Addressing barriers to optimal oral anticoagulation use and persistence among patients with atrial fibrillation: Proceedings, Washington, DC, December 3-4, 2012

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Approximately half of patients with atrial fibrillation and with risk factors for stroke are not treated with oral anticoagulation (OAC), whether it be with vitamin K antagonists (VKAs) or novel OACs (NOACs); and of those treated, many discontinue treatment. Leaders from academia, government, industry, and professional societies convened in Washington, DC, on December 3-4, 2012, to identify barriers to optimal OAC use and adherence and to generate potential solutions. Participants identified a broad range of barriers, including knowledge gaps about stroke risk and the relative risks and benefits of anticoagulant therapies; lack of awareness regarding the potential use of NOAC agents for VKA-unsuitable patients; lack of recognition of expanded eligibility for OAC; lack of availability of reversal agents and the difficulty of anticoagulant effect monitoring for the NOACs; concerns with the bleeding risk of anticoagulant therapy, especially with the NOACs and particularly in the setting of dual antiplatelet therapy; suboptimal time in therapeutic range for VKA; and costs and insurance coverage. Proposed solutions were to define reasons for oral anticoagulant underuse classified in ways that can guide intervention and improve use, to increase awareness of stroke risk as well as the benefits and risks of OAC use via educational initiatives and feedback mechanisms, to better define the role of VKA in the current therapeutic era including eligibility and ineligibility for different anticoagulant therapies, to identify NOAC reversal agents and monitoring strategies and make knowledge regarding their use publicly available, to minimize the duration of dual antiplatelet therapy and concomitant OAC where possible, to improve time in therapeutic range for VKA, to leverage observational data sets to refine understanding of OAC use and outcomes in general practice, and to better align health system incentives. (Am Heart J 2014;168:239-247.e1.)

Approximately 3 million US adults have been diagnosed with atrial fibrillation (AF).[1,2] Registries have consistently shown that about half of these patients with risk factors for stroke are not treated with oral anticoagulation (OAC).[3,4] Among patients treated with vitamin K antagonists (VKAs), the quality of anticoagulation control is often poor[5]; and many permanently discontinue treatment.[6] Assuming a 5% annual stroke rate among untreated patients and a two-thirds reduction in stroke with warfarin or the novel OACs (NOACs), approximately 50,000 strokes per year are preventable in the United States alone.[7]

Vitamin K antagonists have recognized limitations. To discuss these limitations and key challenges regarding the development of alternatives, stakeholders from academia, government, and industry convened on July 25-27, 2005.[8] Aligned with the principles laid out in that meeting, randomized clinical trials established, and have led to regulatory approval of, 3 NOACs that are at least as or more efficacious than VKA for stroke prevention (Figure 1).[9–11] But even with the introduction of dabigatran to the market, overall rates of OAC for AF have not increased.[12] To address continued barriers to OAC use, including warfarin, and to propose solutions, a second meeting took place in Washington, DC, on December 3-4, 2012. Leaders from academia, government, industry, and professional

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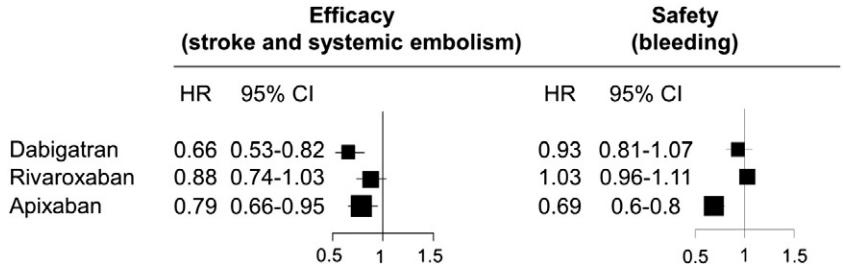
Figure 1



Efficacy (intention-to-treat) and safety of novel oral anticoagulants available in the United States.

societies (online Appendix Table) were challenged to identify barriers to effective use of OAC and to develop corresponding recommendations to surmount them. Results of a trial demonstrating the efficacy of a fourth NOAC, edoxaban, were released after this meeting and were therefore not specifically addressed in the discussion.[13] Nonetheless, many of the issues considered also apply to edoxaban. The aim of this article is to summarize these think-tank discussions and recommendations (Table I).

Barriers to oral anticoagulant initiation and persistent use

Lack of awareness of stroke risk and the risks and benefits of oral anticoagulation. At least one-third of patients diagnosed with AF are unaware of the associated stroke risk.[14,15] Although awareness of stroke risk is increasing among physicians, [16] OAC use varies considerably according to specialty, with primary care physicians prescribing OAC less commonly than cardiologists.[17] Unfortunately, time during outpatient clinical encounters is often limited; and AF may be only one of several comorbidities to be addressed in any given office visit, particularly by general practitioners. The decision to initiate an OAC and the associated education of patients and family members around the use of OAC take considerable time and resources. Further, there may be differential knowledge of the relative risks and benefits of different anticoagulation therapies,[18] particularly with the recent approvals of NOACs. These factors may partially explain the observed difference in OAC prescription rates among specialties.

Lack of awareness of the potential use of novel oral anticoagulants for VKA-unsuitable patients. Novel OACs have several advantages over VKAs, the most salient of which is lower risk of intracranial hemorrhage and hemorrhagic stroke found for all of the NOACs. Others include lack of need for therapeutic monitoring and a modest but worthwhile reduction in mortality found in several clinical trials. Having been in use for >60 years, VKA nonetheless remains the dominant treatment for stroke prevention in AF. In the modern therapeutic era, patient selection factors for warfarin therapy compared with NOACs may not be immediately apparent. Moreover, concern over use of VKAs—and often over issues specific to VKA therapy such as the need for close international normalized ratio (INR) monitoring—is a common reason for not using OAC of any type. Historically, a variety of reasons not to use OAC have been put forward.[18] The misperception that aspirin is sufficiently effective for stroke prevention and substantially safer than the novel drugs appears to be a significant contributor to the problem of OAC undertreatment.

Lack of recognition of expanded eligibility for oral anticoagulation. The improved adverse effect profile of NOACs over VKAs may alter OAC eligibility. In fact, guidelines have evolved to recommend OAC for patients with at least 2 CHA_2DS_2-VASc risk factors and to be preferred or considered for patients with at least 1 CHA_2DS_2-VASc risk factor.[19,20] Furthermore, patients not commonly thought to be at high risk for stroke may nonetheless derive benefit from the NOACs, which have lower risk of hemorrhagic stroke and intracranial hemorrhage.[21,22]

The threshold for OAC initiation is determined by the benefit of treatment balanced against the risk of adverse events, notably serious bleeding. The most recent study comparing warfarin to antiplatelet therapy, ACTIVE-W, found that warfarin had a favorable risk-benefit balance among patients with a $CHADS_2$ score of 1.[23] Newer data strongly indicate that even relatively low-risk patients with AF benefit substantially from anticoagulant therapy, best shown to date with apixaban.[24] Patients at lower risk of stroke with a $CHADS_2$ score of 1 made up as much as one-third of the population in several of the NOAC clinical trials.[10,11] In the AVERROES trial, patients with $CHADS_2$ score of 0 or 1 had significant relative and absolute reductions in stroke with apixaban versus aspirin (6/1,004 [0.54%/y] vs 16/1,022 [1.41%/y], hazard ratio 0.38, 95% CI 0.14-0.93) but a comparable risk of major bleeding (6/1,004 [0.54%/y] vs 6/1,022 [0.53%/y], hazard ratio 1.02, 95% CI −0.32-3.26).[25] However, neither professional guidelines nor the Food and Drug Administration (FDA)–approved labeling supports initiating

Table I. Barriers to OAC use and corresponding recommendations to improve treatment rates

Barriers	Recommendations
Knowledge gaps about stroke risk	Increase awareness of stroke risk and of benefits of OAC use via multifaceted educational initiatives.
Lack of understanding about why half of patients with AF and risk of stroke are not treated with OACs	Systematically study reasons patients are not on OAC and develop individualized approaches to intervene where appropriate.
Lack of appreciation that aspirin has little ability to prevent stroke in people with AF	Highlight data showing that OAC is far more effective than aspirin at preventing stroke in AF.
Lack of data collection and feedback in clinical practice	Develop tools to identify patients with AF, risk factors for stroke, and use of OAC with online feedback to providers.
Lack of appreciation that NOACs can be used for many VKA-unsuitable patients	Clarify which VKA-unsuitable patients can be treated with NOACs and define the current role of VKA including where NOACs should not be used.
Lack of appreciation of expanding eligibility for OAC	Better define OAC eligibility and ineligibility, and benefits and risks for patients who have a single $CHADS_2$ or CHA_2DS_2VASc risk factor.
Lack of availability of reversal agents and anticoagulant effect monitoring for NOACs	Identify and develop NOAC reversal agents and monitoring strategies, and organize and disseminate knowledge regarding their use; emphasize the importance of prevention of serious bleeding as the most important way to prevent bleeding-related complications.
Concern about bleeding risk of OAC in the s etting of dual antiplatelet therapy	Minimize the duration of dual antiplatelet therapy and concomitant OAC use.
Concern about bleeding risk of OAC with concomitant aspirin	Limit use of aspirin to patients with a clear indication, such as recent acute coronary syndrome.
Lack of recognition of the short half-lives and short anticoagulant effects of NOACs	Educational efforts to distinguish management concerns of procedures and bleeding with NOACS compared to VKAs
Uncertainty about practical issues in use of NOACs	Develop and disseminate simple tools, including Web-based ones, to guide safe and effective use of NOACs.
Lack of health system–level understanding of and efforts to improve quality of AF care	Develop systems to measure, feedback, guide intervention, and incentivize optimal use of OAC at systems level; advocate use of OAC performance measures with feedback to providers and health systems as appropriate.
Concern about suboptimal time in therapeutic range for VKA	Promote organized, high-quality anticoagulation services for patients on warfarin.
Concern over spontaneous reports of bleeding events	Continue monitoring and reporting of OAC adverse events in a systemic way (rather than sporadic reports with no denominator) that provides accurate estimates of risk.
Costs of NOACs and complexity and lack of understanding of insurance coverage	Catalogue available costs, assistance programs, coverage programs.

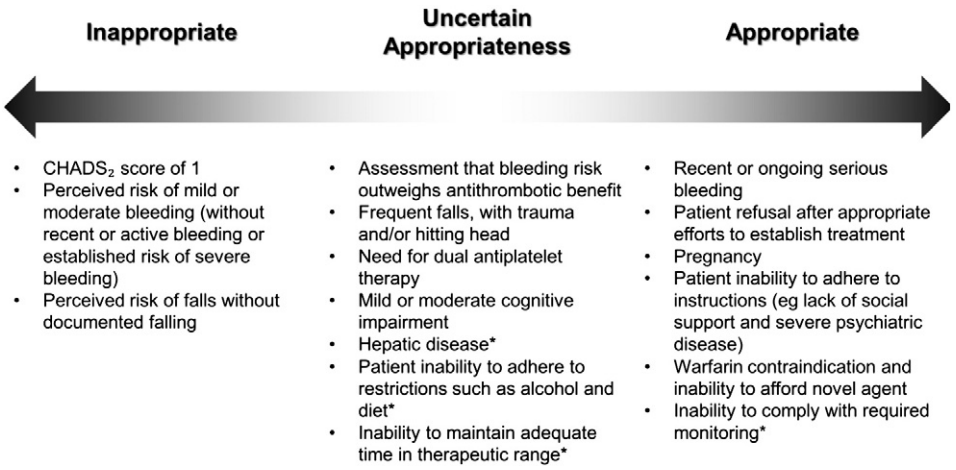
OAC among AF patients with a $CHADS_2$ score of 0; and the most recent European and American College of Cardiology/American Heart Association guidelines recommend no antithrombotic therapy for patients with CHA_2DS_2-VASc score of 0.[19,20]

Improving stroke risk stratification could allow identification of patients for treatment who were not previously thought to benefit from OAC. The discriminatory power of the $CHADS_2$ score is moderate,[26] suggesting that its use may result in patients whose true stroke is low receiving OAC, whereas those with a relatively high stroke risk may not. Data show that accounting for female sex, age 65 to 74 years, and vascular disease (as in the CHA_2DS_2-VASc score) adds discriminatory power,[27,28] particularly among those with a $CHADS_2$ score of 0 or 1.[29] Cardiac biomarkers, including high-sensitivity troponin and N-terminal proB-type natriuretic peptide, as well as creatinine clearance may further improve prognostic power.[30–32]

Lack of reversal agents and lack of ability to monitor effects of novel oral anticoagulants. Clinicians are uncomfortable with the absence of good anticoagulation reversal strategies for the NOACs. Concern exists regarding life-threatening hemorrhage on NOACs, particularly in patients requiring invasive procedures and especially when those are needed emergently.[33] Monitoring of NOAC treatment effect may be desirable in these situations, in the event of an overdose, and in advance of planned procedures such as cardioversion when there are questions about drug compliance and concern with the thrombosis risk associated with inconsistent anticoagulation. Unfortunately, reversal options and monitoring strategies and how they may inform care are not well defined.[34,35]

Bleeding risk of oral anticoagulants, particularly in the setting of dual antiplatelet therapy. Dual antiplatelet therapy (including following coronary stent placement) and OAC are indicated for acute coronary syndromes and AF,

Figure 2



Reasons for unsuitability for oral anticoagulation among patients with AF and CHADS ≥1 and/or CHADS-VASc ≥2.*Applicable to VKA only.

respectively. The combination of disease processes poses a therapeutic dilemma, as bleeding risk is significantly elevated when antiplatelet and antithrombotic therapies are used simultaneously. Compared with aspirin alone, triple therapy with aspirin, VKA, and clopidogrel increases bleeding 4-fold.[36] When prasugrel rather than clopidogrel is used, bleeding rates may be even higher.[37] There is a similar increase in risk when adding a NOAC to aspirin and clopidogrel, with a 3- to 4-fold increased risk in major bleeding events.[38,39] The use of ticagrelor or prasugrel rather than clopidogrel might be expected to further elevate bleeding risk in this setting, although empiric data are lacking. More data on these issues are needed to inform clinical decision making.

Suboptimal time in therapeutic range for VKA. Vitamin K antagonists have a narrow therapeutic window, and the amount of time spent in therapeutic range (TTR) varies. Although cause and effect are unproven in the absence of randomized data, low TTR is generally associated with increased risk of bleeding and of stroke[40]; conversely, in some data sets, patients with a high TTR are more prone to bleeding, presumably related to higher TTR being mainly due to less time in subtherapeutic range.[41] Achieving a higher TTR, and possibly lower event rates, is possible through regular INR monitoring with timely and appropriate dose adjustment.[42] However, monitoring can be burdensome for many patients, particularly those who do not have ready access to a medical facility. The inconvenience of monitoring may lead patients to decide against starting VKA, to decrease adherence, or to discontinue treatment altogether.

Fear of bleeding events with novel oral anticoagulants. Vitamin K antagonist–associated bleeding is common in clinical practice. By contrast, no information was available regarding bleeding rates associated with NOACs in general practice until recently, although bleeding rates appeared generally similar to warfarin in clinical trials of NOACs.[43] Following the approval of dabigatran in October 2010, a substantial number of reports of serious and fatal bleeding events were submitted to the US FDA's Adverse Event Reporting System. The number of reports of bleeding associated with dabigatran was considerably higher than the number of reports with warfarin. These findings contrasted with those of a large controlled trial, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), which showed that bleeding rates with dabigatran 150 mg twice a day and warfarin were similar and that bleeding was less with dabigatran at the 110-mg twice a day dose. Concern regarding dabigatran-associated bleeding rippled through the medical literature and the lay press alike. Because adverse drug effects that were not detected in clinical trials can appear when a drug is broadly used, regulatory authorities have a responsibility to understand and respond to such concerns. Detailed review of the spontaneous reports did not identify any unknown risk factors for bleeding, and dabigatran was generally used in accordance with its FDA label. The FDA responded with careful analyses of insurance-claim and administrative data from the Mini-Sentinel database, which has the advantage, compared to spontaneous reports, of a clearly defined denominator of patients on dabigatran and on warfarin as well as a systematic report of all observed clinically significant bleeding events associated with each drug. Dabigatran-associated bleeding rates were clearly not increased compared with warfarin; and in fact, bleeding on dabigatran appeared similar to if not lower than bleeding on warfarin.[44]

Table II. Reasons for use of VKAs (rather than NOACs) in AF

Patient stable on warfarin with high time in therapeutic range and patient decision to forgo the reduced risk of intracranial hemorrhage
Mechanical prosthetic valves
Clinically significant mitral stenosis
Severe renal insufficiency
Inability to afford novel agents

Costs and insurance coverage. The total costs of care using NOACs compared with warfarin may not be very different.[45] Although costs of NOACs themselves are substantially higher than VKA, savings associated with NOACs occur in the clinical sphere with fewer intracranial bleeding events and a reduced need for monitoring. As a result, dabigatran has been recommended as a therapeutic option for AF patients in the United Kingdom.[45] In the United States, VKAs and associated monitoring are affordable for most patients with regard to "out-of-pocket" costs; but NOACs are less so. Whether NOACs are included in various formularies and to what degree their costs are covered are variable. The tiered structure of Medicare Part D, for example, may not fully reflect the clinical benefits (and related health care system savings) of the products. In the instances in which a NOAC is covered, out-of-pocket costs are at times difficult to ascertain prior to filling a prescription. Moreover, with the "donut hole," patients may be held accountable for a greater amount of the cost of NOACs depending on the costs of their other drugs. Finally, coverage for NOACs (and individual patient's ability to pay) may vary over time, leading to transitions to VKA and associated adverse outcomes.[46]

Other potential barriers to oral anticoagulant use. Additional barriers to oral anticoagulant use include drug-drug interactions, unwanted adverse effects such as gastritis or potentially myocardial infarction,[10] or a requirement that drugs be administered with food. Although the monitoring needs for VKA are generally thought of as a negative factor, discouraging use, regular monitoring measures adherence and the interface with expert health care providers might improve adherence. In the case of the NOAC, there is a need for alternative strategies to assess and enhance adherence.

A major issue highlighted at this meeting was the lack of clear explanation of the failure of many patients with risk factors for stroke to be treated with OAC and the lack of a framework to categorize these patients in a way that can inform treatment improvement initiatives.

Recommendations

A series of recommendations was developed around the need to better define why AF patients are not being treated with OAC, to develop methods to measure performance and provide feedback, to improve education with practical guidance for safe and effective use of the novel oral anticoagulants, to leverage coverage and health policy opportunities, and to test and implement interventions at a health system level. Many uncertainties call for additional research. Specific recommendations are provided below.

Define reasons for oral anticoagulant underuse classified in ways that can guide intervention to improve use. Although numerous studies have documented that only about half of AF patients with risk factors for stroke are treated with an OAC in various health care settings, the specific reasons are less well known. There was consensus in the working group that better understanding of why so many patients are not being treated is a high priority. Challenges around safe and effective use of warfarin, such as documented or perceived inability to comply with monitoring, are a commonly given reason. Multiple reasons are often reported in individual patients. Patient and/or physician preference for antiplatelet therapy is a frequently cited reason, but this presumably reflects a lack of understanding of how inferior antiplatelet therapy is compared to OAC. Concern with potential bleeding is an important factor, and the lack of reversal agents for the NOACs is a widely expressed concern among physicians even though this may be less of a problem due to their relatively short half-lives. Reasons to withhold OAC therapy could be categorized into 2 domains: according to whether it is a patient-, a provider-, or a system-level reason and according to whether it is appropriate, inappropriate, or of uncertain appropriateness (Figure 2).

Increase the awareness of stroke risk and the value of oral anticoagulant use via impactful educational initiatives. Patient educational efforts should focus on the threat of preventable stroke despite AF's often asymptomatic nature. Educational initiatives should target a broad array of physician groups involved in the management of AF patients. To maximize the yield of patient-provider interactions, the development of decision aids for shared decision making,[47] multifaceted educational materials, and point-of-care decision support is needed. Although it is logical to focus on educating cardiologists, education of primary care physicians, hospitalists, emergency physicians, and advanced practice providers will be essential to guide improved care. Case-based studies, interactive teaching methods, education embedded into patient care environments, and assessment of education effectiveness are important elements of improvement efforts. Identifying barriers to use and opportunities to guide optimal use of OACs at a health system level is an important priority.

Collect data and feedback performance regarding oral anticoagulant use among eligible patients to providers. "If you don't measure it, you can't improve it" is an appropriate adage for anticoagulation for AF. An important question is defining who should be treated

with OAC. Although this seems simple on the surface, identification of such patients using electronic health records in the United States has been challenging. Although the $CHADS_2$ risk factors are easy to measure, they may not be easy to assess in an electronic medical record without specifically collecting information on whether or not they are present. A crucial question, as yet unanswered, is "How much AF is enough to warrant treatment?" The trials studying anticoagulants have generally included patients with a clinical diagnosis of AF who were either in AF at the time of enrolment or who had 2 documented episodes 2 weeks apart. Six-minute episodes of silent AF in older patients with cardiac devices are associated with a 2.5-fold risk of subsequent stroke,[48] but more studies are needed to determine if OAC is beneficial for these patients.

To measure performance in clinical care, patients with AF must be identified, the presence of stroke risk factors must be assessed, and the use of OAC and presence of contraindications should be determined.[49] Several quality improvement initiatives addressing this are under way, including the American College of Cardiology's PINNACLE-AF registry,[50] the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF),[51] the Global Anticoagulant Registry in the FIELD (GARFIELD) registry,[52] and the American Heart Association's Get With The Guidelines program.[53] Traditional registries, although helpful in assessing how populations are being treated, are not well suited to providing measurement and feedback in real time to improve care for individual patients. Much more work needs to be done to enhance measurement, feedback, and broad interventions to improve the use of OAC, including the use of appropriate electronic tools and incentives at the health system level. A data warehouse in a health system could be used to identify candidates for OAC treatment and follow-up on a system level rather than solely relying on individual physicians to make appropriate decisions in real time. The increasing availability of electronic health records represents a rich opportunity for broad, real-time assessment and feedback of therapeutic decisions and clinical outcomes. Improvement in standardized electronic decision support tools may enhance the point-of-care use of OAC. Oral anticoagulation adherence may be enhanced electronically by providing reminders to patients on their mobile devices that their prescription refill time has lapsed. These strategies, in conjunction with data analytics of the health system data warehouse, may provide a true "safety net" for select patients.

Define who should receive VKAs rather than novel oral anticoagulants. Patients who have been on warfarin for a significant period of time, are on a stable dose with stable INRs, and can comply with frequent monitoring may prefer to stay on warfarin despite a higher risk of intracranial hemorrhage. Similarly, a NOAC may not be suitable for patients with advanced renal disease, for example, creatinine clearance < 25 to 30 mL/min. Rare patients may develop intolerance to NOACs but can tolerate VKA. Novel OACs are approved for use in "nonvalvular" AF. The term *nonvalvular atrial fibrillation*, however, needs further definition because more than one-quarter of patients in some of the trials of NOACs had moderate or severe valvular abnormalities, with consistent treatment effects in that subgroup.[54] The novel agents should not be used in patients with significant mitral stenosis (who were excluded from the trials) or with mechanical prosthetic valves (for which the novel agent tested was neither safe nor effective).[55] Finally, out-of-pocket expenses may be substantially less with warfarin compared with a NOAC (Table II); and higher cost will continue to be an important barrier for many patients.

Identify NOAC reversal agents and monitoring strategies. It is important to recognize that although vitamin K, fresh frozen plasma, and prothrombin complex concentrates reverse the coagulation test effects of VKAs, their effectiveness on reducing bleeding and its consequences is much less well established. Furthermore, data regarding risk of NOAC-associated periprocedural bleeding are reassuring, including data from the RE-LY trial showing similar or lower serious bleeding with dabigatran than with warfarin, even among patients undergoing emergent procedures.[56] This may be due, in part, to their shorter half-life in comparison with VKA such that the effect is largely gone 1 to 2 days after the last dose. Nonetheless, research to identify ways to quickly reverse the effect of NOACs and monitor their anticoagulant effect is needed and is under way.[57,58] Andexanet α, for example, is a recombinant protein that functions as a factor Xa decoy; it has shown promise with regard to reversing effects of oral factor Xa inhibitors.[59] A monoclonal antibody fragment antidote for dabitatran is under development.[60] As more data become available, there will be a value in making NOAC reversal strategies widely interpretable and accessible, perhaps analogous to the poison control model.[61] A Web site or hotline to provide guidance on this and other practical issues regarding all NOACs may be useful. It will be important to engage hematology specialists and to demonstrate how institutional protocols can help guide care. Along these lines, reviews providing practical guidance are currently available.[35,62,63] Helping providers deal with everyday practical issues in the use of the novel drugs is important in enhancing their safe and effective use.

Minimize the duration of dual antiplatelet therapy and concomitant OAC use. Among AF patients undergoing percutaneous coronary interventions, a bare metal stent is preferable to a drug-eluting stent in the absence of a clear need for the latter. Among patients with a significant bleeding diathesis and acceptably low stroke risk, consideration can be given to temporarily suspending OAC and resuming it when an antiplatelet agent is no longer required. Guidelines have encouraged avoiding aspirin when using VKA unless there is a clear indication,

that is, within a year of a myocardial infarction. Such advice is likely to be applicable to the novel agents as well. Avoiding aspirin may result in important reductions in bleeding.

Improve time in therapeutic range for patients on warfarin. Organized anticoagulation services have been shown to improve care and outcomes for patients on VKA. Scheduling and ensuring appropriate follow-up are part of this systematic approach. International normalized ratio checks should generally occur at least monthly among those on a stable dose and more often among those requiring dosing adjustments.[49] Automated telephone or electronic appointment reminders may aid in the process. Alternatively, use of point-of-care INR devices may also improve TTR. In a randomized clinical trial, INR self-testing was comparable to in-office venous blood draws with regard to bleeding and stroke rates.[64] The safety of self-monitoring has been demonstrated in several other clinical trials.[65] Accordingly, the Veterans Affairs health care system recently revised their anticoagulation policy to allow self-testing in place of venous plasma testing. If outcomes are improved, this strategy may be adopted by other healthcare systems.

Leverage observational data sets to refine understanding of oral anticoagulant use and outcomes (effectiveness and safety) in general practice. Using the Mini-Sentinel database, the FDA has demonstrated its ability to assess the rate and impact of spontaneous bleeding reports in a timely way.[44] As electronic health records become more widespread and interconnected, this process is expected to become more useful; and safety signals may even be detected in real time. The large number of bleeding events attributed to dabigatran versus warfarin in spontaneous reports to the FDA was thought to be driven largely by a heightened awareness of the dabigatran bleeding because of the drug's novelty, leading to a larger fraction of events that were reported for dabigatran compared with warfarin, a familiar drug known to cause bleeding.[66] Such a reporting bias is always possible in a spontaneous reporting system. As noted, the Mini-Sentinel sites, including all parts of the health care system, did not have such a bias. A similar effect may be observed when other NOACs are used more widely.

Better align health system incentives. The full set of patient outcomes over the care cycle should be weighed against total costs for the patient's condition, rather than the costs borne by a single payor. Educational programs should be designed that include systems improvement to measure, provide feedback on, provide tools for, and establish incentives to guide optimal OAC for AF. An important step is to be able to identify the AF population with electronic health records. A system is needed to categorize patients not being treated in a way that assesses their risks and can lead to specific interventions that will improve their care. The goal is to enhance value for patients, rather than simply focusing on cost containment. Patients with AF should be fully educated regarding risk of stroke and its consequences. Further, out-of-pocket expenses of OACs in various formularies should be made clear. With therapeutic benefit and costs in mind, patients will be better equipped to make appropriate, informed decisions regarding whether to use OAC and what insurance coverage best suits them. An important opportunity will be to advocate for use of OAC performance measures[49] with feedback to providers and health systems as appropriate.

Define other indications for oral anticoagulants. Further research is needed regarding the risk of subclinical or silent AF and the role of OAC to modify that risk, regarding the risk and benefit of OAC with antiplatelet therapy following acute coronary syndrome, and about many of the practical issues regarding OAC use around the time of procedures and management of bleeding.

Conclusions

It is estimated that 50,000 preventable strokes occur annually in the United States alone related to suboptimal anticoagulation care for AF. In view of the opportunity to improve care and public health, interventions to improve OAC use are needed at the levels of patients, providers, and health care systems. Patients and providers would benefit from increased awareness of stroke risk and the effects of treatment, which may be achieved with the implementation of educational initiatives and feedback mechanisms. A better-delineated role of VKA in the current therapeutic era, better-defined OAC eligibility and ineligibility, increased knowledge and dissemination of practical advice on safe and effective use of OAC, and better evidence to guide antithrombotic therapy with AF and coronary stenting may help health care providers make more informed decisions with their patients. Finally, improvements can be made from a system standpoint, including supporting higher-quality use of warfarin, measuring and feeding back quality of care, and better aligning incentives in integrated health systems.

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Appendix A

Appendix Table I. Think-tank meeting participants

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