OPEN

Current Gaps in the Provision of Safe and Effective Anticoagulation in Atrial Fibrillation and the Potential for Factor XI-Directed Therapeutics

Shaun G. Goodman, MD, MSC,† Denis Roy, MD,‡ Charles V. Pollack, Jr, MA, MD,§ Kori Leblanc, PHARMD,¶ Kevin F. Kwaku, MD, PHD,‖ Geoffrey D. Barnes, MD,** Marc P. Bonaca, MD, MPH,†† Mellanie True Hills, CSP,‡‡ Elena Campello, MD,§§ John Fanikos, RPH, MBA,¶¶ Jean M. Connors, MD,‖‖ and Jeffrey I. Weitz, MD****

The global prevalence of atrial fibrillation is rapidly increasing, in large part due to the aging of the population. Atrial fibrillation is known to increase the risk of thromboembolic stroke by 5 times, but it has been evident for decades that well-managed anticoagulation therapy can greatly attenuate this risk. Despite advances in pharmacology (such as the shift from vitamin K antagonists to direct oral anticoagulants) that have increased the safety and convenience of chronic oral anticoagulation in atrial fibrillation, a preponderance of recent observational data indicates that protection from stroke is poorly achieved on a population basis. This outcomes deficit is multifactorial in origin, stemming from a combination of underprescribing of anticoagulants (often as a result of bleeding concerns by prescribers), limitations of the drugs themselves (drug–drug interactions, bioaccumulation in renal insufficiency, short half-lives that result in lapses in therapeutic effect, etc), and suboptimal patient adherence that results from lack of understanding/education, polypharmacy, fear of bleeding, forgetfulness, and socioeconomic barriers, among other obstacles. Often this adherence is not reported to treating clinicians, further subverting efforts to optimize care. A multidisciplinary, interprofessional panel of clinicians met during the 2023 International Society of Thrombosis and Haemostasis Congress to discuss these gaps in therapy, how they can be more readily recognized, and the potential for factor XI-directed anticoagulants to improve the safety and efficacy of stroke prevention. A full appreciation of this potential requires a reevaluation of traditional teaching about the "coagulation cascade" and decoupling the processes that result in (physiologic) hemostasis and (pathologic) thrombosis. The panel discussion is summarized and presented here.

Key Words: anticoagulation, atrial fibrillation, DOAC, drug adherence, Factor XI

(*Crit Pathways in Cardiol* 2024;23: 47–57)

INTRODUCTION

Since its conception, the provision of safe and effective long-term anticoagulation to prevent the thromboembolic complications of atrial fibrillation (AF) has been one of the most precarious balancing acts in medicine. In 1976, Gurewich[1] wrote:

> *"Anticoagulant therapy has certain unique features that tend to complicate its appropriate use. For example, the beneficial effect of anticoagulants can usually be appreciated only by a statistical evaluation of clinical trials. By contrast, the hemorrhagic complications are all too obvious in the individual patient. This places a special onus on physicians who see their therapeutic failures and not their successes."*

Today, having encountered successive generations of anticoagulant options for stroke prevention in AF [from warfarin and heparin to low-molecular-weight heparin and direct oral anticoagulants (DOACs)] that have spanned 5 decades, clinicians are still forced to walk a tightrope between the need to reduce thromboembolic risk—with whichever anticoagulant approach they choose—and the need to minimize bleeding complications as a result of that therapy. The challenge for prescribers is exacerbated by uncertainty about assessments of relative risk, by incomplete knowledge of the true impact of the inappropriate use of reduced dose regimens of DOACs, and by the overemphasis by clinicians and patients on bleeding risk in the context of an incomplete understanding of the risk and implications of stroke. Patient nonadherence to prescribed therapy, which may be attributable to fear or experience of bleeding, forgetfulness, other personal reasons for missing doses, or inadequate education on the consequences of subtherapeutic anticoagulation in AF, also contributes to suboptimal outcomes.[2]

In June 2023, in association with the annual congress of the International Society on Thrombosis and Haemostasis, in Montréal, Québec, Canada, a multidisciplinary, interprofessional expert panel was convened to discuss the causality and consequences of these issues and to explore the potential for new anticoagulants directed against coagulation factor (F)XI to address unmet needs. In the authors' evidence-driven dialogue, various perspectives on the gaps and deficiencies of current provision of stroke prevention in AF were discussed.

*From the Division of Cardiology, St Michael's Hospital, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, ON, Canada; †Canadian VIGOUR Centre and Division of Cardiology, University of Alberta, Edmonton, AB, Canada; ‡Department of Medicine and Research Center, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada; §Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, MS; ¶Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; ‖Department of Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH; **Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI; ††Division of Cardiology, CPC Clinical Research, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO; ‡‡StopAfib.org, American Foundation for Women's Health, Decatur, TX; §§Department of Medicine, General Internal Medicine and Thrombotic and Hemorrhagic Diseases Unit, Padova University Hospital, Padova, Italy; ¶¶Department of Pharmacy, Brigham and Women's Hospital; ‖‖Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and ***Department of Medicine, McMaster University, Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada.

Reprints: Shaun G. Goodman, Division of Cardiology, St Michael's Hospital, Peter Munk Cardiac Centre, University Health Network, University of Toronto, 30 Bond Street, Room 6-034 Donnelly, Toronto, ON M5B 1W8, Canada. E-mail: shaun.goodman@unityhealth.to.

ISSN: 1003-0117/24/232-47
DOI: 10.1097/HPC.0000000000000351

CURRENT GAPS

AF is a burgeoning problem worldwide (Fig. 1).[3] The increasing prevalence of AF is driven by several factors, including aging of the population, the similarly increasing prevalence of concomitant heart failure, longer survival after cardiac ischemic events, and unprecedented prevalence of obesity. The Centers for Disease Control and Prevention estimates that 12.1 million people in the United States will have AF in 2030.[4] In Europe, prevalent AF in 2010 was ≈9 million among individuals older than 55 years and is expected to reach 14 million by 2060.[5,6] However, despite recognition of these epidemiological trajectories, and the well-established efficacy of anticoagulation for stroke prevention in AF, suboptimal management of stroke risk persists. Both registry and prescription claims data have consistently demonstrated that approximately 40%–60% of patients with AF and a guideline-based indication for stroke prevention (CHA_2DS_2-VASc ≥2) are not prescribed oral anticoagulants (OACs).[7] This may be a passive scenario (missing or inaccurate AF diagnosis, limited health care access, inadvertent patient nonadherence, and effects of pill burden) or an active one [physician underprescribing (usually because of bleeding concerns), patient nonadherence, or lack of adequate patient education]. Other contributing factors are the recognition that current "best therapy" (DOACs, as per international society guidelines[8–10]) remains suboptimal for some patients with AF, including those with advanced age, severe renal dysfunction, frailty, or active malignancy. Furthermore, the short half-lives of the DOACs mean that the level of anticoagulation may be subtherapeutic after missing even a single dose.

The need for safe and effective anticoagulation—for multiple indications—is well recognized. Thrombosis is responsible for 1 in 4 deaths globally and remains a leading cause of morbidity.[11] The underuse of anticoagulation therapy for stroke prevention in patients with AF is one of the greatest public health issues facing cardiovascular patients.[7]

BALANCING STROKE PROTECTION AND BLEEDING RISK

The primary obstacle to managing and preventing thrombosis is concern for, or frank fear of, bleeding. Advances in anticoagulation therapy have largely been driven by the need to reduce bleeding risk. DOACs represent a substantial achievement of that goal, as major bleeding—particularly intracranial bleeding but not necessarily gastrointestinal bleeding—occurs less frequently with DOACs than with vitamin K antagonists (VKAs) such as warfarin. In addition, DOACs are more convenient to administer than VKAs, have fewer drug–drug interactions (DDIs) and drug–diet interactions, and do not require anticoagulation monitoring or dose titration. However, despite lower rates of all-cause mortality—attributable to fewer fatal bleeding events with DOACs than with VKAs[12]—DOAC-related bleeding remains a concern, with major and clinically relevant nonmajor (CRNM) bleeds occurring at a rate of about 10%–12% per year.[13]

While major bleeding events complicate the long-term care of patients with AF, CRNM bleeds, which are captured in clinical trials of stroke prevention, may also deter clinicians and patients from

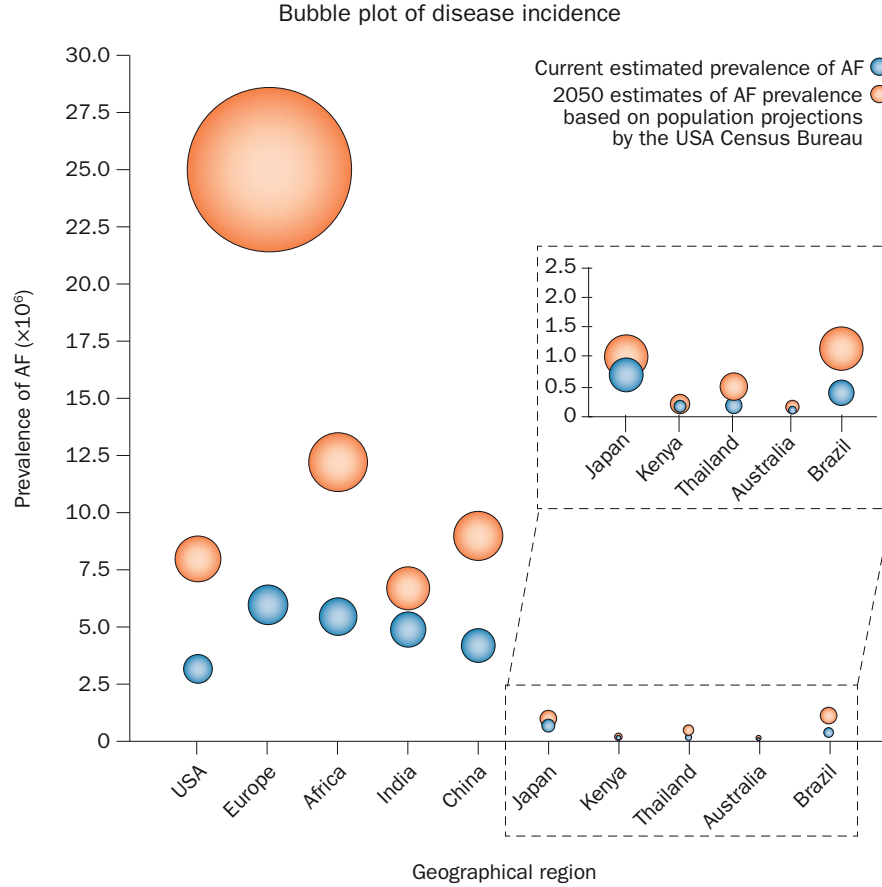

FIGURE 1. Global prevalence of AF and estimated increase of AF in different regions. Adapted from *Nat Rev Cardiol* 2014;11:639–654.[3]

initiating or continuing anticoagulation therapy. In addition, patients may experience and be troubled by what clinicians term "minor" or "nuisance" bleeds such as slow healing of small cuts, easy bruising, epistaxis, gingival bleeding with toothbrushing, or hemodynamically insignificant but visible hematuria, hematochezia, or hemorrhoidal bleeding. As discussed later, these events are perhaps better termed "patient-relevant bleeds," because they can be much more impactful on patients' quality of life than the more clinical terms "minor" or "nuisance" bleeds might convey.[14] Such events may prompt patients to reduce or skip doses, pause, or—in as many as 1 in 20 cases[15]—discontinue DOAC therapy, often without notifying their physician, suggesting that "nuisance" is a misnomer.

Unfortunately, despite the pharmacologic advance represented by the DOACs over VKAs, tension persists between achieving effective stroke prevention and avoiding excess bleeding risk. Patients' perceptions about stroke risk and their very tangible experience of bleeding events may differ sharply from the clinician's goal to avoid stroke at any "reasonable" cost. In other cases, patients may be more fearful of a disabling stroke than their clinicians, who instead focus on their perception of unacceptable risk for bleeding with conventional anticoagulation.[16] Clinician assessment of stroke risk with a validated instrument such as CHA_2DS_2VASc scoring correlates with provision of stroke prevention therapy, but there appears to be a plateau to that relationship. In a report from the American College of Cardiology National Cardiovascular Data Registry's PINNACLE (Practice Innovation and Clinical Excellence), each 1-point increase in the CHA_2DS_2VASc score was associated with an increased likelihood of providing an OAC prescription compared with aspirin-only prescription [adjusted odds ratio (OR), 1.163; 95% confidence interval (CI), 1.157–1.169; $P < 0.001$].[17] However, OAC prescription did not exceed 50% even in higher-risk patients with CHA_2DS_2VASc scores over 4.[17] Regardless of prescribing patterns, other data indicate that the risk of discontinuation of OAC treatment among AF patients is concerning, particularly among patients with prior bleeding.[18]

These discussions are replete with conflicting data. Divergent information comes from 2 studies comparing patient and physician attitudes about stroke prevention in AF that were conducted 22 years apart (2001 and 2023). Both found that patients with AF who are not receiving anticoagulation are more willing to consider anticoagulation than are their physicians.[19,20] In 2001, the most striking difference between physicians and patients was in the thresholds for the risk of bleeding with warfarin and aspirin, in that patients were willing to accept a much higher risk of bleeding for an associated reduction in the risk of stroke. Physicians as a group showed little consistency as to how much risk of excess bleeding was acceptable.[19] In 2023, however, 56% of patients expressed concern about bleeding, compared with 46% who were concerned about stroke, while the top physician-cited issues were low AF burden (34%), patient refusal (33%), fall risk (21%), and high bleeding risk (20%).[21] Therefore, there is a persistent gap between patient and physician perceptions of bleeding and stroke risk.

CLINICAL ISSUES IMPACTING ANTICOAGULATION DECISION-MAKING

Clinical factors such as older age, perceived frailty, dementia, and preexisting anemia were the most common reasons why clinicians chose not to prescribe anticoagulation for stroke prevention in a large payer database review of nearly 400,000 patients.[22] The importance of these factors is highlighted by the observation that, in 2020, OAC was initiated within 12 months after incident AF diagnosis in only 33% of patients, leaving two-thirds of eligible patients untreated.[22] Frailty in particular appears to represent a significant impediment to OAC prescription,[23] although frailty often coexists with advanced age and other comorbidities that might confound that association and impact practice. Frail patients are less likely to receive an anticoagulant than those without frailty, and, if anticoagulated, frail patients are more likely to receive warfarin than a DOAC. Therefore, although the introduction of DOACs has increased anticoagulation rates, these drugs have not resolved treatment gaps for frail patients with AF.[23]

Another issue that often accompanies advancing age and complicates anticoagulation prescribing in AF is progressive renal insufficiency.[24] Observational studies indicate that one-third of patients with AF also have chronic kidney disease (CKD).[25] Of note, compared with AF patients without CKD, those with CKD are less likely to be treated with rhythm control, or receive OAC, and have higher rates of both major bleeding and stroke when anticoagulants are prescribed.[25,26] A population-based study of bleeding risk associated with OACs in patients with heart failure and AF in the US Veterans Administration health system found that death and bleeding were lower with DOACs than with VKAs across all renal function levels and clinical subgroups. A >20% decline in renal function occurred in 53% of DOAC-treated patients at some point during follow-up, which would have required dose reduction in 11% of patients, and was associated with increased bleeding.[27]

Besides renal function-driven dosing considerations—which vary among available DOACs—there are other potential contributors to suboptimal anticoagulation with DOACs attributable to pharmacokinetics, bioavailability, and DDIs.[28] In a Canadian study of more than 36,000 patients prescribed DOACs for stroke prevention in AF, 11% had a documented concomitant use of a potentially interacting P-glycoprotein or CYP3A4 inducer or inhibitor.[29] For all adverse DDIs reported, inappropriate DOAC prescribing had occurred in 63% of dispensations. There was a significantly higher risk of death [hazard ratio (HR), 1.58; 95% CI, 1.47–1.70; $P < 0.001$] when a DDI was identified, but not a higher risk for stroke (HR, 0.99; 0.83–1.17; $P = 0.89$) or major bleeding (HR, 1.22; 0.94–0.158; $P = 0.13$).[29]

UNDERPRESCRIBING AND UNDERDOSING

Perhaps because of these overlapping issues, both underprescribing and underdosing of DOACs for stroke prevention in AF appear to be common. For example, the apixaban dose for AF is recommended to be reduced by half if at least 2 of 3 characteristics are present: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.[30] Driven by potential concerns for bleeding, however, the reduced dose is often prescribed inappropriately, thereby reducing efficacy while still imparting an anticoagulant-related bleeding risk.[31] In a Canadian registry of DOAC prescribing practice for stroke prevention in AF, the standard recommended dose was prescribed in 76% of patients and the reduced dose in 24%. Concordance of the standard dose with Health Canada prescribing information occurred in 95% of patients, but the reduced dose was concordant in only 58% of cases, suggesting that 42% of patients inappropriately received a reduced dose regimen.[32] In the Systematic Assessment of Geriatric Elements in Atrial Fibrillation (SAGE-AF) cohort, over 20% of older patients with AF treated with DOACs were prescribed an inappropriate dose, with most being underdosed. DDIs were common; per those investigators, other factors that influenced prescription of guideline-nonadherent doses were perception of higher bleeding risk, presence of kidney dysfunction, and lack of familiarity with dosing guidelines.[33]

Similarly, in an Israeli study of newly diagnosed AF patients prescribed DOACs, 39% received off-label dose-reduced treatment. Underdosing was associated with an increased risk of the composite thrombotic outcome of death/stroke/MI [adjusted HR, 1.57 (95% CI, 1.34–1.83); $P < 0.001$] and a higher rate of bleeding [adjusted HR, 1.63 (1.14–2.34); $P = 0.008$].[34] Another analysis of a large US administrative database of DOAC-treated AF patients with a renal indication for dose reduction showed

that 43% were potentially overdosed, which was associated with a higher risk of major bleeding (HR, 2.19; 95% CI, 1.07–4.46), but no statistically significant difference in stroke. Among patients in this study with no renal indication for dose reduction, 13% were potentially underdosed. Specifically in apixaban-treated patients, this underdosing was associated with a higher risk of stroke (HR, 4.87; 1.30–18.26) but no statistically significant decrease in major bleeding (HR, 1.29; 95% CI, 0.48–3.42) compared with standard dose apixaban.[35]

While it appears that stroke prevention therapy with DOACs in AF is more convenient and less burdensome for patients than VKA, many studies have shown that convenience does not necessarily translate to improved patient adherence.[36] Furthermore, hazards from nonadherence can occur early given the short half-lives of DOACs; while the short half-life is an advantage when scheduling invasive procedures or when managing bleeding events, this is also associated with a rapid loss of effectiveness when a dose is missed. This is a critical issue for agents that must provide continuous protection against thrombotic events while also carrying a constant bleeding liability that persists even with underdosing.[37]

Because the half-lives of DOACs range from 5 to 14 hours, drug levels may be very low by the time the next dose is taken.[38–40] Per Figure 2, an extra dose (Fig. 2B) or a missed dose (Fig. 2C) may result in a greater bleeding risk or a greater thrombotic risk, respectively, especially in patients receiving a once-daily dosing regimen.[40] This is a prevalent and consequential issue. A systematic review of 48 real-world evidence studies that included some 570,000 patients with AF indicated that one-third of DOAC-treated patients had poor adherence to therapy. The typical patient missed one DOAC dose every 4 days, associated with a 39% increase in thrombotic events.[41] Availability of a pharmacologic strategy that provides a sustained treatment effect without a corresponding increase in bleeding risk would improve outcomes with anticoagulation for AF.

POLYPHARMACY

Another issue that may interfere with optimal delivery of stroke prevention in AF with DOACs is pill burden. Polypharmacy (taking ≥5 medications per day) is common in older patients who are at greater risk of AF and of stroke and bleeding.[42,43] Cognitive impairment in older populations can also impact their ability to track medications and successfully manage a high pill burden.[43] As the average patient with AF has 5 significant comorbidities,[44] it is not surprising that 75% of patients with AF experience polypharmacy.[45] The consequences of polypharmacy and pill burden in AF are well documented. For example, a systematic review and meta-analysis examining the association of polypharmacy with health outcomes in AF demonstrated a 36% increase in all-cause mortality among patients taking 5–9 medications and an 84% increase in all-cause mortality for those taking more than 9 medications.[46] Those pill burdens similarly corresponded with increased rates of major bleeding (HR, 1.32; 95% CI, 1.14–1.52; $P < 0.001$ and HR, 1.68; 1.35–2.09; $P < 0.001$, respectively) and CRNM bleeding (HR, 1.12; 1.03–1.22; $P < 0.01$ and HR, 1.48; 1.33–1.64; $P < 0.01$, respectively).[46]

Further, polypharmacy and pill burden are associated with poorer general function and physical measures of quality of life in patients with chronic disease,[47,48] particularly AF.[49,50] Pill burden and polypharmacy are also independently associated with poorer medication adherence and, consequently, with worse clinical outcomes. Nonadherence is related to the number of medications, particularly in patients with cardiovascular disease.[51] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, patients taking 9 or more concomitant drugs had a significantly higher rate of study drug discontinuation (1%) than did those on 6–8 drugs (15%) or 0–5 drugs (14%).[52]

Finally, polypharmacy is also associated with a heightened risk of DDIs with the risk increasing in an almost exponential manner with the number of drugs taken.[47,53] DDIs with DOACs in AF can increase the risks for both ischemic stroke and hospitalization for major bleeding.[54]

ANTICOAGULATION ADHERENCE IN ATRIAL FIBRILLATION

All these issues interfere with patient adherence to stroke prevention therapy with DOACs. Adherence, as distinct from persistence, is a measure of the extent to which a patient adheres to a prescribed dose and interval of their medication regimen. Adherence is usually expressed as a proportion of doses taken divided by the prescribed regimen. Typically, "good" adherence is defined as 80% or better by that measure,[55] which, given the loss of thrombosis protection risked by missing a single DOAC dose,[41] might be considered a "soft" goal on which we should improve. Persistence is a measure of continuing use (in time) of a prescribed therapy. Thus, these are different measures with distinct impacts because the behavioral drivers of adherence and persistence differ.

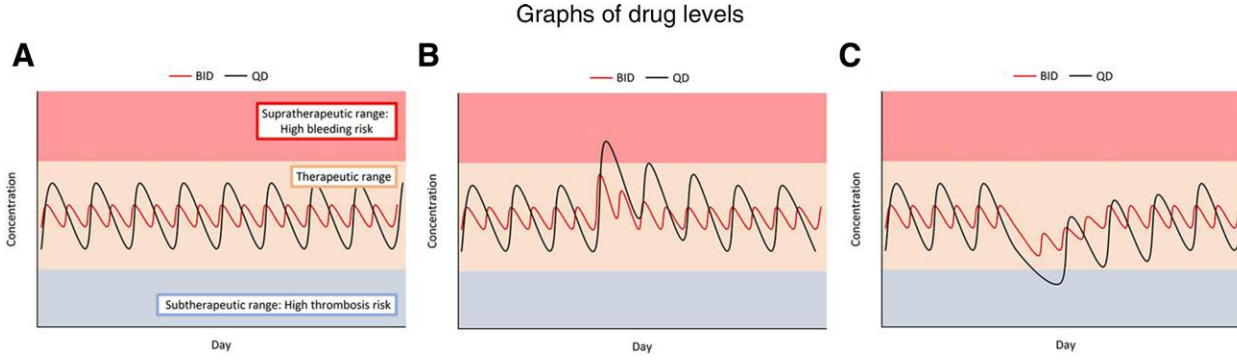

FIGURE 2. Theoretical pharmacokinetic profile of a DOAC in serum and gastrointestinal lumen: a dose X administered once daily (QD, black line), and a dose X/2 administered twice daily (BID, red line). A, Taking proper regimen. B, Taking an extra tablet may result in a higher peak (and higher level of anticoagulation) in the QD than in the BID regimen. C, A single missed DOAC dose may deviate the concentration downward from the therapeutic range (and therefore inadequate anticoagulation) more severely in the QD regimens than in the BID regimens. Adapted from *Am Heart J Plus* 2022;22:100203.[40]

A conceptual model has identified explicit attitudes toward medications that affect adherence as well as implicit attitudes and time preferences [eg, immediate (as in pain relief) vs. delayed (avoiding future complications) gratification]. These drivers are also impacted by individual-level social determinants of health such as economic or logistical barriers to accessing medications.[56] Adherence truly begins with prescribing (hopefully at an appropriate dose, to avoid underprescribing) and the patient then filling the prescription. Already, potential barriers to adherence have been encountered: writing the prescription, interacting with the pharmacy, and paying for the medication. The next step is taking the medication as it was prescribed—another opportunity for suboptimal adherence. Furthermore, at some point (eg, 30 or 90 days) for chronic anticoagulation in AF, the prescription must be refilled, and the process repeated. Adherence to VKAs can be assessed by monitoring the international normalized ratio and therefore the prescriber has an objective means of evaluating adherence. However, the international normalized ratio is not measured in those on DOAC therapy and prescribers must rely on self-reported adherence, which may be limited in its reliability.[57]

A theoretical model around adherence specific for anticoagulation therapy has several key elements[58]:

- Knowledge base: to promote adherence, patients should be educated about the purpose of, and long-term need for, stroke prevention in AF.
- Short- and long-term motivation: can be supported by a clear understanding of the perceived health risks and consequences of nonadherence, and by education and involvement of caregiver/family.
- Support with habit formation: help with creating a personalized system for habit formation to identify and remove barriers to adherence. Provide reminders for doses, supporting a self-efficacy loop to say, for example, "Yes, I'm going to take a pill today, I'm going to continue to take a pill over and over again."
- Other factors: individualized for the patient, taking into consideration demographics, personality, attitude, mental health, and values systems.

The personal and societal gains from improved adherence with stroke prevention in AF have been clearly described.[59] As noted previously, one missed dose may result in a decrease in the DOAC concentration to a subtherapeutic level, which can render them predisposed to thrombosis, and the typical patient misses a dose every 4 days.[41] Data from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), the pivotal outcome study comparing dabigatran to VKA, showed that during a median of 2 years of follow-up, 76% of patients were "adherent" at the 80% level. Follow-up of the 24% of patients who were nonadherent showed increased adverse outcomes for both efficacy and safety, with those patients sustaining higher rates of stroke, all-cause mortality, major bleeding, and all bleeding.[60] A previously cited systematic review and meta-analysis of 48 real-world evidence studies showed that the proportion of AF patients with good adherence to anticoagulation therapy was 66% and that DOAC nonadherence was associated with an increased risk of stroke (HR, 1.39; 95% CI, 1.06–1.81).[41] Further, nonadherence has a substantial economic cost: adherence to DOAC therapy over 12 months led to a reduction in overall health care costs as higher drug acquisition costs were offset by lower medical (inpatient and outpatient) costs among adherent patients.[61]

A recent study examining reasons for nonadherence to apixaban in 419 patients with AF with a mean CHA_2DS_2VASc score of 3.2 ± 1.6 reported adherence scores ≥80 (termed "mild" nonadherence) in two-thirds and scores <80 ("poor" adherence, as per above) in one-third.[62] In all groups, forgetfulness was a significant self-reported contributor to nonadherence, and it was the predominant problem among those with poor adherence. Additional issues associated with adherence score <80 included: not believing the DOAC was needed [OR, 12.24 (95% CI, 2.25–66.47)]; medication cost [OR, 3.97 (95% CI, 1.67–9.42)]; and fear of severe bleeding [OR, 3.28 (95% CI, 1.20–8.96)]. Patients with adherence scores <80 were also asked to identify practices that would help "a great deal/a lot" to increase adherence. Interestingly, and undermining a key perceived advantage of DOACs over VKA, bloodwork to evaluate drug efficacy was cited by 56%. Physician counseling about adherence was identified by 55%, and having an available reversal agent was cited by 39%. Of the 43% of the patients who did not disclose their nonadherence to their providers, forgetfulness was a predominant problem.[62]

ADVERSE EVENTS AFFECT ADHERENCE

Finally, data reveal that DOAC-related adverse events negatively impact adherence. Thus, in RE-LY, annual event rates were higher in nonadherent than adherent patients for stroke and systemic embolism (3.1% vs. 1.0%), all-cause death (7.8% vs. 2.7%), major bleeding (6.2% vs. 2.7%), and all bleeding (28.7% vs. 19.1%; all $P < 0.0001$). After an event, patients were even more likely to become nonadherent [adherence after stroke or systemic embolism, 30.3% (vs. 51.5% before the event), after major bleeding, 33.4% (vs. 60.6%), and after all bleeding, 66.7% (vs. 72.9%); all $P < 0.0001$].[60] Therefore, the relationship between poor adherence and adverse events is bidirectional, suggesting a need for new or different stroke prevention approaches for AF patients that improve adherence.

The distinction was made earlier between clinically classed "minor" or "nuisance" bleeds and *patient-relevant* bleeding that has a deleterious impact on adherence to OAC. At International Society on Thrombosis and Haemostasis 2023, new observational data were presented that illustrate why clinicians should be more attuned to these "minor" bleeding complications.[14] In November 2022, a global survey of over 3000 adult patients prescribed anticoagulants was conducted in association with StopAfib.org and the National Blood Clot Alliance to explore the frequency and impact of bleeding problems that did not—at the patients' own discretion—trigger medical evaluation. Of respondents, 59% reported experiencing a bleeding problem, most commonly easy bruising or slow healing of small cuts or injuries. Menorrhagia, epistaxis, and gingival or hemorrhoidal bleeding were also frequently reported. An emotional impact of such events was reported by 47% of patients who described being anxious or fearful about bleeds or bruises that occurred with routine activities, embarrassed about their appearance because of a recent bleed or bruise, and having an underlying fear of a future bleed that may be serious or even fatal.

More than half of these patients had adjusted their lifestyles in response to these "patient-relevant" bleeds, for example, by spending less time engaging in sports, hobbies, or travel, or by changing their choice of apparel to ensure better coverage of bruises. The risk of injury when working in the kitchen, in the garden, or when cleaning house was often cited as a concern that prompted curtailment of such activities.

More than one-quarter of these patients confirmed they had considered pausing, or had paused, their anticoagulant therapy, due to bleeding problems; 7% did not consult their doctor before interrupting therapy. Finally, the greater the emotional or lifestyle impact of a recent bleed, the greater was the reported interest in a new anticoagulant that would lower bleeding risk while still offering reliable stroke protection. The potential development of just such an anticoagulant strategy—one that addresses all measures of safety including patient-relevant bleeding as well as the issues of adherence, pill burden, underprescribing and underdosing, and DOAC-related pharmacokinetics and DDIs as discussed earlier—was the subject of the remainder of the authors' discussions.

THE POTENTIAL FOR FACTOR XI-TARGETED THERAPEUTICS

FXI is an attractive target for new anticoagulants for several reasons, most notably the longstanding recognition of the impact and implications of congenital FXI deficiency. Unlike hemophilia, FXI deficiency—which is prevalent among Ashkenazi Jews[54]—is rarely associated with spontaneous bleeding.[63] With major injury, surgery, or childbirth, it is associated with prolonged bleeding but not a hemorrhagic proclivity.[64] Genetic epidemiology and Mendelian randomization studies involving large cohorts of subjects indicate that low FXI levels (typically defined as <20% of normal) are associated with a reduced risk of thrombosis [venous thromboembolism (VTE) and ischemic stroke], but without an increased risk for major bleeding.[65] In a 10,000-patient Ashkenazi cohort, the incidence of VTE was lower in those with FXI deficiency (FXI activity <50%) compared with those with normal FXI activity [adjusted HR, 0.26 (95% CI, 0.08–0.84)].[66] Moreover, high levels of FXI are a risk factor for thrombosis.[67] These effects are consistent with FXI exerting both procoagulant and antifibrinolytic activities, yielding a cardiovascular benefit that may protect FXI-deficient subjects.

The results of animal studies also support FXI as a target for new anticoagulants: FXI-deficient mice were protected from occlusive thrombosis in the vena cava after partial ligation[68] and from injury-induced thrombosis in the arterial system.[69] Furthermore, such mice had no increase in bleeding after tail amputation and only a minor increase in bleeding in a saphenous vein reinjury model.[70] Such findings of attenuation of thrombosis without a bleeding penalty, seen with FXI inhibition or knockout, differ from the experience with oral FXa inhibitors in these models. The DOACs are very effective at preventing thrombosis in animal models but, with increasing doses, there is a dose-dependent increase in bleeding.[71]

These findings suggest that selective inhibition of FXI may dissociate thrombosis from hemostasis. Pursuing this concept requires a reimagining of the coagulation cascade as it has been traditionally understood—with 2 pathways (extrinsic and intrinsic) converging into a common pathway[72]—with the net result being the formation of a fibrin clot. One might imagine "good clots" and "bad clots"; good clots are involved in the formation of hemostatic plugs that form at sites of vascular injury to seal the leaks and prevent bleeding. Hemostatic plugs are predominantly extravascular in location. Bad clots, on the other hand, are those that form inside the heart, or in arteries or veins and block blood flow, thereby causing a stroke or a myocardial infarction in arteries, or deep vein thrombosis that can embolize to the lungs. Because current anticoagulants target clotting factors in the common pathway of coagulation, they cannot discriminate between "good clots" and "bad clots."

Normal hemostasis, resulting in hemostatic plugs or "good clots," is triggered by the high concentrations of tissue factor (TF) located in the hemostatic envelope surrounding blood vessels. TF initiates explosive "good clot" formation through the extrinsic and common pathway.[73] FXI is mostly dispensable for this process. In contrast, pathologic thrombosis or "bad clots" are triggered by small amounts of TF exposed at sites of atherosclerotic plaque disruption inside arteries or by the TF expressed on the surface of activated leukocytes or microvesicles tethered to the inside wall of veins. These small amounts of TF initiate clotting but for the clots to become occlusive, amplification of coagulation through activation of FXI by thrombin is essential.[73] Because FXI is essential for thrombosis but mostly dispensable for hemostasis, FXI inhibitors can uncouple thrombosis from hemostasis, thereby providing safer anticoagulation.[74]

This disconnection is depicted in Figure 3.[75] The impact of DOACs (which target FXa or thrombin in the common pathway) and VKAs (which reduce the levels of coagulation proteins in the extrinsic, intrinsic, and common pathways) impact hemostasis, while selective inhibition of FXI effectively suppresses the pathological thrombosis pathway, while leaving the physiological hemostasis pathway largely unaffected. The risk of bleeding is thereby minimized.

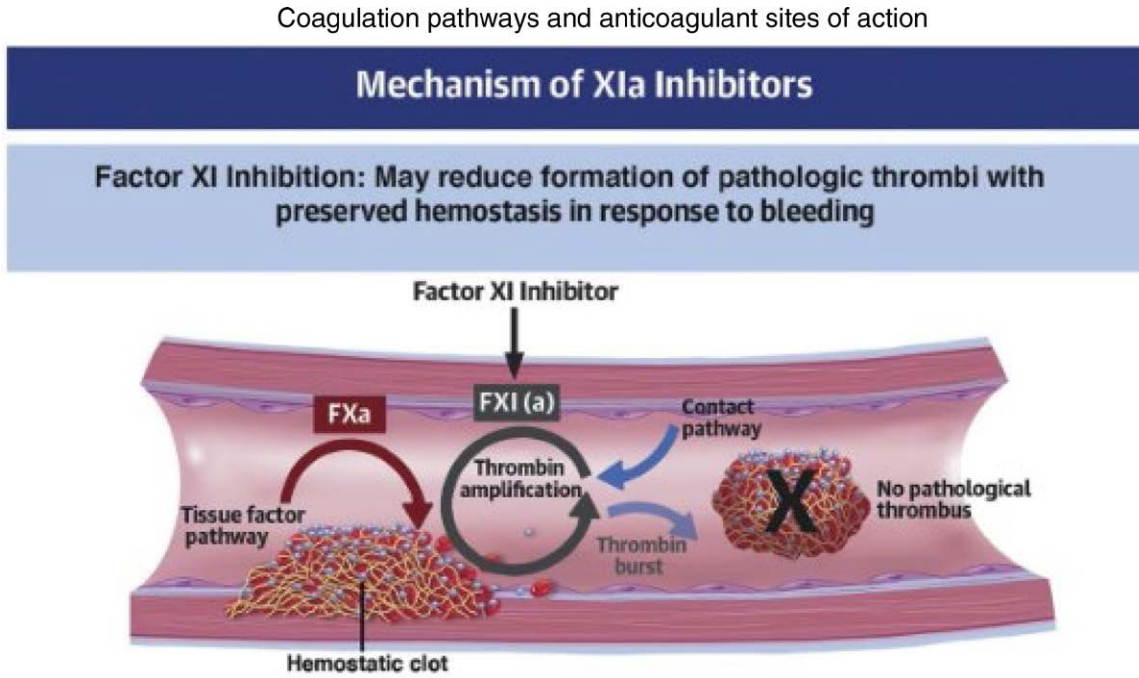

FIGURE 3. Direct oral anticoagulants and VKAs all act on the common pathway, inhibiting both hemostasis and pathologic thrombus formation. By specifically and only inhibiting FXI, it may be possible to reduce the risk of thrombi while preserving the functionality of the clotting cascade in response to bleeding. Adapted from *J Am Coll Cardiol* 2023;81:771–779.[75]

Multiple approaches to selective FXI inhibition are being investigated. Antisense oligonucleotides such as fesomersen (administered subcutaneously monthly)[76] target the synthesis of FXI in the liver, while aptamers [eg, factor eleven inhibitory aptamer, dosed intravenously or subcutaneously daily[77]) bind FXI and block its activity. FXI-directed antibodies (eg, abelacimab,[78] osocimab[79]), which are given by subcutaneous or intravenous injection, bind to FXI and block its activation and/or activity. Small-molecule inhibitors (eg, asundexian,[80] milvexian[81]), which are administered orally, bind reversibly to the active site of FXIa and block its activity.

Abelacimab is unique among current agents in that it binds to the catalytic domain of FXI with high affinity and locks it in a zymogen conformation, thereby preventing its activation by FXIIa or thrombin.[78] Because the mechanism of action of abelacimab specifically prevents FXIa from ever forming, it closely recapitulates the biology of congenital FXI deficiency and the cardioprotection that it confers.[66] Typical of antibody activity, abelacimab has a long half-life and requires subcutaneous injection only once per month, which simplifies the treatment process and may improve patient adherence. Preclinical and clinical studies have confirmed that there is no need to adjust abelacimab dosing for age or for renal or hepatic dysfunction, and given the specific targeting of the antibody, there is no potential for DDIs or accumulation in patients with kidney failure. Therefore, abelacimab may be particularly well suited for long-term anticoagulation as required for stroke prevention in AF.

The closest similarity between emerging FXI-directed therapeutics and DOACs is between apixaban or rivaroxaban and the oral small-molecule drugs asundexian and milvexian. Apixaban is given twice daily, has a rapid onset and offset of action, exhibits 27% renal elimination, and has the potential for DDIs with potent P-glycoprotein or CYP3A4 inducers or inhibitors.[30] Asundexian and milvexian also have rapid onset and offset of action, are dosed once or twice daily, and have some renal elimination and the potential for DDIs, but importantly may carry less bleeding liability. In contrast, the antibodies abelacimab and osocimab—which also carry less bleeding liability versus conventional anticoagulants—are highly targeted therapies, have no renal excretion, and no DDIs, allowing for consistent dosing regimens regardless of renal or hepatic status. Mechanistic differences among the better studied agents are shown in Table 1.

As described earlier, the primary difference between DOACs and FXI inhibitors is the potential of the latter to attenuate thrombosis without increasing major bleeding risk. Osocimab has been studied in phase 2 but has not yet progressed to phase 3. Asundexian and milvexian have recently progressed to phase 3, and abelacimab is already in phase 3 evaluation for both stroke prevention in AF and for treatment of cancer-associated VTEs. Foundational phase 2 experience with these agents for thromboprophylaxis after total knee arthroplasty is summarized in Figure 4.[76]

EXPERIENCE TO DATE WITH FACTOR XI/XIA-TARGETED THERAPEUTICS IN ATRIAL FIBRILLATION

Following the roundtable discussion leading to this manuscript, 2 signal announcements occurred in the development of FXI-targeted therapeutics in AF. The first was the presentation of early results from the phase 2b study of safety and proof-of-concept for stroke prevention in the AZALEA-TIMI 71 study (NCT04755283).

Having shown its antithrombotic potential and safety in knee arthroplasty,[74] abelacimab was studied in AZALEA-TIMI 71 to compare its safety with that of rivaroxaban in patients with AF at moderate-to-high risk of stroke. The trial was an event-driven, randomized, active-controlled, blinded endpoint, parallel-group study that compared 2 blinded doses of abelacimab with open-label rivaroxaban on the rate of major or CRNM bleeding. The trial's Independent Data

TABLE 1. Mechanistic Differences Among Several Investigational FXI/FXIa Inhibitors

	Abelacimab	Osocimab	Fesomersen	Asundexian	Milvexian
Agent	Monoclonal antibody (fully human)	Monoclonal antibody (fully human)	Antisense oligonucleotide	Small molecule	Small molecule
Mode of action	FXI inhibition	FXIa inhibition	↓ FXI synthesis	FXIa inhibition	FXIa inhibition
Administration	Subcutaneous or intravenous	Subcutaneous or intravenous	Ssubcutaneous	Oral	Oral
Frequency of dosing	Monthly, once	Monthly, once	Weekly to monthly	Daily, once	Daily, twice
Onset of action	Rapid	Rapid	Slow	Rapid	Rapid
Offset of action	Slow	Slow	Slow	Rapid	Rapid
Renal clearance	No	No	No	Some	Some
Drug–drug interactions	No	No	No	Possible	Possible
CYP3A4 interaction	No	No	No	Yes	Yes

Adapted from *Hamostaseologie* 2021;41:104–110.[11]

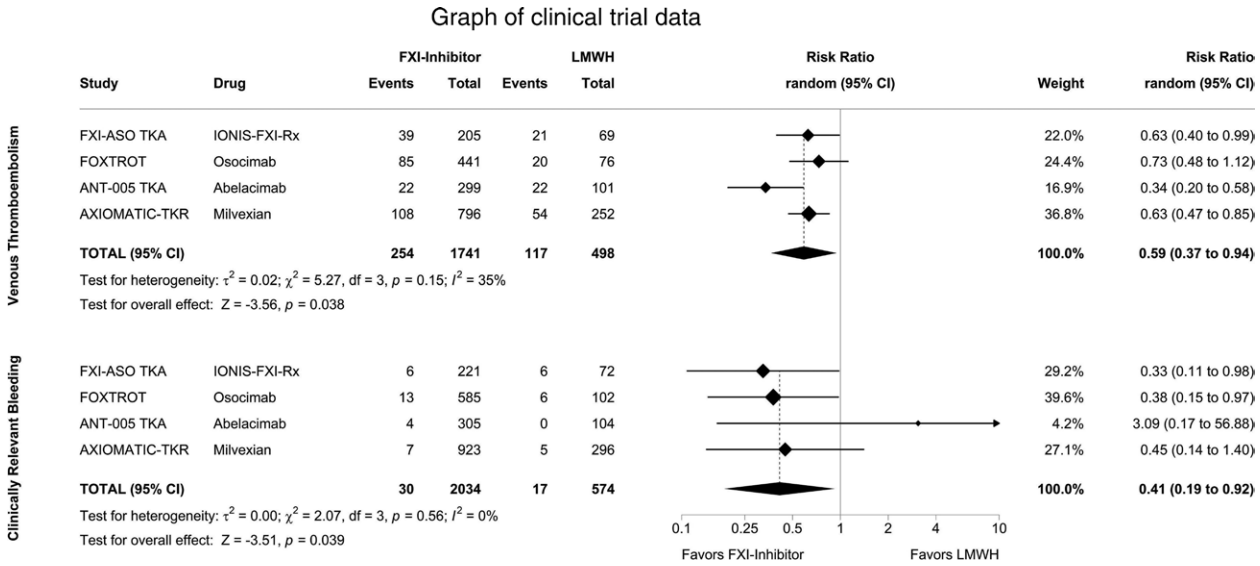

FIGURE 4. Meta-analysis of phase 2 studies comparing FXI inhibitors with enoxaparin in total knee replacement. Adapted from *Front Cardiovasc Med* 2022;9:903029.[76]

Monitoring Committee (IDMC) recommended that the trial end early (after 52% of the targeted safety endpoints had occurred) due to the "substantially greater than anticipated reduction in major and clinically relevant nonmajor bleeds in the abelacimab arms compared to rivaroxaban and a benefit:risk favoring abelacimab." Results presented at the American Heart Association 2023 Scientific Sessions demonstrated that the 150 mg monthly dose of abelacimab, the dose being studied in ongoing phase 3 trials, inhibited FXI activity by 99% (95% CI, 98–99) and substantially reduced bleeding compared with rivaroxaban: a 67% (45–81; $P < 0.0001$) decrease in major or CRNM bleeding, a 74% (39–89; $P = 0.002$) decrease in major bleeding, and a 93% (50–99; $P = 0.008$) decrease in major gastrointestinal bleeding.[82] In addition to stopping the trial early, the IDMC recommended that an open-label extension of the study be initiated to continue patients on abelacimab or switch patients from rivaroxaban to abelacimab.

The data from AZALEA-TIMI 71 lend strong support to the safety profile of abelacimab versus DOACs and contribute to validation of the "FXI hypothesis" that specific inhibition of FXI with an agent that essentially mimics the congenital FXI-deficient state can provide AF patients with consistent anticoagulation that is safer than that provided by a DOAC. The phase 3 LILAC-TIMI 76 trial (NCT05712200) is currently enrolling as a placebo-controlled evaluation of the effect of abelacimab on the rate of ischemic stroke or systemic embolism in high-risk AF patients (age, 65–74 years and $CHA_2DS_2VASc \geq 5$ or age, ≥75 years and $CHA_2DS_2VASc \geq 4$) who have been deemed by their physicians or by their own decision to be unsuitable for oral anticoagulation therapy. Therefore, the control arm in the LILAC-TIMI 76 trial is placebo, as eligible patients enter the study on no ongoing anticoagulation treatment. Positive results from LILAC-TIMI 76 would therefore potentially extend the benefits of anticoagulation to many of the 40%–60% of patients with AF and a CHA_2DS_2-VASc score ≥2[7] who currently are not protected against stroke, including those who have been excluded because of bleeding history, bleeding concerns, or dynamic issues around adherence, pill burden, or DDIs.

The oral small-molecule FXIa inhibitor asundexian was studied in the phase 2 PACIFIC-AF trial, a randomized, double-blind, dose-finding study in which asundexian (20 mg or 50 mg once daily) was compared with apixaban 5 mg twice daily in patients aged 45 years or older with AF, a CHA_2DS_2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk.[83] Ratios of incidence proportions for the primary endpoint of major or clinically relevant nonmajor bleeding were 0.50 (90% CI, 0.14–1.68) for asundexian 20 mg (3 events), 0.16 (0.01–0.99) for asundexian 50 mg (1 event), and 0.33 (0.09–0.97) for pooled asundexian (4 events) versus apixaban (6 events), though the total number of events was quite small. The rates of adverse events were similar in the 3 treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.[83]

Asundexian (50 mg once daily) was next being studied in the phase 3 OCEANIC-AF trial (NCT05643573) compared to apixaban. Eligible patients had CHA_2DS_2-VASc score ≥3 if male or ≥4 if female, or CHA_2DS_2-VASc score of 2 if male or 3 if female, and various enrichment criteria. In November 2023, the IDMC for the OCEANIC-AF recommended that the trial be stopped early for "inferior efficacy of asundexian versus the control arm." No additional details about the OCEANIC-AF trial are available at this time. It is notable that in contrast to the development of other FXI inhibitors, a phase 2 proof-of-concept efficacy study in total knee arthroplasty was not carried out with asundexian. Consequently, the correlation between the over 95% FXIa target engagement reported with the 50 mg dose of asundexian and clinical outcomes could not be assessed in the phase 2 program. It is therefore possible that the asundexian dose used in OCEANIC-AF was too low. In support of this possibility, the ongoing phase 3 LIBREXIA-AF trial (NCT 05757869), which is comparing milvexian with apixaban, is evaluating a milvexian dose of 100 mg twice daily, a dose that is 4-fold higher than the dose of asundexian used in OCEANIC-AF.[84] In contrast, abelacimab provides the most potent inhibition of FXI because it blocks FXIa generation rather than inhibiting FXIa activity. The safety of long-term FXI inhibition with abelacimab relative to rivaroxaban was revealed in the AZALEA-TIMI 71 trial. The results of the ongoing LIBREXIA-AF and LILAC-TIMI 76 trials will provide information on the efficacy of FXI inhibition for stroke prevention in AF.

It is noteworthy that the same IDMC that recommended closing OCEANIC-AF for inferior efficacy of asundexian versus apixaban in AF has recommended that OCEANIC-Stroke trial continue enrollment. That study (NCT05686070) is evaluating the same dose of asundexian but in a different setting—secondary prevention of

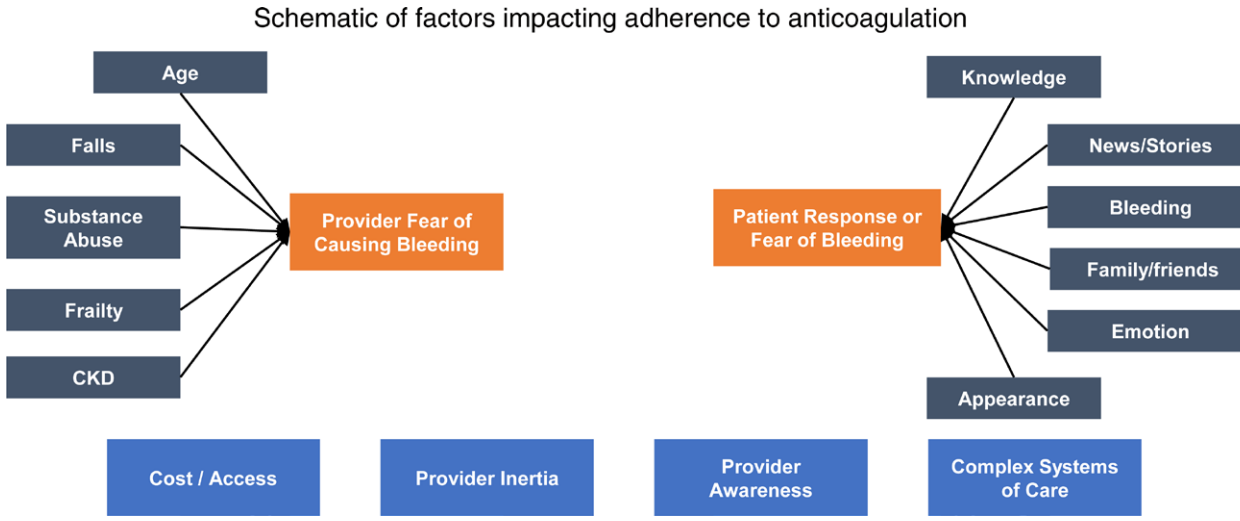

FIGURE 5. Underutilization of anticoagulation in atrial fibrillation is a complex issue (courtesy of M.B.).

noncardioembolic stroke or high-risk transient ischemic attack within 7 days of acute event, and with a different comparator (placebo) and as add-on antithrombotic therapy, as most patients will also receive antiplatelet agents.

EXPERT PANEL SUMMARY: OPTIMISM FOR THE FUTURE

Stroke prevention in AF has advanced dramatically over the past 5 decades, but large gaps in stroke prevention care remain. Both registry and claims data have consistently demonstrated that approximately 40%–60% of patients with AF and a guideline-based indication for stroke prevention (CHA_2DS_2-VASc of ≥2) are not adequately treated with OACs.[7]

The panel discussed the many reasons for this sobering reality, including pharmacokinetics, DDIs, bleed risk, underprescribing, underdosing, provider and patient education, and several social and health system considerations, as the leading reasons why (Fig. 5).

However, an improved understanding of the coagulation cascade and the differentiation of the hemostatic and thrombotic pathways offers a pathophysiologic basis for optimism about a FXI-targeted approach to chronic anticoagulation. Despite the current challenges with existing therapies, the authors remain optimistic that FXI-targeted therapies will address many of the limitations of DOACs, just as DOACs addressed many of the limitations of VKA therapy. The ongoing phase 3 trials with FXI inhibitors in AF and in other conditions requiring anticoagulation an opportunity to advance the care of patients in need of highly effective, but safer options.

"The upcoming decade may witness advances in anticoagulant therapy beyond those achieved with the DOACs. Success in targeting FXI could herald an end to the more than 70-year stronghold of thrombin and FXa as targets for anticoagulants."
—James C. Fredenburgh and Jeffrey I. Weitz[11]

DISCLOSURES

Funding for the expert panel meeting and for open access to this article was provided by Anthos Therapeutics. The authors are solely responsible for the content of the manuscript. The authors declare that they have no conflict of interest.

References

1. Gurewich V. Guidelines for the management of anticoagulant therapy. *Semin Thromb Hemost*. 1976;2:176–196.
2. Salmasi S, Loewen PS, Tandun R, et al. Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. *BMJ Open*. 2020;10:e034778.
3. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014;11:639–654.
4. CDC. *Atrial Fibrillation*. cdc.gov. Centers for Disease Control and Prevention. October 14, 2022. Available at: https://www.cdc.gov/heartdisease/atrial_fibrillation.htm. Accessed January 25, 2024.
5. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751.
6. Di Carlo A, Bellino L, Consoli D, et al; National Research Program: Progetto FAI. La Fibrillazione Atriale in Italia. Prevalence of atrial fibrillation in the Italian elderly population and projections from 2020 to 2060 for Italy and the European Union: the FAI project. *EP Europace*. 2019;21:1468–1475.
7. Pokorney SD, Gersh BJ, Ahmad A, et al. Stroke prevention in atrial fibrillation: closing the gap. *Am Heart J*. 2019;210:29–38.
8. Jogler JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2023. *Accessed June 29, 2023*. doi:10.1161/CIR.0000000000011932023.
9. Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.
10. Andrade JG, Aguilar M, Atzema C, et al; Members of the Secondary Panel. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2020;36:1847–1948.
11. Fredenburgh JC, Weitz JI. Factor XI as a target for new anticoagulants. *Hamostaseologie*. 2021;41:104–110.
12. Bouget J, Balusson F, Maignan M, et al. Major bleeding risk associated with oral anticoagulant in real clinical practice. a multicentre 3-year period population-based prospective cohort study. *Br J Clin Pharmacol*. 2020;86:2519–2529.
13. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with

atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962.
14. Yi B, Lipworth K, Burrows S, et al. OC 21.4 patient-relevant bleeding events among patients taking anticoagulant medication. *Res Pract Thromb Haemost*. 2023;7:272.
15. O'Brien EC, Holmes DN, Thomas L, et al. Therapeutic strategies following major, clinically relevant nonmajor, and nuisance bleeding in atrial fibrillation: findings from ORBIT-AF. *J Am Heart Assoc*. 2018;7:e006391.
16. Choudhry NK, Anderson GM, Laupacis A, et al. Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis. *BMJ*. 2006;332:141–145.
17. Hsu JC, Maddox TM, Kennedy KF, et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE registry. *JAMA Cardiol*. 2016;1:55–62.
18. Kachroo S, Hamilton M, Liu X, et al. Oral anticoagulant discontinuation in patients with nonvalvular atrial fibrillation. *Am J Manag Care*. 2016;22:e1–e8.
19. Devereaux PJ, Anderson DR, Gardner MJ, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ*. 2001;323:1218–1222.
20. Cannon CP, Kim JM, Lee JJ, et al; Benchmarking an Oral Anticoagulant Treatment Rate in Patients with Nonvalvular Atrial Fibrillation (BOAT-AF) Investigators and Research Coordinators. Patients and their physician's perspectives about oral anticoagulation in patients with atrial fibrillation not receiving an anticoagulant. *JAMA Netw Open*. 2023;6:e239638.
21. Cannon M, Christopher P, Sutherland J, et al. Abstract 14202: the Benchmarking an Oral Anticoagulant Treatment Rate in Patients With Nonvalvular Atrial Fibrillation (BOAT-AF) Study: a prospective, multicenter study evaluating perspectives on use of oral anticoagulation using a patient survey and clinical review by the treating physician among patients not currently treated with oral anticoagulation. *Circulation*. 2018;138:A14202–A14202.
22. Ko D, Lin KJ, Bessette LG, et al. Trends in use of oral anticoagulants in older adults with newly diagnosed atrial fibrillation, 2010-2020. *JAMA Netw Open*. 2022;5:e2242964.
23. Orlandi M, Dover DC, Sandhu RK, et al. The introduction of direct oral anticoagulants has not resolved treatment gaps for frail patients with nonvalvular atrial fibrillation. *Can J Cardiol*. 2022;38:77–84.
24. Qamar A, Bhatt DL. Stroke prevention in atrial fibrillation in patients with chronic kidney disease. *Circulation*. 2016;133:1512–1515.
25. Washam JB, Holmes DN, Thomas LE, et al. Pharmacotherapy for atrial fibrillation in patients with chronic kidney disease: insights from ORBIT-AF. *J Am Heart Assoc*. 2018;7:e008928.
26. Olesen JB, Lip GYH, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625–635.
27. Jackevicius CA, Lu L, Ghaznavi Z, et al. Bleeding risk of direct oral anticoagulants in patients with heart failure and atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007230.
28. Steffel J, Collins R, Antz M, et al; External reviewers. 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *EP Europace*. 2021;23:1612–1676.
29. Sandhu RK, Islam S, Dover DC, et al. Concurrent use of P-glycoprotein or cytochrome 3A4 drugs and non-vitamin K antagonist oral anticoagulants in non-valvular atrial fibrillation. *Eur Heart J Qual Care Clin Outcomes*. 2022;8:195–201.
30. *Eliquis Prescribing Information*. Available at: http://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed February 23, 2024.
31. Weitz JI, Eikelboom JW. Appropriate apixaban dosing: prescribers take note. *JAMA Cardiol*. 2016;1:635–636.
32. Leblanc K, Bell AD, Ezekowitz JA, et al; OPTIMAL AF Investigators. Non-vitamin K antagonist oral anticoagulant (NOAC) use and dosing in Canadian practice: insights from the Optimising Pharmacotherapy in the Management Approach to Lowering Risk in Atrial Fibrillation (OPTIMAL AF) Programme. *Int J Clin Pract*. 2020;74:e13625.
33. Sanghai S, Wong C, Wang Z, et al. Rates of potentially inappropriate dosing of direct-acting oral anticoagulants and associations with geriatric conditions among older patients with atrial fibrillation: the SAGE-AF study. *J Am Heart Assoc*. 2020;9:e014108.
34. Arbel R, Sergienko R, Hammerman A, et al. Effectiveness and safety of off-label dose-reduced direct oral anticoagulants in atrial fibrillation. *Am J Med*. 2019;132:847–855.e3.
35. Yao X, Shah ND, Sangaralingham LR, et al. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol*. 2017;69:2779–2790.
36. Barnes GD, Piazza G; Global Anticoagulation Roundtable Working Group. Barriers to stroke prevention in atrial fibrillation: insights from the global anticoagulation roundtable. *Int J Cardiol Heart Vasc*. 2022;42:101096.
37. Ferreiro JL, Sibbing D, Angiolillo DJ. Platelet function testing and risk of bleeding complications. *Thromb Haemost*. 2010;103:1128–1135.
38. Roberti R, Iannone LF, Palleria C, et al. Direct oral anticoagulants: from randomized clinical trials to real-world clinical practice. *Front Pharmacol*. 2021;12:684638.
39. Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. *Thromb Haemost*. 2018;118:437–450.
40. Ido T, Sasaki S, Sotomi Y, et al. Twice- or once-daily dosing of direct oral anticoagulants and gastrointestinal bleeding in patient with atrial fibrillation. *Am Heart J Plus*. 2022;22:100203.
41. Ozaki AF, Choi AS, Le QT, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2020;13:e005969.
42. Qato DM, Wilder J, Schumm LP, et al. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med*. 2016;176:473–482.
43. *Medication Overload: America's Other Drug Problem*. Lown Institute. Available at: https://lowninstitute.org/reports/medication-overload-americas-other-drug-problem/. Accessed August 17, 2023.
44. Chamberlain AM, Alonso A, Gersh BJ, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: a population-based study. *Am Heart J*. 2017;185:74–84.
45. Shaikh F, Pasch LB, Newton PJ, et al. Addressing multimorbidity and polypharmacy in individuals with atrial fibrillation. *Curr Cardiol Rep*. 2018;20:32.
46. *Polypharmacy and health outcomes in atrial fibrillation: a systematic review and meta-analysis*. Open Heart. Available at: https://openheart.bmj.com/content/7/1/e001257. Accessed August 17, 2023.
47. Wastesson JW, Morin L, Tan ECK, et al. An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opin Drug Saf*. 2018;17:1185–1196.
48. Van Wilder L, Devleesschauwer B, Clays E, et al. Polypharmacy and health-related quality of life/psychological distress among patients with chronic disease. *Prev Chronic Dis*. 2022;19(E50):1–10.
49. Abu HO, Saczynski JS, Mehawej J, et al. Clinically meaningful change in quality of life and associated factors among older patients with atrial fibrillation. *J Am Heart Assoc*. 2020;9:e016651.
50. Mant J, Hobbs FR, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493–503.
51. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med*. 2005;165:1147–1152.
52. Focks JJ, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ*. 2016;353:i2868.
53. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish prescribed drug register. *Drug Saf*. 2007;30:911–918.
54. Lee JY, Oh IY, Lee JH, et al. Drug-drug interactions in atrial fibrillation patients receiving direct oral anticoagulants. *Sci Rep*. 2021;11:22403.
55. Brown MT, Bussell J, Dutta S, et al. Medication adherence: truth and consequences. *Am J Med Sci*. 2016;351:387–399.
56. Krousel-Wood M, Craig LS, Peacock E, et al. Medication adherence: expanding the conceptual framework. *Am J Hypertens*. 2021;34:895–909.
57. Stephenson JJ, Shinde MU, Kwong WJ, et al. Comparison of claims vs patient-reported adherence measures and associated outcomes among patients with nonvalvular atrial fibrillation using oral anticoagulant therapy. *Patient Prefer Adherence*. 2018;12:105–117.
58. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm*. 2012;18:527–539.
59. Kearney M, Fay M, Fitzmaurice DA. Stroke prevention in atrial fibrillation: we can do better. *Br J Gen Pract*. 2016;66:62–63.
60. Millenaar D, Schumacher H, Brueckmann M, et al. Cardiovascular outcomes according to polypharmacy and drug adherence in patients with atrial fibrillation on long-term anticoagulation (from the RE-LY Trial). *Am J Cardiol*. 2021;149:27–35.
61. Deshpande CG, Kogut S, Willey C. Real-world health care costs based on medication adherence and risk of stroke and bleeding in patients treated with novel anticoagulant therapy. *J Manag Care Spec Pharm*. 2018;24:430–439.

62. Tarn DM, Shih K, Tseng CH, et al. Reasons for nonadherence to the direct oral anticoagulant apixaban. *JACC Adv*. 2023;2:100175.
63. Löwenberg EC, Meijers JCM, Monia BP, et al. Coagulation factor XI as a novel target for antithrombotic treatment. *J Thromb Haemost*. 2010;8:2349–2357.
64. Seligsohn U. Factor XI deficiency in humans. *J Thromb Haemost*. 2009;7:84–87.
65. Georgi B, Mielke J, Chaffin M, et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. *Stroke*. 2019;50:3004–3012.
66. Preis M, Hirsch J, Kotler A, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood*. 2017;129:1210–1215.
67. Meijers JC, Tekelenburg WL, Bouma BN, et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med*. 2000;342:696–701.
68. Wang X, Smith PL, Hsu MY, et al. Effects of factor XI deficiency on ferric chloride-induced vena cava thrombosis in mice. *J Thromb Haemost*. 2006;4:1982–1988.
69. Wang X, Cheng Q, Xu L, et al. Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. *J Thromb Haemost*. 2005;3:695–702.
70. Ay C, Hisada Y, Cooley BC, et al. Factor XI-deficient mice exhibit increased bleeding after injury to the saphenous vein. *J Thromb Haemost*. 2017;15:1829–1833.
71. Monroe DM, Hoffman M. A mouse bleeding model to study oral anticoagulants. *Thromb Res*. 2014;133:S6–S8.
72. Becker RC, Spencer FA. Historical perspectives in hemostasis, coagulation, and fibrinolysis: a foundation for understanding thrombotic disorders and developing effective treatment. In: Becker RC, Spencer FA, eds. *Fibrinolytic and Antithrombotic Therapy: Theory, Practice, and Management*. Oxford University Press; 2006.
73. Mackman N. Role of tissue factor in hemostasis, thrombosis, and vascular development. *Arterioscler Thromb Vasc Biol*. 2004;24:1015–1022.
74. Hsu C, Hutt E, Bloomfield DM, et al. Factor XI inhibition to uncouple thrombosis from hemostasis: JACC review topic of the week. *J Am Coll Cardiol*. 2021;78:625–631.
75. Harrington J, Piccini JP, Alexander JH, et al. Clinical evaluation of factor XIa inhibitor drugs: JACC review topic of the week. *J Am Coll Cardiol*. 2023;81:771–779.
76. Nopp S, Kraemmer D, Ay C. Factor XI inhibitors for prevention and treatment of venous thromboembolism: a review on the rationale and update on current evidence. *Front Cardiovasc Med*. 2022;9:903029.
77. Donkor DA, Bhakta V, Eltringham-Smith LJ, et al. Selection and characterization of a DNA aptamer inhibiting coagulation factor XIa. *Sci Rep*. 2017;7:2102.
78. Yi BA, Freedholm D, Widener N, et al. Pharmacokinetics and pharmacodynamics of abelacimab (MAA868), a novel dual inhibitor of factor XI and factor XIa. *J Thromb Haemost*. 2022;20:307–315.
79. Beavers CJ, Wayne NB. Osocimab: a novel agent in preventing venous thromboembolism. *J Cardiovasc Pharmacol*. 2020;76:645–649.
80. Heitmeier S, Visser M, Tersteegen A, et al. Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. *J Thromb Haemost*. 2022;20:1400–1411.
81. Dilger AK, Pabbisetty KB, Corte JR, et al. Discovery of milvexian, a high-affinity, orally bioavailable inhibitor of factor XIa in clinical studies for antithrombotic therapy. *J Med Chem*. 2022;65:1770–1785.
82. Ruff C. Abstract 24578. Late-breaking science abstracts and featured science abstracts from the American Heart Association's Scientific Sessions 2023 and late-breaking abstracts in resuscitation science from the Resuscitation Science Symposium 2023. *Circulation*. 2023;148:e282–e317.
83. Piccini JP, Caso V, Connolly SJ, et al; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet*. 2022;399:1383–1390.
84. Weitz JI, Strony J, Ageno W, et al; AXIOMATIC-TKR Investigators. Milvexian for the prevention of venous thromboembolism. *N Engl J Med*. 2021;385:2161–2172.