the varying health system-, provider-, and patient-related factors that contribute to anticoagulant undertreatment. Differences in the ways providers may approach prescribing various anticoagulants (e.g., warfarin vs. NOACs) and a better understanding of the reasons underlying

suboptimal adherence by patients (e.g., differences in patient concerns regarding risk of stroke vs. perceived bleeding risks with anticoagulation) should also be considered. Surveillance resources that measure and track thromboembolic outcomes (e.g., stroke) and underlying indications (e.g., AF) need to be identified and explored for their strengths and limitations. Likewise, it will also be necessary to review evidence-based prevention strategies that specifically target use of anticoagulants in patients for whom they are most beneficial and that promote patient compliance/adherence. Although the ADE Action Plan does not directly address considerations that are specific to underuse of anticoagulants, it is hoped that aiming collective patient safety initiatives at better prevention of anticoagulant-related harms will foster health system-, provider-, and patient-level changes that will facilitate more confidence in anticoagulant therapy in the patient populations for whom it stands to be most beneficial.

Surveillance

Optimal use of anticoagulants requires accurate, timely, and adequately representative information on the "real-world" risks of bleeding complications.

Clinical trials evaluating the safety profile of various anticoagulants often exclude populations at highest risk of ADEs (e.g., older adults and patients with renal insufficiency). In addition, clinical trials are insufficiently powered to detect ADEs, have limited ability to examine drug-drug or drug-disease interactions that often contribute to ADEs in "real-world" settings, and include care processes that are not part of routine clinical practice [71]. For these reasons, postmarketing surveillance, like that currently conducted through various Federal systems, is crucial for estimating and characterizing the burden of anticoagulant-related harms in clinical practice or "real-world" settings.

Some Federal surveillance systems are currently capable of assessing the national scope of anticoagulant ADE burden. In addition, Federal Agencies involved in direct patient care (e.g., IHS, VHA) have the capacity to capture regional- and facility-level information on the quality of anticoagulant management. **Table 3** provides a summary of anticoagulant ADE-related metrics currently collected by Federal surveillance systems.

Table 3. Summary of Metrics Related to Anticoagulant ADEs Collected by Federal Surveillance Systems

Geographic Scope	Data Collection Methods	Anticoagulation Management or ADE Metrics: Inpatient Settings	Anticoagulation Management or ADE Metrics: Outpatient Settings
National ADE Incidence	Administrative claims and/or EHR data	***AHRQ (NIS)**** ▪ Inpatient stays with ICD-9-CM codes (964.2)* and E-codes (E934.2)*	***FDA (Sentinel Initiative, Mini-Sentinel):**** ▪ ED visits, hospitalizations for bleeding events and ADE signals (e.g., MI on dabigatran)
National ADE Incidence (+/-Rates)	Medical record review	***AHRQ (MPSMS): **** ▪ Inpatient stays with combination of laboratory triggers and signs/symptoms in the medical record associated with UFH, LMWHs, or warfarin	***CDC (NEISS-CADES):*** ▪ ED visits, emergent hospitalizations for laboratory abnormalities (e.g., elevated INR), bleeding events, medication errors, and other ADEs relevant to anticoagulants diagnosed by treating clinician and documented in medical record narrative
National-, Regional-, and Facility-Level Spontaneous Reports	Voluntary reporting	***DOD (Patient Safety Reporting System)*** ▪ Any clinician-diagnosed or patient-reported ADEs ***FDA (FAERS):*** ▪ Any clinician-diagnosed or patient-reported ADEs ***VA (VA ADERS):*** ▪ Any clinician-diagnosed or patient-reported ADEs	***DOD (Patient Safety Reporting System)*** ▪ Any clinician-diagnosed or patient-reported ADEs ***FDA (FAERS):*** ▪ Any clinician-diagnosed or patient-reported ADEs ***VA (VA ADERS):*** ▪ Any clinician-diagnosed or patient-reported ADEs
Regional-, Facility-Level ADE Incidence—Quality Improvement	Administrative claims and/or EHR data	***VA:*** ▪ Anticoagulation process measures (e.g., out-of-range INR values, vitamin K orders, transfusions), ADEs (e.g., bleeding events)	***DOD (Pharmacovigilance Defense Application System):*** ▪ Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes ***VA (VA Integrated Databases):*** ▪ Outpatient clinic visits, ED visits, hospitalizations using relevant ICD-9-CM codes and/or CPT codes for bleeding events, other relevant ADEs, and ADE signals (e.g., MI on dabigatran) ***BOP, IHS, VA:*** ▪ Anticoagulation process measures (e.g., TTR, out-of-range INR values, vitamin K orders, INR monitoring frequency)

*ICD-9-CM 964.2 refers to "Poisoning by anticoagulants" and E934.2 refers to "External Causes of Injury and Poisoning, Anticoagulants."

**In 2015, the Medicare Patient Safety Monitoring System (MPSMS) will be replaced by the Quality and Safety Review System (QSRS). QSRS will aim to facilitate measurement of ADEs associated with additional types of anticoagulants.

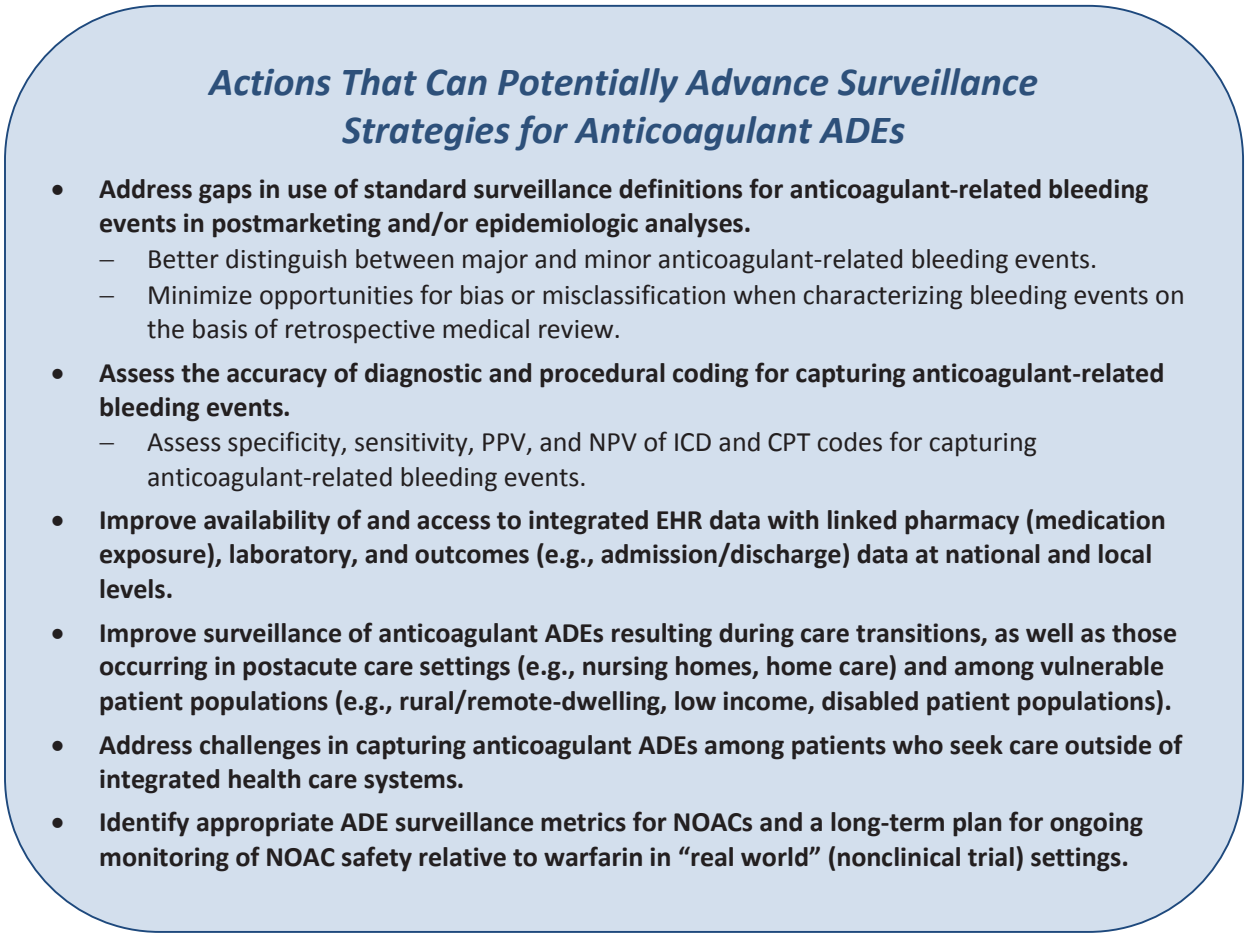
***Currently, FDA Sentinel Initiative covers over 125 million lives; however, these do not constitute a nationally representative sample.

Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; E-code= external cause of injury code; ED = emergency department; EHR = electronic health record; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NIS = nationwide inpatient sample; TTR = time in therapeutic range; UFH = unfractionated heparin

Future Federal strategies will have to address challenges in capturing anticoagulant ADEs on the basis of surveillance data.

Although current Federal surveillance systems are capable of capturing an array of important outcomes reflective of anticoagulant ADEs, as well as process measures related to anticoagulant management, several challenges related to optimal surveillance of anticoagulant-related harms remain. Specifically, future Federal surveillance strategies will have to address challenges in capturing anticoagulant ADEs on the basis of validated diagnostic codes, using consistent definitions of bleeding, collecting data on ADEs occurring in settings that have otherwise been poorly studied (e.g., care transitions, nursing homes, home care), and monitoring ADEs associated with NOACs (for which well-established process measures are currently lacking). Opportunities to advance anticoagulant ADE surveillance strategies are summarized in **Figure 7**.

Figure 7. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Surveillance Strategies for Anticoagulant ADEs



Abbreviations: ADE = adverse drug event; CPT = Current Procedural Terminology; EHR = electronic health record; ICD = International Classification of Diseases; NOAC = new oral anticoagulant; NPV = negative predictive value; PPV = positive predictive value

Monitoring anticoagulant ADEs on the basis of administrative claims data or population-based surveillance is challenging. First, ICD-9-CM codes, including External Causes of Injury codes (E-codes), have been commonly relied on to assess anticoagulant-related bleeding risks in postmarketing and epidemiologic studies [72, 73, 74]; however, very few studies have validated the accuracy of diagnostic and procedural codes in identifying the true frequency of anticoagulant-related bleeding events [75, 76, 77]. Second, the use of E-codes to capture anticoagulation-related bleeding is highly problematic because of the poor sensitivity of these types of codes for capturing ADEs, including anticoagulant ADEs [76]. Third, although definitions of major and minor bleeding in relation to anticoagulants have been universally agreed on for some time [78], these definitions are not consistently applied across postmarketing and epidemiologic studies, rendering comparisons of studies somewhat challenging [78]. Fourth, NOACs present a unique challenge to anticoagulant ADE surveillance in that they currently lack well-established process measures (e.g., laboratory coagulation markers) to facilitate adequate monitoring of harms [22]. Few surveillance systems are able to provide robust information regarding anticoagulant ADEs occurring as a result of care transitions issues [79], or occurring in nursing home or home care settings, and there are insufficient data on anticoagulant ADEs resulting in hospital readmissions. Integrated health care data that allow linking of exposure (e.g., anticoagulant prescription) and outcome variables (e.g., subsequent emergency department visit or hospitalization for bleeding event) across care settings will be important for furthering the understanding of the burden and impact of anticoagulant ADEs across care transitions, as well as for implementing and assessing prevention efforts across the patient care spectrum [80].

Evidence-Based Prevention Tools

Evidence-based guidelines and prevention strategies/tools that aim to carefully balance the thromboembolic and hemorrhagic risks associated with anticoagulants are available [4]. However, given the complex and rapidly evolving nature of the field of antithrombotic management, opportunities for advancement in the area of prevention remain. Although it is acknowledged that there is a subset of especially high-risk anticoagulated patients for whom bleeding cannot be prevented despite optimal care, there remains a large proportion of anticoagulant ADEs that may be amenable to prevention, particularly in outpatient settings [9, 81]. A summary of existing Federal prevention strategies/tools that address safe and effective management of anticoagulation therapy are summarized in **Figure 8**.

Figure 8. Federal Assets Related to Safe Management of Anticoagulation Therapy, as Identified by the National Quality Strategy Priorities

Resources for Safer Care—Health Care Provider Knowledge

- **BOP:**
  - **Anticoagulation Protocol** (for warfarin, heparin, NOACs)—Includes dosing algorithms, guidelines to manage high INR values, guidelines to manage anticoagulation therapy in patients requiring invasive procedures, and bridge therapy protocols
- **IHS:**
  - **National Anticoagulation Training Program**—3-day certificate training program providing specialized training in anticoagulation and disease management; other Federal partners (BOP, DOD, VA) also participate
- **VA:**
  - **Educational opportunities** for health care providers include anticoagulation-related cases for grand rounds and teaching cases for medical, nursing, and pharmacy staff; Web-based education courses (e.g., self-learning modules, live broadcasts on anticoagulation management, and CE programs on anticoagulation safety)

Resources for Patient and Family Engagement

- **ACL:**
  - Community organizations offer programs that have been or are currently supported, in part, by Federal funds, such as
    1. **Stanford Chronic Disease Self-Management Program**—6-week program to help participants better manage their medications, including information about anticoagulants
    2. **HomeMeds℠ Medication Management System**—Multidisciplinary collaborative providing patient counseling, reassessment, and adjustment of medication regimens for older adults in various nonacute health care settings (e.g., home care)
- **AHRQ:**
  - **Patient education information sheet** ("Blood Thinner Pills: Your Guide to Using Them Safely") **& video**
- **FDA:**
  - **Medication guides** (e.g., available for apixaban, dabigatran, rivaroxaban, and warfarin)

Resources for Communication and Coordination of Care

- **AHRQ:**
  - **Project RED**—Includes a number of medication-related strategies (e.g., active medication reconciliation, medication teaching for patients and caregivers, development of medication list for patients and their health care providers)
- **BOP, IHS:**
  - **Anticoagulation Management Electronic Flowsheet**—Integrates laboratory and pharmacy data in one location, in an easily accessible format, in close to real time
- **VA:**
  - **Traveling Veterans Directory**—Addresses challenges associated with care coordination for Veterans seeking care at different VA medical facilities when traveling
  - **Anticoagulation Management Tool**—Designed to simplify the complex, time-consuming processes required to manage outpatient anticoagulant medications and allows health care providers to enter outside laboratory results, review laboratory data, record activities on an anticoagulation flowsheet; creates a loss to followup list; calculates TTR; and develops complications reports
  - **Electronic consults and templates**—Coordinates care with outpatient anticoagulation clinics on discharge

Figure 8. Federal Assets Related to Safe Management of Anticoagulation Therapy, as Identified by the National Quality Strategy Priorities (continued)

Resources for Science-driven Prevention and Treatment

- **BOP, DOD, IHS, VA:**
  - **Systematic and coordinated** anticoagulation management models of care (e.g., anticoagulation clinics, support for warfarin PST/PSM)
- **VA:**
  - **Medication Use Evaluation Tracker (MUET)**—Available for dabigatran and rivaroxaban to identify and intervene on inappropriate use and prevent potential ADEs
  - **Electronic Clinical Decision Support templates**—For ordering and monitoring NOACs

Resources to Promote Best Practices within Communities

- **VA:**
  - **Shared Resource Center**—Lists strong clinical practices, tools, and patient education materials related to anticoagulation management

Abbreviations: ADE = adverse drug event; INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-Monitoring; PST = patient self-testing; TTR = time in therapeutic range

Inpatient Settings

Compared with other medications, anticoagulants are more likely to cause harm to hospitalized patients because of a variety of factors, including complex dosing, the need for frequent monitoring, and transitions between parenterally and orally administered agents (e.g., in preparation for surgery or at time of hospital discharge). Goals and strategies for improving anticoagulation management in inpatient settings have been identified. For example, The Joint Commission (TJC) has identified the National Patient Safety Goal (NPSG) 03.05.01: "Reduce the likelihood of patient harm associated with the use of anticoagulant therapy," which includes the performance element: "Evaluate anticoagulation safety practices, take action to improve practices, and measure the effectiveness of those actions in a time frame determined by the organization" [82]. Care processes that meet these goals may include use of approved protocols for the initiation and maintenance of anticoagulant therapy; use of programmable pumps for UFH therapy; implementation of policies that address baseline and ongoing laboratory monitoring for anticoagulants; and education regarding anticoagulant therapy for prescribers, staff, patients, and families [82].

The Institute for Safe Medication Practices (ISMP) "Pathways for Medication Safety" toolkit describes a comprehensive set of tools to help hospitals adopt a "process-driven, systems-based" approach to reduce medication errors and improve patient care [83]. Systematic processes to facilitate inpatient anticoagulation safety can include such strategies as use of standardized anticoagulation dosing protocols when appropriate, implementation of technology (e.g., computerized physician order entry,

bar code scanning, programmable infusion pumps, and dose range checking), human or computer-based alert systems, and multidisciplinary approaches to anticoagulation management [30].

The National Quality Forum (NQF), which works to identify and achieve consensus on national health care quality measures, has also endorsed a patient safety goal for reducing anticoagulant-related harms through Safe Practice #29 (Anticoagulation Therapy): "Organizations should implement practices to prevent patient harm due to anticoagulant therapy" [84].

Goals such as those set by TJC, NQF, and ISMP suggest that multidisciplinary, coordinated, and systematic processes will be critical in facilitating reductions in anticoagulant ADEs among hospitalized patients [29, 82, 83, 84]. Challenges that will need to be addressed to reduce inpatient anticoagulant ADEs may include

- Consideration of the acuity and complexity of the hospitalized patient population and the need for individualized treatments (relative to outpatient settings)
- Lack of a nationally recognized, widely shared, comprehensive set of best practices or standards focusing specifically on safe use of anticoagulants in hospitalized patient populations
- Need for multifaceted interventions to deliver high-quality anticoagulation management
- Difficulty in translating clinical guidelines into ready-to-use inpatient health care quality metrics (i.e., high-quality anticoagulation "process" measures are not as easily measured in inpatient relative to outpatient settings)

Opportunities for advancing anticoagulant ADE prevention strategies/tools in inpatient settings, as identified by the NQS Priorities, are summarized in **Figure 9** and discussed further below.

Figure 9. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Inpatient Settings

Safer Care	▪ **Improve provider knowledge of high-quality inpatient anticoagulation management through provider education** ▪ **Improve dissemination of/increase accessibility to evidence-based, high-quality inpatient anticoagulation management strategies/tools** ▪ **Address gaps in evidence and provider knowledge with regard to management of NOACs through development of guidelines/algorithms for safe use (e.g., clinician guidance for laboratory testing)**
Effective Communication and Coordination of Care	▪ **Improve EHR tools to enable provider access to real-time, integrated, linked pharmacy-laboratory data to facilitate seamless access to pertinent medication and laboratory results**, for example, – Support development of electronic flowsheets that display trends in daily labs, concomitant medications, reversal medications, etc., that are specific to and can support optimal anticoagulation management – Support development of clinical decision support tools specific to anticoagulation management ▪ **Better integrate anticoagulation-specific targets into currently existing care transition models**
Science-Driven Prevention and Treatment	▪ **Promote a multidisciplinary, coordinated, and systematic approach to inpatient anticoagulation management;** for example, – "Anticoagulation rounds", pharmacist-/nurse-managed anticoagulation services, "Anticoagulation Stewardship." "culture of safety" in anticoagulation management ▪ **Better address safe use of anticoagulants commonly utilized in inpatient settings (e.g., heparin) and NOACs in nationally recognized health care quality/patient safety measures and in nationally recognized clinical guidelines**

Promotion of Best Practices Within Communities	▪ **Identify and promote adoption of standards that constitute high-quality anticoagulation management (e.g., "Anticoagulation Center of Excellence")** ▪ **Improve dissemination and sharing of strategies and results from large-scale, quality-improvement learning initiatives targeting anticoagulant ADE prevention among health care systems/facilities**

Abbreviations: ADE = adverse drug event; EHR = electronic health record; NOAC = new oral anticoagulant

Gaps remain in the availability and successful dissemination of evidence-based strategies for optimizing inpatient anticoagulation management.

Despite widespread recognition of the important contribution of anticoagulants to preventable harm in inpatient settings, there remain key areas in which use of these agents could be optimized among hospitalized patients. These include: (1) wider development and dissemination of inpatient-specific anticoagulation management guidelines, (2) standardization of key coagulation parameters across laboratory systems, and (3) improvement of anticoagulation-related training and education of inpatient providers. Although standardized dosing protocols have a role in promoting effective and safe dosing of certain anticoagulants in inpatient settings [30], these cannot be relied on exclusively, as anticoagulant management in hospitalized patients requires more extensive considerations than can be afforded by dosing protocols alone (e.g., emergently holding and restarting anticoagulation and managing bleeding or reversing anticoagulation). Development and dissemination of institutional guidelines that are evidence based, evaluated, and revised as necessary, and that leverage multidisciplinary teams may be important in that regard [28, 29]. Mechanisms that Federal partners could leverage to facilitate spreading best practices across facilities should also be explored. In addition, to the extent that clinical laboratory approaches/assays are known to differ among institutions [85], there appears to be an important need to identify the role that Federal Agencies could play in promoting standardization of key coagulation parameters across laboratories (e.g., achieving alignment in Activated Partial Thrombosis Time [aPTT] and antifactor Xa assays across hospital laboratories). Further, the introduction of the NOACs to the market requires that tools be developed to ensure that clinical laboratories and providers are equipped and educated regarding appropriate use of laboratory tests with these agents. Anticoagulation training programs may need to be expanded to better target educational needs of inpatient anticoagulation providers, who have to take into account unique considerations when managing anticoagulation for acute or critically ill patients. Below is further discussion of these and other areas in which Federal Agencies could play an important role in advancing evidence-based prevention strategies targeted at minimizing anticoagulant ADEs.

Federal Agencies should play a role in advancing health IT–based strategies, including EHR standards, to further inpatient anticoagulant ADE prevention.

The acuity and complexity of the hospitalized patient population requires that providers have access to real-time, integrated, linked pharmacy–laboratory data to facilitate seamless access to pertinent medication and laboratory data, and deliver optimal inpatient anticoagulation management [29]. Processes and tools for inpatient anticoagulation management should be integrated with the EHR to facilitate accurate and efficient communication of clinical and laboratory information pertinent to inpatient anticoagulation management. Integration of pharmacy order entry systems with laboratory reporting systems will support the timely review of key laboratory values prior to ordering, dispensing, or administering anticoagulants. Examples might include tools such as an electronic anticoagulation management flowsheet that displays trends in such metrics as daily labs, concomitant medications, and reversal medications specific to anticoagulation management. Regardless of the health IT-based approaches taken to optimize safety of inpatient anticoagulation delivery, innovative health IT in this area should be prioritized on the basis of evidence; be tested in collaboration with facilities and providers; function efficiently in current workflow; and deliver accurate, timely, and clinically relevant content [86]. Unintended consequences of any new health IT-based approaches to care should also be taken into consideration prior to implementation.

Federal Agencies that provide direct patient care play an important role in advancing evidence-based strategies for anticoagulant ADE prevention.

Currently, evidence-based guidelines or tools that address high-quality anticoagulation management in inpatient settings exist primarily at the level of a single health system or facility. Some organizations, such as the Anticoagulation Forum—a nonprofit, multidisciplinary organization with a goal of improving quality of care among patients taking antithrombotic medications—are leading strategies that foster dissemination of best practices and prevention strategies across health care systems and facilities [87]. However, there remains tremendous opportunity to learn about high-quality facility strategies and tools from Federal partners that provide direct patient care (e.g., BOP, DOD, HRSA, IHS, and VA). One such example from the VA National Center for Patient Safety is summarized in **Table 4**.

Table 4. Department of Veterans Affairs—National Center for Patient Safety "Actions From VA and Non-VA Facilities To Control Vulnerability" From Anticoagulation

System	Action
Storage	▪ Limit the availability of anticoagulant drugs from floor stock to reduce misadministration.
Ordering	▪ Establish weight-based heparin protocols (to improve consistency) with education on exclusion and inclusion criteria. Closely monitor for success and failures and adjustment of protocols, as necessary.
Preparation	▪ Standardize one size/concentration of IV bags for continuous IV heparin, using an even number of units per mL [e.g., 50 units per mL] to simplify calculations. ▪ Limit the size of the infusion bag of heparin to reduce risk if free flow or overinfusions occur (250 mL vs. 500 mL). ▪ Provide heparin in dosage forms that are as close as possible to what is ordered (e.g., 5,000-unit or 10,000-unit vials for bolus use).
Distribution	▪ Use manufacturer's premade solutions to reduce compounding and labeling errors.
Administration	▪ Establish a food and drug interaction program/policy that addresses enteral feedings and warfarin administration. ▪ Establish double-check systems to verify correct pump settings and calculations. ▪ Enforce review of order before drug administration. ▪ Include drip charts on the infusion bags to improve the ability to adjust rates without mathematical errors.
Therapeutic Management	▪ Establish a pharmacy-based inpatient anticoagulation service to improve monitoring, followup, and transitioning to warfarin. ▪ Standardize the monitoring of anticoagulant laboratory work so that clinical changes are detected early (e.g., hemoglobin, platelets).

Source: U.S. Department of Veterans Affairs—National Center for Patient Safety. (2012, December 13). Anticoagulation Vulnerability. Available at: http://www.patientsafety.va.gov/professionals/hazards/anticoag.asp.

Federal Agencies should support the dissemination and uptake of evidence-based strategies for anticoagulant ADE prevention across health care systems and facilities.

The Centers for Medicare & Medicaid Services' (CMS) Center for Medicare & Medicaid Innovation (CMMI)–led Partnership for Patients Initiative serves as an example of the way Federal funding could enhance private sector efforts to prevent anticoagulant ADEs and facilitate the sharing of evidence-based prevention strategies across facilities. The goals of the Partnership for Patients Initiative are to make care safer by reducing hospital-acquired conditions and improve care transitions by decreasing preventable complications during transitions from one health care setting to another. Since 2011, the Partnership for Patients initiative has supported large networks of health systems and hospitals (Hospital Engagement Networks [HENS]) across the country by providing strategies aimed at monitoring safe use of warfarin in inpatient settings [88, 89]. Example metrics related to inpatient anticoagulation management include

- INR >5 per 1,000 patient days
- Percentage of patients on warfarin with INR outside threshold

- Anticoagulant ADE per 1,000 patient days
- Percentage of patients on warfarin receiving warfarin education
- Percentage of patients on warfarin who have dose management protocols
- Percentage of patients on heparin dosing protocol
- Percentage of acute care inpatients on warfarin and/or heparin with evidence of an INR or aPTT performed during the hospitalization

As of May 2013, there were more than 650 hospitals participating in the Partnership for Patients Initiative with at least 6 months of data related to inpatient warfarin safety. Mechanisms such as those employed by the HENs to rapidly disseminate information about successful quality improvement initiatives may be helpful in spreading best practices across facilities and in preventing adoption of ineffective strategies.

Federal partners should lead efforts to promote the concept of "anticoagulation stewardship" to reduce anticoagulant ADE burden.

Not all health care facilities may be able to rely primarily on health IT-based systems to improve inpatient anticoagulation management. Consequently, Federal Agencies could support other multidisciplinary and systematic approaches to anticoagulation management at the health system level. Such strategies may include nurse- or pharmacist-managed inpatient anticoagulation services and "multidisciplinary anticoagulation rounds" that include representatives from medicine, pharmacy, nursing, and patient safety [90, 91, 92, 93]. In addition, promoting the concept of "anticoagulation stewardship" may contribute to promotion of a culture of safety specifically around anticoagulants [94, 95, 96]. The concept of anticoagulation stewardship refers to a multidisciplinary, coordinated, and systematic approach to care. This is analogous to the successful approach used to improve antibiotic use in inpatient settings [97]. As with efforts to implement successful and sustainable antibiotic stewardship programs, anticoagulation stewardship will likely require a commitment from health system leadership, including support in the form of funding and resources, engagement of a key health care provider who can champion anticoagulation stewardship efforts, and identification of methods and key metrics by which to continuously assess outcomes associated with such efforts [97].

Outpatient Settings

Although prescribing of NOACs is increasing, recent data available (2011) suggest that warfarin remains the most commonly utilized oral anticoagulant in outpatient settings [7, 30]. Nationally recognized clinical guidelines from the American College of Chest Physicians (ACCP) recommend that health care

providers who manage oral anticoagulation therapy do so in a "systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, followup, and good patient communication of results and dosing decisions" [4]. Systematic and coordinated anticoagulation care is usually defined as a specialized program of patient management that focuses exclusively on managing oral anticoagulation therapy. This differs from routine medical care, in which a patient's own physician or a variety of physicians provides care without systematic coordination. Features of such services generally include

- A program directed by a single physician whose primary responsibility revolves around oversight of oral anticoagulation management services
- Delivery of care by pharmacists, registered nurses, nurse practitioners, or physician assistants following a physician-approved protocol
- Centralized management of a population of patients with direction provided by different primary or referring physicians for individual patients [98].

Federal Agencies that provide direct patient care should continue to explore opportunities to improve uptake of evidence-based, systematic, and coordinated models of anticoagulation management.

In outpatient hospital departments and in the community, anticoagulation clinics (or "Coumadin clinics") are the settings that most often deliver systematic and coordinated oral anticoagulation management. In the United States, it is estimated that there are approximately 3,000 such anticoagulation clinics [99]. The VA has long embraced the model of anticoagulation clinic services. In an internal survey conducted in 2008, more than 95 percent of VA medical facilities were identified as having specialized outpatient anticoagulation management (including anticoagulation clinics) [100].

There is a large and longstanding body of evidence which indicates that anticoagulation clinic services are associated with improved anticoagulation management relative to "usual medical care," as reflected by such measures as higher time in therapeutic range (TTR), higher proportion of INR values within target ranges, and reductions in emergency department visits and hospital admissions for thromboembolic and hemorrhagic outcomes (including major and fatal bleeding episodes) [37, 101, 102]. Anticoagulation clinics have also demonstrated reductions in health care costs by $800 to $1,600 per patient per year [98, 103]. Research results suggest that health systems could expand the use of anticoagulation clinics and still save money [104]. Despite this evidence, it is estimated that only 30 percent to 40percent of U.S. patients receiving oral anticoagulation therapy are enrolled in such clinics

[99]. Barriers to wider enrollment in anticoagulation clinics range from provider-related factors (e.g., fear of loss of autonomy in providing anticoagulation care), patient-related factors (e.g., lack of physical proximity to such services for rural/remote patient populations), systems-related factors (e.g., concerns regarding benefits of such services combined with implementation costs, training of staff), and economic factors (e.g., challenges in payment/coverage for these services).

The barriers that are most likely amenable to being addressed by Federal Agencies are those related to provider/patient education and economic barriers. Provider education programs such as the National Anticoagulation Training Program coordinated by IHS (in which BOP, DOD, and VA facilities also participate) may serve as a model of a systematic approach to deliver education around optimal anticoagulation management. Public–private partnerships with organizations such as the Anticoagulation Forum, which also is facilitating widely and easily accessible formats for provider education aimed at improving the quality of anticoagulation care, could also be considered. Potential opportunities for overcoming economic barriers related to wider uptake of anticoagulation clinic services are discussed further below under the subheading "Incentives and Oversight."

It is important to note that establishing an anticoagulation clinic is only the first step toward reducing anticoagulation ADEs. Larger challenges remain, including ensuring that patients are referred to, or utilize, such clinics and optimizing communication among providers caring for the same patient within and outside these clinics. This is especially true for patients who do not regularly seek care in integrated health care systems and for rural/remote populations. Barriers to physically accessing clinics may also exist for older adults, regardless of where they reside, because of such factors as having limited mobility, being home bound, and having cognitive impairment [105].

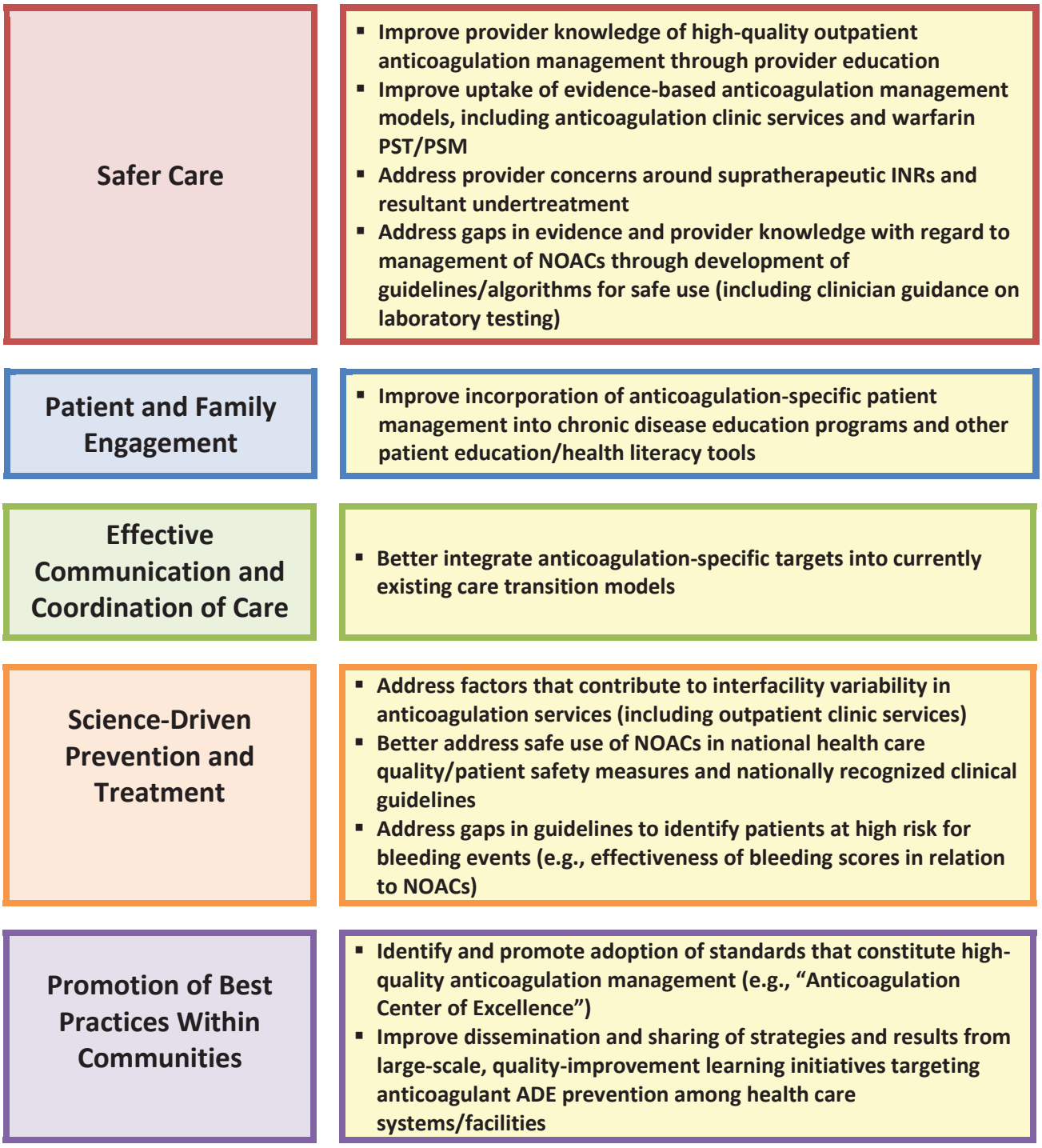
Even for those with access to anticoagulation clinic services, challenges surrounding their effective use remain, including recognition that some patients are at especially high risk for bleeding despite the use of systematic and coordinated models of anticoagulation management. In addition, some patients may not be appropriate candidates for such services (e.g., rural/remote patients or patients with poor adherence to scheduled visits). Finally, use of anticoagulation clinic services may be more effective for the prevention of thromboembolic events than for prevention of hemorrhagic events [35, 101, 102, 106]. Nevertheless, studies of anticoagulation clinic services have generally demonstrated positive, substantial impacts on all fronts of anticoagulation management, including effectiveness, safety, and costs.

Because of some of these limitations of anticoagulation clinic services, alternative models of oral anticoagulation management have also been adopted [107, 108, 109]. Patient self-testing (PST) of INR and patient adjustment of their anticoagulant dose (patient self-management, or PSM) have proved to be effective strategies for improving warfarin effectiveness and safety outcomes [4]. However, current nationally recognized clinical guidelines recommend that these modalities be limited to patients who are "motivated and can demonstrate competency in self-management strategies, including the self-testing equipment" [4]. As with anticoagulation clinic services, there is a need to facilitate better identification of patients who are appropriate candidates for PST/PSM models of care and to improve uptake of such models of care for those patients when appropriate. For patients residing in rural/remote areas, increasing access to pharmacist services and telephone-based management may be effective strategies to assist general practitioners in the management of their anticoagulated patients [101, 107, 108].

Although the introduction of NOACs will shift some use away from warfarin, it is likely that coordinated anticoagulation management services will continue to play an important role in the care of patients receiving NOACs. Anticoagulation clinic services may evolve into areas such as: identifying appropriate patient candidates for these new agents, transitioning safely among older and newer agents, monitoring patients during interruption of therapy (e.g., periprocedural period), ensuring accurate age-dependent and/or renal function-dependent dose adjustments, helping to define the use and interpretation of potential laboratory coagulation parameters (e.g., thrombin time and antifactor Xa), providing patient education (e.g., counseling patients on the importance of adherence because of the shorter half-lives of the newer agents relative to warfarin and the increased risk of thrombosis during interruptions of therapy), and general coordination and communication of anticoagulation management issues among a patient's multiple providers [79].

In addition, several of the critical elements of warfarin patient education will continue to be relevant for the NOACs. These elements include patient recognition and understanding of signs and symptoms of bleeding/stroke, appropriate dosing/administration instructions, and education on the potential for drug–drug and drug–herbal interactions. As these agents become more widely prescribed, evidence-based prevention strategies/tools that better address the safe use of NOACs will need to be developed. Specific areas in which such tools could be targeted are discussed below under the subheading "Research (Unanswered Questions)." Opportunities for advancing anticoagulant ADE prevention strategies/tools in outpatient settings for both warfarin and NOACs, as identified by the NQS Priorities, are summarized in **Figure 10.**

Figure 10. Opportunities for Advancing Anticoagulant ADE Prevention Strategies/Tools, as Identified by the National Quality Strategy Priorities—Outpatient Settings



Abbreviations: INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-management; PST = patient self-testing

Note About Use of Pharmacogenomics-Guided Dosing To Optimize Warfarin Safety

Genetic variations are among the most important determinants of variability in warfarin dosing requirements [110]. For this reason, pharmacogenomic testing has been a longstanding research area of interest for optimization of warfarin safety and effectiveness. Dosing algorithms that incorporate pharmacogenomic considerations (e.g., http://www.warfarindosing.org) have been explored for their comparative effectiveness, their relative utility among different populations (e.g., Black vs. non-Black patients), and their impact on such end points as percentage of out-of-range INRs and time in therapeutic range [111, 112, 113, 114]. However, challenges in integrating pharmacogenomics into clinical practice have hindered uptake of pharmacogenomics-guided warfarin management [115]. For example, many medical centers currently do not have warfarin pharmacogenomics testing capabilities and thus rely on outsourcing to clinical laboratories with long turnaround times for results [116, 117]. In addition, the cost of pharmacogenetic testing is generally not reimbursed by public and private insurance plans [116, 117]. Finally, the integration of pharmacogenomics data with clinical decision support software to guide therapy has not been fully realized [115]. Most recently, data from the largest pharmacogenomics clinical trial in the U.S. population to date indicate that genotype-guided warfarin dosing strategies do not affect anticoagulation control, as measured by time in therapeutic range, time to achievement of first INR, time to stable INR dose, or a composite safety end point of overcoagulation and undercoagulation (time to any INR of ≥4, major bleeding episodes, or thromboembolism) [118]. Given the challenges and limitations associated with pharmacogenomics-guided warfarin management seen to date, it will be important to focus future public health efforts on supporting other strategies, such as improving clinicians' ability to select the most appropriate anticoagulant agents for their patients; facilitating patient access to the most appropriate anticoagulation management modality; bolstering laboratory standards and communication infrastructure around key coagulation parameters; and supporting improved communication among laboratories, providers, and patients [110].

Federal Agencies should explore ways to better incorporate effective anticoagulation ADE prevention strategies in long-term care and care transitions settings.

Long-term Care (LTC) Settings

More needs to be learned about the quality and outcomes associated with anticoagulation therapy in institutional and noninstitutional LTC settings, including the extent of adoption and application of best practices for anticoagulant ADE prevention [119]. Barriers to providing high-quality anticoagulation

management in LTC settings have not been thoroughly studied; however, in nursing homes, these may include provider concerns around supratherapeutic INRs and resultant undertreatment of nursing home residents, provider fear of loss of professional autonomy in anticoagulation management through use of dosing nomograms or guidelines, and costs of implementing dosing support tools/resources (e.g., nomograms, clinical decision support software). In LTC settings such as nursing homes, there may be a need to better address risks/benefits associated with point-of-care (POC) INR monitoring versus venipuncture, dosing practices, rates of achieving appropriate INR and TTR goals, management strategies for elevated INRs or bleeding events, and overall quality assurance processes associated with nursing home anticoagulation management. Communication challenges may be one of the foremost barriers to delivering optimal anticoagulation management in LTC settings. Limited accessibility to EHRs outside a particular facility and the challenge of transmitting pertinent anticoagulation-related data elements in an efficient manner to a remote provider that can manage patients' anticoagulation may complicate anticoagulation services in LTC settings. Strategies aimed at improving anticoagulation safety and providing high-quality anticoagulation management in LTC settings may include

- Standardizing anticoagulation management treatment approaches across LTC settings, which may include facilitating and promoting uptake of currently available guidelines, such as American Medical Directors Association (AMDA) Antithrombotic Therapy in the Long-Term Care Setting guidelines [119], or developing LTC-specific anticoagulation management tools/resources (e.g., EHR-based clinical decision support tools)
- Determining reimbursement barriers to POC INR testing, as well as to management/oversight responsibilities for anticoagulation services
- Providing strategies for facility-based active and ongoing surveillance of anticoagulation safety-related metrics, including ones targeting adequate monitoring transitions to or therapy with NOACs
- Improving use of anticoagulant ADE prevention strategies/tools (e.g., dosing nomograms, clinical decision support, facility policies/guidelines, and preprinted medication orders that identify patient specific goals/target INR ranges)
- Identifying a single anticoagulation provider (e.g., nurse practitioner, consultant pharmacist, anticoagulation clinic pharmacist) who takes primary responsibility for anticoagulation management

In home care settings, provision of in-home laboratory services is limited by reimbursement challenges; this can contribute to inadequate monitoring of postacute patients discharged to these settings.

Changes in reimbursement policy for the use of portable INR devices in home care settings may allow for more frequent laboratory monitoring to prevent possible complications from anticoagulation therapy in these settings. Alternatively, adequate staff training in skills required to perform in-home laboratory draws may improve the validity of laboratory results obtained in these settings. In addition, significant lag time in reporting laboratory results to laboratory portals for nurses or consultant pharmacists to review may result in delayed action taken for anticoagulation management. For this reason, there may be a need for more centralized EHR tools that promote data exchange and facilitate provider access to real-time, linked pharmacy–laboratory data. Finally, limits on prescribing privileges for nurse practitioners resulting from requirements, such as physician approval of recommendations or patient encounter prior to physician approval, may limit more efficient and timely anticoagulation management in home care settings.

Care Transitions

Inpatient and ambulatory anticoagulation management services are an essential component of care transitions. Although several care transitions models have been developed with the goal of improving the hospital discharge process and reducing readmission rates, few address issues of care transitions into, within, and out of the hospital that are specific to anticoagulation management [79]. Anticoagulated patients will likely remain at high risk for ADEs as long as there remain suboptimal systems for communication between inpatient and outpatient providers, limited ability to access medication lists and laboratory results for patients who are managed outside of integrated health care systems, and limits in capability of disparate EHRs to exchange pertinent information.

Strategies targeted at improving care transitions for anticoagulated patients have not been thoroughly studied. However, in one study, when inpatient pharmacist-directed anticoagulation services were involved in providing warfarin dosing and monitoring, as well as the coordination of care from inpatient to outpatient settings, improvements were seen in care transition metrics, including enrollment in outpatient anticoagulation clinics, documented inpatient-to-outpatient provider contact, documented inpatient provider-to-anticoagulation clinic communication, and patient followup within 5 days of hospital discharge [93]. Patient education, a core tenet of care transition models, may also play a key role in anticoagulant ADE prevention during care transitions. Patient education is a critical component of safe care transitions [79], and it plays an important role in preventing anticoagulant ADEs. Patient education about warfarin therapy has been associated with stability of therapy, as measured by TTR [120] and reductions in hemorrhagic and thromboembolic events [121, 122]. Similarly, reductions in

hospital readmission rates have been demonstrated among patients who received education regarding therapy with low-molecular-weight heparin and fondaparinux, relative to patients who did not receive anticoagulant education [123]. However, patient education in and of itself will not likely be sufficient to mitigate the public health burden of anticoagulant ADEs at the population-based level [124]. For example, one study found that current warfarin patient information sheets provided at the time of dispensing often exclude recommended essential or important knowledge items and are at reading levels that are far above what is recommended for presentation of health information to laypersons [125, 126]. In addition, the extent and quality of anticoagulation education delivered outside of anticoagulation clinic services are difficult to assess through existing data sources.

Another core tenet of care transition models is medication reconciliation [79], commonly defined as "the process of reviewing a patient's complete medication regimen at the time of admission, transfer, and discharge, and comparing it with the regimen being considered for the new setting of care" [127]. Medication reconciliation as a care transition strategy is important to reduce potential medication discrepancies. Although studies that have evaluated medication reconciliation have demonstrated a positive impact on reductions in medication errors or potential ADEs, an impact on reductions in actual medication-related harms (e.g., as reflected by emergency department visits or hospital readmissions for ADEs) remains to be seen [128, 129, 130, 131]. It remains unclear whether this is because medication reconciliation historically has not targeted the highest-risk drugs or patients or because it is probably insufficient alone, without additional postdischarge monitoring and care coordination (e.g., clinic-based support or home visits) [79, 129, 130]. Future studies should explore the incorporation of anticoagulant-targeted interventions in care transition strategies that include bundled strategies comprising medication reconciliation (e.g., ensuring appropriate transition from warfarin to NOAC), and hand-offs (e.g., ensuring that information about goal INR, dose, anticoagulant and/or primary care provider are communicated) across the continuum of care [79].

Incentives and Oversight

From the perspective of HHS, incentive and oversight levers potentially can be applied to advance anticoagulant ADE prevention through several strategies **(Appendix D)**. Some of the HHS levers include statutory-based programs such as those noted in CMS programs related to coverage of services (e.g., National Coverage Determinations [NCDs]), financial incentive programs (e.g., EHR Incentive Program), and survey and certification processes (e.g., compliance with Conditions of Participation). Other

financial incentive programs, such as the EHR Incentive Program, can potentially be leveraged to facilitate and promote integration of anticoagulation management best practice principles into the overall health IT infrastructure. With that goal in mind, during development of the ADE Action Plan, the FIW for Anticoagulant ADEs collaborated closely with the HHS Office of the National Coordinator for Health IT (ONC) to identify health care quality measures specific to anticoagulant safety that were potentially amenable to incorporation into the EHR-based quality measure strategies; these measures are currently under exploration by ONC for possible incorporation into Stage 3 EHR Meaningful Use (MU) requirements. CMS quality reporting programs (e.g., Hospital Inpatient Quality Reporting, Physician Quality Reporting System, and Long-Term Care Hospital Quality Reporting) and quality rating systems (e.g., Five-Star Quality Rating System for nursing homes) are also critical mechanisms for quality improvement in health care, most notably through their use of clinical quality measure data for payment, public reporting, or to assist patients in identifying quality of care within facilities. Other CMS-related levers may exist within additional programs, such as Quality Improvement Organizations (QIOs). Maintaining and supporting positive impacts brought about by QIOs in their work to reduce ADEs could serve as an additional strategy for advancing Federal efforts to promote anticoagulation safety. Several of these programs are described in more detail in Section 4: "Incentives & Oversight Opportunities."

Regardless of the specific strategy chosen to advance Federal incentives and oversight policies targeting anticoagulant ADE prevention, it will be important to develop policies that extend across health care settings (i.e., traverse inpatient to outpatient settings); reflect joint responsibility of the various provider groups (e.g., physicians, nurses, and pharmacists); can be shared across facilities/boundaries (e.g., through learning networks); can be closely evaluated for unintended consequences, including additional costs and burden to the health care system; can be continuously re-evaluated for relevance and impact; and can reflect alignment and consistency across the various Federal Agencies.

Federal partners should consider existing quality measures and initiatives to incentivize and advance anticoagulant ADE prevention efforts.

The ADE Action Plan recognizes that health care quality measures and quality reporting programs are an integral part of the HHS strategy for quality improvement in health care. Several Federal Agencies (e.g., AHRQ, CMS, VA) have well-established quality initiatives that provide important mechanisms for improving outcomes and protecting patient safety. Further exploration of these initiatives is warranted to evaluate the benefits, feasibility, and costs of incorporating new, validated measures of anticoagulant ADEs into these initiatives. These new measures can potentially complement efforts already underway to gauge and improve use of anticoagulants. For example, the CMS Hospital Compare program, which captures

information about quality of care from more than 4,000 Medicare-certified hospitals [132, 133], has newly incorporated important indicators of anticoagulation safety as part of publicly reported hospital quality measures (e.g., "Patients with blood clots who were treated with an intravenous blood thinner, and then were checked to determine if the blood thinner was putting the patient at an increased risk of bleeding" and "Patients with blood clots who were discharged on a blood thinner medicine and received written instructions about that medicine") [132, 133]. Other federally endorsed patient safety and quality measures, such as AHRQ's Patient Safety Indicators (PSIs) and Prevention Quality Indicators (PQIs), can potentially be explored for appropriateness and utility of incorporating complications of anticoagulation therapy [134]. PSIs provide information on potential in-hospital complications and adverse events following surgeries, procedures, and childbirth; PQIs are a set of measures that that can be used with hospital inpatient discharge data to identify quality of care for "ambulatory care sensitive conditions" [134].

Current National Quality Forum (NQF)–endorsed measures of anticoagulation quality care mainly gauge appropriateness of anticoagulation use [135]. These measures are critical for assessing whether patients who are candidates for anticoagulation receive this therapy to meet the important goal of achieving reductions in stroke and other thromboembolic outcomes (e.g., VTE, PE), especially in light of data indicating underutilization of anticoagulation in patients for whom it is indicated [61, 62, 136]. However, there remains a need for measure concepts that track centrally important markers of anticoagulant safety (e.g., bleeding). The few currently available NQF-endorsed measures that address anticoagulant safety are mainly focused on surrogate markers of safe warfarin use (e.g., NQF #0555, NQF #0556). It may be necessary to explore new measure that: (1) reflect more updated approaches to optimizing anticoagulation management (e.g., percentage of patients with warfarin time in therapeutic range), (2) include metrics for safe use of agents other than warfarin (i.e., NOACs), (3) address patient populations who are especially vulnerable to ADEs (e.g., elderly) or are based in high-risk settings where such measure concepts do not currently exist (e.g., LTCs, nursing homes, home), and (4) assess clinical outcomes rather than surrogate indicators of anticoagulation safety (e.g., admissions or readmissions for anticoagulant-related bleeding rather than the number of times a laboratory value is obtained). This last component is important in that Federal quality initiatives have already moved toward development of measure concepts focused on clinical outcomes. Outcome-based measures will also be especially important for assessing safe use of NOACs, for which laboratory metrics of effectiveness and safety either are currently not available or are very limited [22]. It is important to recognize, however, that developing reliable outcome-based measures of anticoagulant safety can be challenging and will need to

be approached after adequate exploration of available data sources, since inadequate data sources or data quality can affect measure validity and feasibility. These challenges are caused in part by complexities inherent in collecting or accessing administrative claims, and chart-extracted or EHR data sources to reliably identify anticoagulant ADEs.

Regardless of which measures are chosen, any new metrics related to anticoagulant ADE prevention will need to reflect updated standards of care, be thoroughly tested and validated, be feasible and useful for reporting, and achieve adequate balance between newer and older anticoagulant agents, as well as between effectiveness (e.g., stroke) and safety (e.g., bleeding) outcomes. Both Federal partners and the non-Federal sector will also have an important role to play in facilitating ease and efficiency of reporting of any new anticoagulation ADE prevention measures by health care systems and providers. Moving forward, it will also be important for Federal partners to initiate discussions and collaborate with non-Federal organizations that also play a role in setting nationally recognized patient safety goals, standards, and quality measures (e.g., The Joint Commission, National Committee for Quality Assurance, Pharmacy Quality Alliance, and Institute for Safe Medication Practices). Such collaborations could facilitate further alignment and advancement of anticoagulation safety goals across Federal and non-Federal programs.

Opportunities to advance the prevention of anticoagulant ADEs through incentives and oversight-based strategies are summarized in **Figure 11**.

Figure 11. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Health Care Policy Strategies for Anticoagulant ADE Prevention

Actions That Can Potentially Advance Health Care Policy Strategies for Preventing Anticoagulant ADEs

- **Inpatient Settings**
  - Expand national health care quality reporting measures to include concepts related to multidisciplinary, systematic, and coordinated models of care (e.g., "Anticoagulation Stewardship").
- **Outpatient Settings**
  - Expand national health care quality reporting measure sets to include measures specific to anticoagulant safety/anticoagulant ADE prevention.
  - Address payment/coverage barriers to uptake of evidence-based, high-quality ADE prevention strategies (e.g., anticoagulation clinics, warfarin PST/PSM).
- **Long-Term Care/Home Care**
  - Nursing homes: Address barriers to more integrated anticoagulation management (e.g., leveraging consultant pharmacist services to deliver anticoagulation management).
  - Home care: Address challenges in POC monitoring and barriers to more seamless communication of anticoagulation laboratory-testing results to anticoagulation management providers.

Abbreviations: ADE = adverse drug event; POC = point of care; PSM = patient self-management; PST = patient self-testing

Currently, there are few existing National Quality Forum–endorsed measures specific to anticoagulation safety.

To date, very few measures that are specific to anticoagulation safety have been endorsed by the National Quality Forum (NQF) **(Table 5)** [135]. Achievement of NQF endorsement is important, as certain CMS statutorily based programs require endorsement of proposed measures prior to adoption as clinical quality measures for Medicare beneficiaries. Furthermore, stakeholders such as hospitals and health insurance providers often adopt NQF-endorsed measures to improve quality of care for their patients and beneficiaries.

Table 5. National Quality Forum (NQF)-Endorsed Health Care Quality Measures Specific to Anticoagulation Safety*

Measure ID	Measure	Measure Description	Steward
NQF 0374	VTE Patients Receiving UFH with Dosages/Platelet Count Monitoring by Protocol (or Nomogram)	Number of patients diagnosed with confirmed VTE who received intravenous UFH therapy with dosages and platelet counts monitored using defined parameters such as a nomogram or protocol	The Joint Commission
NQF 0375	VTE Discharge Instructions	Number of patients diagnosed with confirmed VTE that are discharged to home, to home with home health or home hospice on warfarin with written discharge instructions that address all four criteria: compliance issues, dietary advice, followup monitoring, and information about the potential for adverse drug reactions/interactions	The Joint Commission
NQF 0555	Lack of Monthly INR Monitoring for Individuals on Warfarin	Average percentage of monthly intervals in which individuals with claims for warfarin do not receive an INR test during the measurement period	CMS
NQF 0556	INR for Individuals Taking Warfarin and Interacting Anti-Infective Medications	Percentage of episodes with an INR test performed 3 to 7 days after a newly started interacting anti-infective medication for Part D individuals receiving warfarin	CMS
NQF 0586	Warfarin PT/INR Test	Percentage of patients taking warfarin during the measurement year who had at least one PT/INR test within 30 days after the first warfarin prescription in the measurement year	Resolution Health, Inc.
NQF 0612	The percentage of patients taking warfarin who had PT/INR monitoring	Percentage of patients taking warfarin who had PT/INR monitoring	Active Health Management

*Note: Measures summarized in this table are specific to ensuring the safe use of anticoagulants (e.g., through patient education or laboratory monitoring). Measures related to ensuring that anticoagulants are prescribed for certain indications (e.g., receipt of VTE prophylaxis, anticoagulation therapy for AF at discharge) are not shown here.

Abbreviations: INR = international normalized ratio; PT = prothrombin time; UFH = unfractionated heparin; VTE = venous thromboembolism

Federal partners should address economic barriers to uptake of evidence-based anticoagulation ADE prevention strategies.

Improved and consistent utilization of evidence-based anticoagulation strategies (e.g., anticoagulation clinics, warfarin PST/PSM) will require considerations related to restructuring payment or coverage. Current economic barriers can be considered as falling into three broad categories: (1) limits on direct payment to nonphysician providers (i.e., pharmacists), who are the primary providers currently delivering care in anticoagulation clinics; (2) limits on physician billing for anticoagulation management services; and (3) challenges in the reimbursement structure for PST/PSM-based strategies.

Limits on direct payment to nonphysician providers (i.e., pharmacists) pose a serious challenge to wider provision of anticoagulation clinic services. Currently under Medicare Part B, pharmacists are considered "non-advanced practice staff" whose services are charged on the physician's bill for provision of "supporting services" in physicians' offices. Pharmacists, in collaboration with physicians, can only report medically necessary evaluation and management (E/M) services associated with managing anticoagulation therapy using "incident-to" Current Procedural Terminology (CPT) code 99211, when appropriate [137, 138]. CPT code 99211 is defined as "an office or other outpatient visit service rendered for the evaluation and management of an established patient, whose nature of presenting problem is 'minimal,' where at least 5 minutes of time is spent performing/supervising such services, and which does not require the presence of a physician." This code can be limiting in that, despite providing a comprehensive patient evaluation and obtaining the clinical specimen (phlebotomy or finger stick), there may be limitations on the use of the billing code in the absence of such factors as adjustment of drug dosage, new medical co-morbidities, or dietary change [137]. Overcoming barriers related to achieving health care provider status for pharmacists in order to facilitate improved integration of anticoagulation clinic services in the delivery of day-to-day patient care will be critical in strategies aimed at anticoagulant ADE prevention. Nevertheless, this specific barrier is beyond the scope of the ADE Action Plan and is better addressed by other key organizations, such as the American Pharmacists Association (APhA). The APhA has identified increasing the value recognition and compensation for pharmacists' clinical services as one of its top strategic priorities [139]. Other groups are also actively working to advance the recognition of pharmacists as health care providers [140].

There are high overhead costs associated with maintaining anticoagulation clinic services; this also serves as a barrier to more widespread adoption of anticoagulation clinic services. Limits on physician billing for these services also may be a barrier to more widespread adoption. Overhead costs impede

individual or small groups of physician providers (who are not part of an integrated health care system and cannot realize the direct cost savings through reductions in emergency department visits or hospitalizations) from initiating and maintaining coordinated anticoagulation clinic services. Currently, providers are limited to seeking reimbursement for PT/INR tests performed, and anticoagulation management services, including those provided via telephone calls (e.g., to report results of INR tests, provide patient education, explain changes in medication dosages), are not directly reimbursable. In the future, it may be necessary to explore whether the currently existing provider payment structure for outpatient anticoagulation-related visits fully captures the minimum services that are medically necessary to ensure optimal anticoagulation management, including all the processes of care required to minimize or prevent anticoagulant ADEs.

Improving access to point-of-care (POC) device testing in patients for whom warfarin PST/PSM is appropriate will also be important in overcoming current barriers to utilization of these particular anticoagulation management strategies [109, 141]. Several areas are amenable to exploration. These include: reevaluation of the adequacy of reimbursement rates for POC testing; minimizing delays in providers' being able to initiate PST/PSM for patients; clearly identifying patient populations for whom PST/PSM are the preferred management modalities (e.g., frail elderly and those residing in LTC facilities who may have physical barriers to accessing anticoagulation clinic services), and removing penalties or restrictions to their ability to access such care; resolving discordance in Medicaid reimbursement rates relative to Medicare rates for PST/PSM; and exploring the role of reimbursement for telephone-based management of patients using PST [109].

Moving forward, it will be important to address the aforementioned economic barriers so as to facilitate advancement of evidence-based ADE prevention strategies for warfarin and NOACs.

Health Information Technology (Health IT)

Limitations in the current health information exchange infrastructure, including lack of interoperability, serve as barriers to anticoagulant ADE prevention efforts.

Electronic exchange of health information, such as laboratory results and care (e.g., discharge) summaries, has been identified as a critical component of delivering optimal patient care; however, several barriers remain in health information exchange infrastructure [142]. For anticoagulation management specifically, improving bidirectional communication among multiple health care providers caring for the same patient may have a very important role in improving care transitions for patients,

especially those most vulnerable to anticoagulant ADEs (e.g., patients undergoing transitions across health care settings) [79, 143]. Health information exchange, as it relates to interoperability between pharmacy and laboratory systems, also affects safe delivery of anticoagulation. In spite of the recognition that enhanced laboratory–pharmacy linkages are key to improving the safety of medications such as anticoagulants [144], challenges remains in the ability of diverse EHR products to exchange this information so as to allow for delivery of more coordinated, effective, and efficient care [145]. Moving forward, policies and standards that better facilitate health information exchange will also facilitate improvement in care delivery, as it pertains to high-risk medications such as anticoagulants.

Opportunities to leverage EHR Meaningful Use requirements to advance anticoagulant ADE prevention should be considered.

During development of the ADE Action Plan, the FIWs for ADEs recognized the importance of health care quality measures in helping to advance ADE prevention efforts. In order to leverage the valuable interagency collaborations brought about during development of the ADE Action Plan, the FIW for Anticoagulant ADEs discussed and identified various health care quality measure considerations specific to anticoagulant ADE prevention and monitoring that were potentially amenable for incorporation into the EHR-based quality measure strategies. The FIW recommended a set of measure considerations (**Table 6)** to the Quality Measures Workgroup of the Health Information Technology Policy Committee. That committee, convened by the ONC, makes recommendations for candidate measures for the Stage 3 EHR MU requirements of the Medicare and Medicaid EHR Incentive Program. This will support and advance anticoagulant ADE prevention and monitoring. In making its recommendations, the FIW for Anticoagulant ADEs chose to recommend metrics based on clinical quality measures that were already in existence, had been endorsed nationally, and had previously undergone a critical review process, or metrics that closely mirrored processes or outcomes outlined by nationally recognized clinical guidelines. After initial recommendation, measures under consideration are submitted to CMS for further reviews, development, and testing. Final measure acceptance is dependent on rigorous and complete internal and external public reviews.

Table 6. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements That Can Potentially Advance Anticoagulant ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs

Metric	Description and Justification
Clinical Quality Measure Concepts—Eligible Providers (Outpatient Settings)	
1. Percent of patients on anticoagulants with INR test 7 to 14 days following out-of-range INR	Proportion of patients ▪ With nonvalvular AF ▪ On chronic warfarin therapy for >180 days before the start and during the measurement period ▪ With previously stable therapeutic INRs, who had an INR test 7 to 14 days after presenting with a single out-of-range INR below or above therapeutic during the measurement period
Rationale	▪ Anticoagulation control, as measured by TTR, is improved by prompt, repeat testing after out-of-range INR values [146, 147] ▪ NQF Measure 0555 (see Table 5)
Clinical Decision Support (CDS) Rule Concepts—Eligible Providers (Outpatient Settings)	
2. INR Retesting Evaluation	Clinical notification to assess need for INR test in patients on chronic warfarin therapy (>180 days) and >30 days since last INR test*
Rationale	▪ NQF Measure 0555 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.1: For patients taking VKA therapy with consistently stable INRs…[recommend] INR testing frequency of up to 12 weeks (Grade 2B). Stable INRs are defined as at least 3 months of consistent results with no need to adjust VKA dosing. When adjustments to the VKA dose are required, a cycle of more frequent INR monitoring should be completed until a consistent pattern of stable therapeutic INRs can be reestablished [4].
3. INR Testing—Interacting Anti-infective Medication	Clinical notification in patients on chronic warfarin therapy (>180 days) for whom treatment with interacting anti-infective medication is initiated to take one of the following actions: Instruct patients to hold warfarin dose, change anti-infective medication, notify anticoagulation provider, schedule INR retest.
Rationale	▪ NQF Measure 0556 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.8: For patients taking VKAs avoid concomitant treatment with certain antibiotics (Grade 2C) [4]
Patient List Recommendation—Eligible Providers (Outpatient Settings)	
4. Last INR Test	▪ Patient lists stratified by INR testing interval/time since last INR test (30 days, 60 days, 90 days, >90 days)
Rationale	▪ NQF Measure 0555 (see Table 5) ▪ 2012 ACCP (Chest) Guidelines—Recommendation 3.1: For patients taking VKA therapy with consistently stable INRs…[recommend] INR testing frequency of up to 12 weeks (Grade 2B) [4]

Table 6. Measure Considerations for EHR (Stage 3) Meaningful Use Requirements That Can Potentially Advance Anticoagulant ADE Prevention, as Proposed by the Federal Interagency Workgroup for ADEs (continued)

Metric	Description and Justification
EHR Functionality/Usability Recommendation—Eligible Hospitals (Inpatient Settings)	
5. Inpatient Electronic Anticoagulation Management Flowsheet	EHRs should have the capacity to display linked pharmacy and laboratory data pertinent to anticoagulation management. An inpatient electronic anticoagulation management flowsheet should display necessary data elements ▪ In one location ▪ In an easily accessible format ▪ As near real-time as possible

Abbreviations: ACCP = American College of Chest Physicians; AF = atrial fibrillation; EHR= electronic health record; INR = international normalized ratio; NQF = National Quality Forum; TTR = time in therapeutic range; VKA = vitamin K antagonist (i.e., warfarin)

*Interval chosen to reflect that some patients may continue to be candidates for more frequent monitoring than every 12 weeks

Federal partners should continue to explore health care quality measures that target optimizing anticoagulation management.

The FIW for Anticoagulant ADEs considered additional metrics in its discussions and articulated areas where there are current gaps in national health care quality measures or EHR requirements as they pertain to anticoagulation safety **(Table 7)**. Some of these measure concepts can be operationalized using non-EHR-based approaches; however, wherever feasible, development of these types of measures with the intent of future adoption by EHRs (including e-prescribing and clinical decision support tools) likely presents the most efficient and forward approach to measurement and minimizes reporting burden for health systems and providers. Health care quality metrics that can potentially be further developed and evaluated as discussed by the FIW included

- Dosing decision support tool for patients receiving chronic warfarin therapy who are not enrolled in a systematic and coordinated anticoagulation management program (e.g., anticoagulation clinic)
- Followup on individual time in therapeutic range (iTTR) <65 percent for patients receiving chronic warfarin therapy
- Identification of patients with increased risk for anticoagulant-related bleeding who require more frequent monitoring (e.g., HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly] score ≥3)

- Appropriate dosing (and if applicable in the future, laboratory outcomes) of NOACs
- Appropriate dosing of and laboratory outcomes for parenterally administered anticoagulant, in addition to low-molecular-weight heparin (e.g., UFH, argatroban)
- Metrics targeting clinical outcomes (e.g., bleeding events) versus limited to process measures
- Metrics targeting transitions of care-based measures (e.g., hospital followup with ambulatory care providers on discharge)

Table 7. Possible Areas for Health Care Quality Measure Concept Development Related to Anticoagulant ADE Prevention and Current Barriers to Development

Measure Concept	Current Barriers to Development
NOACs ▪ Dosing, adherence, and transitions among older and newer agents	Evolving and early science Lack of well-established laboratory markers for safety/ effectiveness (e.g., laboratory monitoring parameters)
Parenterally administered anticoagulants (hospital uses of anticoagulants) ▪ Pertinent laboratory monitoring parameters	Lack of consensus and/or uniformity across sites as to what constitutes optimal process measures (e.g., interfacility variations in target aPTTs)
Outcomes-based metrics ▪ Bleeding events	Quality of diagnostic and procedural coding for capturing anticoagulant-related bleeding events poorly explored to date
Care transitions-related metrics	Associated with complex, difficult-to-measure process metrics (e.g., hand-offs, communication between inpatient and outpatient providers)

Abbreviations: ADE = adverse drug event; aPTT = activated partial thromboplastin time; NOAC = new oral anticoagulant

Research (Unanswered Questions)

As anticoagulation management practices evolve and new anticoagulant agents are introduced into clinical practice, there are research opportunities that can potentially advance the field of anticoagulation safety and for which Federal resources could be leveraged. These unanswered questions are summarized in **Figure 12**.

Unanswered questions remain regarding the most efficient ways of identifying patients at highest risk for anticoagulant-related bleeding.

One area of future research that Federal partners may be able to support relates to the need to identify the impact of and reduce bleed rates in patients with underlying pathological lesions who are especially predisposed to bleed. This research could entail better evaluating strategies that facilitate selection of

the appropriate anticoagulation treatment, given the patient's history, or more efficiently identifying and implementing early preemptive treatment (e.g., colonoscopic polypectomy for patients with colorectal polyps, proton pump inhibitor therapy for patients with peptic ulcers). This research would comport with evaluation of strategies aimed at better understanding factors that contribute to anticoagulant-related bleeding risk (e.g., drug–drug interactions, concomitant use of antiplatelet drugs, and genomic polymorphisms).

Further research and real-world experience with NOACs are needed.

Clinical trials take place in controlled conditions and often exclude patient populations at highest risk for ADEs (e.g., older adults, children, pregnant women, patients with hepatic and renal insufficiency). This is also largely true for clinical trials that have been carried out to date for NOACs; for this reason, the safety and efficacy of NOACs in real-world settings requires further exploration. It will be important for Federal partners to support research that furthers development of the evidence base in key areas of NOAC management and safety, including (1) monitoring and assessing patients for medication adherence, which is critical for ensuring optimal anticoagulation control with the NOACs, given their short half-lives; (2) patient-centered approaches to selection of NOACs that balance an individual patient's risk of thromboembolism with the risk of bleeding and take into account the differences among these agents in their efficacy and safety profiles; (3) development, use, and interpretation of potential laboratory markers for NOACs; and (4) development and dissemination of effective strategies for reversal of major or life-threatening bleeding associated with NOACs. Cost-effectiveness studies comparing NOACs to warfarin will also be important [148, 149]. Future economic analyses should take into account factors relating to the real-world application of these agents, including medication adherence; special populations; level of anticoagulation control for warfarin, as measured by TTR; and costs of anticoagulation services. For the first time in more than 5 decades, health care providers are now faced with a multitude of medication choices for oral anticoagulation. Additional research is needed to assist providers in identifying appropriate candidates to initiate or transition to these new agents, taking into account a variety of patient-related factors, including indication for anticoagulation therapy, INR stability, geographical access to laboratory INR monitoring, history of medication nonadherence, co-morbid conditions, and concomitant drugs [22].

Advancing anticoagulant ADE prevention efforts will require that Federal partners address emerging issues associated with safe use of NOACs.

Although the introduction of NOACs represents a significant advancement in the management of thromboembolic disease, there are a number of challenges in use of NOACS, including: a lack of well-

established reversal strategies in the event of toxicity; the unclear role of clinical laboratory assays to monitor levels of effectiveness or safety (e.g., in the event of thromboembolic or hemorrhagic events, prior to invasive procedures, in the presence of interacting drugs or declining renal function); as well as lack of health care provider familiarity with their use [22]. In addition, much remains to be learned about NOACs in relation to their use in real-world scenarios (e.g., dosing in organ dysfunction, impact of drug–drug interactions). There appear to be two primary areas in which Federal partners could engage private sector stakeholders to facilitate ADE prevention strategies in relation to NOACs. First, Federal/private collaboration may be important for developing algorithms to facilitate selection of the optimal NOAC according to individualized, patient-centered, risk–benefit assessments (e.g., history of previous exposure to anticoagulants, history of INR stability, co-morbidities, concomitant medications, pharmacogenomics, costs, or clinical laboratory test results). Collaboration also could facilitate the development of consensus guidelines/tools that define the care processes that constitute high quality of care or adequate "monitoring" of NOACs. Second, Federal partners may be able to leverage the resources of organizations, such as the North American Specialized Coagulation Laboratory Association (NASCOLA) [150], to develop and disseminate clinical guidance for providers regarding appropriate use of laboratory monitoring parameters to monitor NOAC effectiveness and safety. Other research opportunities in the area of advancing NOAC safety include

- Management of severe bleeding episodes (e.g., reversal protocols)
- Periprocedural management medication interruptions for surgical or invasive procedures
- Transitions among older and newer agents.

With regard to pharmacogenomic testing, there may be value in identifying patients who are at highest risk for anticoagulant-related harms from the various NOACs [117]. Identifying these patients would be especially important, given the lack of routine bedside clinical and laboratory monitoring capacity that is currently available for these agents and the need to aid providers to the fullest extent possible in selecting the agents most appropriate for their patient(s).

Figure 12. Federal Interagency Workgroup Recommendations for Actions That Can Potentially Advance Research Strategies for Anticoagulant ADE Prevention

Actions That Can Potentially Advance Research Areas for Anticoagulation Safety

Clinical Science Domain

(AHRQ, CDC, FDA, public–private sector collaborations)

- Identify barriers to utilization of anticoagulation clinic services and warfarin PST/PSM utilization.
- Identify factors that facilitate broader uptake of evidence-based anticoagulant ADE prevention strategies.
- Identify factors that contribute to interclinic variability among anticoagulation clinic services (e.g., differences in patient risk profiles, targeting of excessively narrow INR target ranges).
- Support development of tools that facilitate optimal real-world management of bleeding events related to NOACs, including development of algorithms to facilitate selection of the optimal anticoagulant agent according to individualized, patient-centered risk-benefit assessments (e.g., history of previous exposure to anticoagulants, co-morbidities, concomitant medications, pharmacogenomics, costs, clinical laboratory test results).

Laboratory/Bench-top Science Domain

(CDC, NIH, public–private sector collaborations)

- Support development and improvement of laboratory assays for NOACs (including monitoring levels of anticoagulation, predicting effectiveness/risk).
- Identify any remaining or new areas where pharmacogenomics-guided anticoagulation management may be useful, including those pertinent to NOACs.

Education Domain

- Support development and evaluation of educational tools and programs related to high-quality anticoagulation management for patients, caregivers, and health care providers.

Abbreviations: ADE = adverse drug event; INR = international normalized ratio; NOAC = new oral anticoagulant; PSM = patient self-management; PST = patient self-testing

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