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ACC SCIENTIFIC STATEMENT

# Direct Oral Anticoagulants in Primary and Secondary Prevention of Thrombotic Events: 2026 ACC Scientific Statement

A Report of the American College of Cardiology

**Writing Committee members**

Dharam J. Kumbhani, MD, SM, FACC, *Chair*

Anastasia L. Armbruster, PharmD, FACC
Richard K. Cheng, MD, MSc, FACC
Jonathan Chrispin, MD, FACC
Urs Fischer, MD
Anne Marie Holbrook, MD, PharmD, MSc
Jose Joglar, MD, FACC
Marie-Antoinette Sevestre, MD

## ABSTRACT

Direct oral anticoagulants (DOACs) have transformed the prevention and treatment of thromboembolic disease, offering predictable pharmacokinetics, fewer interactions, and improved safety compared with vitamin K antagonists. Over the past decade, DOACs have become the preferred oral anticoagulants for most patients with atrial fibrillation and venous thromboembolism; yet, important gaps remain in their optimal implementation across diverse clinical scenarios. Despite strong evidence supporting their efficacy and safety, DOACs continue to be underutilized and sometimes inappropriately dosed, particularly among patients at elevated thrombotic risk and in populations historically underrepresented in randomized trials.

This American College of Cardiology Scientific Statement provides a comprehensive, evidence-based overview of established and emerging indications for DOAC therapy in primary and secondary prevention of thrombotic events. Key domains include anticoagulation in atrial fibrillation, acute and extended treatment of venous thromboembolism, management in special populations (including patients with chronic kidney disease, liver dysfunction, cancer, obesity, frailty, prior bleeding, and valvular heart disease), periprocedural anticoagulation, and antithrombotic strategies following stroke, left atrial appendage closure, and catheter ablation. The document also addresses practical considerations such as drug selection, dosing strategies, duration of therapy, bleeding risk assessment, management of anticoagulant-related bleeding, drug-drug interactions, adherence, and cost-related barriers to care. This statement is intended to complement existing clinical practice guidelines by synthesizing evolving data, clarifying areas of uncertainty, and supporting individualized, patient-centered decision making. By addressing both evidence and implementation challenges, this document aims to improve the appropriate and equitable use of DOACs across the spectrum of thrombotic disease.

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## INTRODUCTION

The American College of Cardiology (ACC) has a long history of developing documents to complement clinical practice guidelines. Among these documents, scientific statements represent a novel approach to inform clinicians about areas where the scientific evidence is new and evolving or where sufficient data are more limited. Anticoagulants are widely used in the prevention and management of thrombotic events, but their clinical indications and use in practice continue to evolve, particularly in specific subpopulations. This scientific statement aims to provide a comprehensive summary of recent guideline recommendations and research findings related to the use of oral antithrombotics.

To accomplish this work, the ACC convened a writing committee in January 2026 via a confidential conference call attended only by writing committee members and ACC staff. A review of seminal publications and outstanding questions was facilitated. Writing assignments were configured according to each committee member's area of expertise, and email correspondence was used to provide critical review of contributed content. Differences were resolved by consensus among the writing committee. A summary of consensus recommendations can be found in Table 1. The committee's work was supported only by the ACC without any commercial input. Writing committee members were all unpaid volunteers. In accordance with ACC's policy on Relationships With Industry and Other Entities, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2.

## DEFINITIONS AND CLASSIFICATIONS

**Cancer-associated thrombus (CAT):** Thrombus diagnosed in the setting of active cancer including cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment has been administered within the past 6 months; or hematological disease that is not in complete remission.

**Major adverse cardiac events (MACE):** Cardiovascular death and life-threatening episodes including acute coronary syndrome (ACS), myocardial infarction (MI), stroke, or any of these.

**Major bleeding:** Clinically significant blood loss, typically including blood loss sufficient to require transfusion, or bleeding into a critical closed space (eg, intracranial, intraocular, or retroperitoneal bleeding).

**Thrombophilia:** A state in which thrombi are more likely to develop, and which can be temporary (eg,

**TABLE 1 Summary of Consensus Recommendations**

**DOACs for primary prevention of VTE and stroke**

- Both DOACs and LMWH are appropriate for VTE prophylaxis post-THA or TKA; DOACs are preferred when possible.
- DOACs are appropriate for use in most patients with valvular heart disease and AF, except those with rheumatic mitral stenosis. In addition, they are inferior to VKAs for patients with mechanical valves in preventing thromboembolic events.
- Routine oral anticoagulation with a DOAC in patients who undergo transcatheter aortic valve implantation without another indication for anticoagulation is not currently recommended.
- For many patients with chronic coronary disease and need for anticoagulation, DOAC monotherapy at regular dosing is a reasonable long-term strategy. In addition, rivaroxaban 2.5 mg twice daily can be considered in conjunction with low-dose aspirin therapy among high-risk patients with CAD or PAD to reduce risk of myocardial infarction, stroke, and cardiovascular death.

**Management and secondary prevention of VTE**

- DOACs are recommended as initial treatment for VTE in most patients except in select populations (eg, mechanical valves, severe renal dysfunction). Loading doses are different from maintenance dosing. Recent data suggest that an apixaban strategy may be superior to a rivaroxaban strategy due to lower bleeding and may be the agent of choice in this setting.
- Extended treatment (beyond 6 months) to prevent VTE should be considered for patients presenting with unprovoked VTE, those with recurrent episodes, and those with high risk profile of recurrence including multiple permanent risk factors. The treatment duration is typically indefinite, but bleeding risk should be reevaluated regularly. DOACs are superior to VKAs for this indication in view of superior efficacy and lower risk of major bleeding compared to warfarin. Aspirin monotherapy has limited benefits for extended treatment of VTE.
- Apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or rivaroxaban 10 mg daily can be used if extended anticoagulant treatment is indicated. Apixaban 2.5 mg twice daily has comparable efficacy to apixaban 5 mg twice daily and is associated with lower major bleeding. Dabigatran 150 mg twice daily can be prescribed for extended treatment; no dose reduction has been tested. Edoxaban has not been tested for extended treatment, but real-life studies suggest good tolerance and efficacy.

**Secondary prevention after acute stroke**

- For people with acute ischemic stroke and AF, DOAC initiation within 4 days reduces the risk of the composite outcome of recurrent ischemic stroke, symptomatic ICH, or unclassified stroke within 30 days. This assumes exclusion of people with very severe stroke, severe space occupying hemorrhagic transformation, or endocarditis.

**OAC in patients with ICH**

- Restarting anticoagulation in people with AF and ICH lowers ischemic events but raises risks of recurrent ICH and major bleeding, without a clear early mortality difference. For most patients, waiting 4–8 weeks is prudent. The net long-term benefit remains uncertain.
- Left atrial appendage closure may be considered to reduce thromboembolic events in people with prior ICH and AF, who are considered unsuitable for long-term OAC therapy (eg, people with imaging or pathological evidence of cerebral amyloid angiopathy).

**Special considerations: DOACs in patients with CKD, liver disease, frailty, obesity, or prior bleeding**

- In CKD stage 4/5 and on dialysis with risk for thromboembolism, there are limited data to guide DOAC use. Apixaban can be considered for nonvalvular AF (with label-concordant dosing). Dabigatran should be avoided in patients on dialysis due to significant renal clearance.
- In individuals with liver disease, the use of OAC is based on Child-Pugh class stages. All DOACs appear safe with Child-Pugh class A. For Child-Pugh class B, apixaban, dabigatran, and edoxaban can be used, whereas rivaroxaban should be avoided. For Child-Pugh class C, there is insufficient evidence to support DOAC use.
- In frail individuals at risk for thromboembolism, apixaban is preferred because it shows consistent benefit across the range of frailty status and poses a lower risk of bleeding.
- In elderly, frail patients in whom standard dose anticoagulation is typically not recommended despite thromboembolism risk, low-dose edoxaban (15 mg daily) can be considered.
- In individuals with class 3 obesity (body mass index ≥40 kg/m$^2$) and at risk for thromboembolism, rivaroxaban or apixaban are appropriate options.
- In patients with a history of prior bleeding or elevated bleeding risk who require anticoagulation, apixaban or low-dose dabigatran (110 mg twice daily) are preferred.

*Continued on the next page*

**TABLE 1 Continued**

**Cancer-associated thrombus (CAT)**
- In selected high-risk ambulatory patients with cancer, prophylactic anticoagulation with a DOAC (apixaban or rivaroxaban) or LMWH (dalteparin or enoxaparin) may be considered.
- DOACs or LMWH can be used to treat CAT. DOACs are generally preferred over LMWH for the treatment of CAT because they are associated with a lower risk of VTE recurrence and a similar overall risk of major bleeding. Among DOACs, the evidence base is strongest for apixaban. Rivaroxaban and edoxaban are also acceptable options for CAT except in urologic, gastrointestinal, and gynecological cancers.
- Long-term, sometimes indefinite anticoagulation should be considered in patients with active cancer after the initial 6 months of treatment. Apixaban 2.5 mg twice daily has similar efficacy to 5 mg twice daily with a lower bleeding risk. Other DOACs have not been tested with a reduced dose strategy for this indication. LMWH can also be considered.

**Anticoagulation after LAAC or AF ablation**
- The optimal regimen for anticoagulation post-LAAC remains uncertain because clinical decisions are driven by individual bleeding risk.
- For individuals with low to intermediate risk for stroke ($CHA_2DS_2$-VASc score ≤3), who maintain sinus rhythm after catheter ablation of AF, discontinuation of OAC 1-year post-AF ablation is a reasonable approach in the absence of other high-risk conditions warranting continued OAC use.

**Monitoring and follow-up**
- Patients receiving DOAC therapy should undergo periodic reassessment of bleeding risk, renal and hepatic function, concomitant medications, and adherence, with closer surveillance in those at higher risk for bleeding or drug accumulation.
- Bleeding risk scores may be used to identify patients who warrant more frequent follow-up but should not be used in isolation to withhold anticoagulation; instead, clinicians should focus on mitigating modifiable bleeding risk factors and reinforcing patient education on signs and symptoms of bleeding.
- At follow-up visits, clinicians should reassess adherence, affordability, drug-drug interactions, interval clinical events, and patient-specific factors to determine whether the selected DOAC and dose remain appropriate.

AF = atrial fibrillation; CAD = coronary artery disease; CAT = cancer-associated thrombus; CKD = chronic kidney disease; DOAC = direct oral anticoagulant; GI = gastrointestinal; ICH = intracerebral hemorrhage; LAAC = left atrial appendage closure; LMWH = low molecular weight heparin; PAD = peripheral artery disease; RCT = randomized controlled trial; THA = total hip arthroplasty; TKA = total knee arthroplasty; VKA = vitamin K antagonist; VTE = venous thromboembolism.

related to prolonged immobility), long-term (eg, related to underlying but treatable disease such as cancer), or lifelong (eg, related to an underlying disease such as protein C deficiency).

**Venous thromboembolism (VTE):** a condition in which a thrombus forms in a vein and possibly migrates into a pulmonary artery or is formed in a pulmonary artery only; VTE comprises the interrelated **deep vein thrombosis** (DVT) and **pulmonary embolism** (PE).

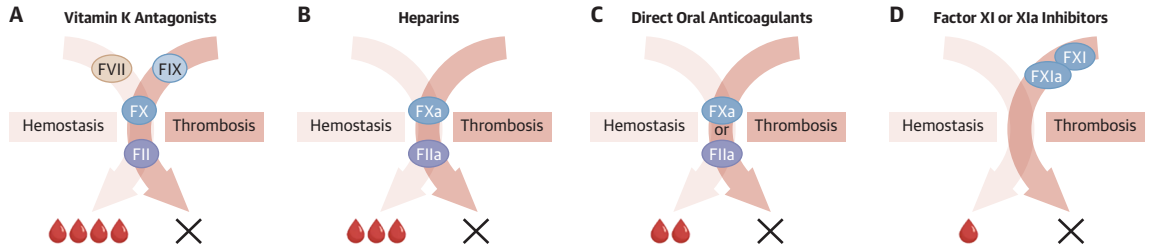
## ABBREVIATIONS

| Abbreviation | Meaning/Phrase |
|---|---|
| ACS | acute coronary syndrome |
| APS | antiphospholipid syndrome |
| AF | atrial fibrillation |
| BMI | body mass index |
| CAD | coronary artery disease |
| CAT | cancer-associated thrombus |
| CKD | chronic kidney disease |
| DAPT | dual antiplatelet therapy |
| DOAC | direct oral anticoagulant |
| DVT | deep vein thrombosis |
| ICH | intracerebral hemorrhage |
| INR | international normalized ratio |
| LAAC | left atrial appendage closure |
| LMWH | low molecular weight heparin |
| MACE | major adverse cardiac events |
| OAC | oral anticoagulant |
| PAD | peripheral artery disease |
| PE | pulmonary embolism |
| RCT | randomized controlled trial |
| THA | total hip arthroplasty |
| TKA | total knee arthroplasty |
| VKA | vitamin K antagonist |
| VTE | venous thromboembolism |

## BACKGROUND

Atrial fibrillation (AF) is the most common arrhythmia globally, affecting an estimated 5 to 10 million individuals in the United States, with prevalence projected to double by 2030.[1] The estimated overall prevalence is approximately 1% to 4% in the general population, increasing to approximately 11% among individuals aged ≥70 years.[2-5] Patients with AF tend to have a higher burden of comorbidities, including heart failure, coronary artery disease (CAD), and valvular heart disease. AF increases the risk of stroke 2- to 5-fold and accounts for 15% to 20% of ischemic strokes.[6-10] Because AF is often asymptomatic and frequently undetected clinically, the

**FIGURE 1 Clotting Targets for Antithrombotic Medications**




Reprinted with permission from Capodanno et al.[34] F = factor.

stroke risk attributed to AF is likely substantially underestimated.[11-13] For the vast majority of patients with AF, treatment with oral anticoagulant (OAC) therapy is associated with significantly lower stroke rates compared with aspirin or placebo.[14-16] Accordingly, the 2023 ACC/American Heart Association (AHA)/Multisociety Guideline for the Diagnosis and Management of AF provides strong support for use of OACs, particularly in those at higher stroke risk, such as those individuals with a high $CHA_2DS_2$-VASc score, presence of certain valvular disease lesions, or other predisposing factors.[17]

VTE, including PE and DVT, affects an estimated 1.2 million individuals annually in the United States, although these estimates are largely based on inpatient data. Because 20% to 33% of patients are treated as outpatients, the true incidence[10,18] is likely underestimated. Approximately 45% to 60% of VTE events are unprovoked, occurring in the absence of identifiable triggers such as immobilization, trauma, surgery, cancer, or hospitalization within the preceding 3 months.[19-21] Further, malignancy increases VTE risk 5- to 7-fold, and roughly 1 in 5 VTE events occurs in patients with active cancer.[22-24] Postoperative VTE occurs in approximately 0.19% of outpatient surgeries.[25] The estimated lifetime risk of VTE is 8.1%, rising to 11.5% among Black individuals.[26] All-cause mortality following a VTE event is high, particularly within the first year (7.5%), and recurrence is common, with 5.3% to 6.1% of patients experiencing a recurrent event within the first year—especially those with cancer.[20,27,28] Anticoagulation is the mainstay of VTE treatment, and after DVT diagnosis, anticoagulants consistently reduce VTE recurrence by 66% to 75%.

Vitamin K antagonists (VKAs), primarily warfarin, were the mainstay for treating VTE and preventing AF-related stroke since the 1950s. Their use is limited by a narrow therapeutic window, frequent monitoring, numerous drug and dietary interactions, and a comparatively lower safety profile. DOACs, also referred to as non-VKA OACs, were developed to overcome these limitations and are now recommended as first-line therapy over warfarin for most patients with AF or VTE requiring anticoagulation. They have overtaken VKA as the most widely used method of OAC, utilized in approximately 80% of patients on an OAC. Despite their widespread availability, approximately 1 in 3 eligible patients do not receive either a DOAC or a VKA.[2,29]

## Pharmacology of commonly used OAC agents

OACs exert their pharmacodynamic effect by interfering with the normal function of clotting factors. Warfarin is rapidly absorbed from the gastrointestinal tract and has high bioavailability. It acts as a VKA by inhibiting vitamin K epoxide reductase, thereby impairing the regeneration of active vitamin K and preventing γ-carboxylation of clotting factors II, VII, IX, and X, as well as proteins C and S. While clotting inhibition happens quickly, warfarin's therapeutic effect is delayed until existing clotting factors are cleared from the blood.[30] The cytochrome P450 system, particularly hepatic CYP2C9, plays a key role in warfarin pharmacokinetics. Several genetic polymorphisms in CYP2C9 have been described and are associated with lower dose requirements and an increased risk of bleeding compared with the wild-type enzyme.[31-33]

DOACs primarily target either factor IIa (thrombin) or factor Xa. Apixaban, edoxaban, and rivaroxaban are direct factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor that acts on both free and fibrin-bound thrombin (**Figure 1**).

The relatively predictable pharmacokinetic profiles of DOACs permit fixed dosing without routine monitoring. However, pharmacokinetic properties vary across agents and may influence drug selection for individual patients. For example, edoxaban and rivaroxaban provide sustained inhibition of thrombin generation for >24 hours and are administered once daily, whereas apixaban and dabigatran have shorter durations of action (~12 hours)

and require twice-daily dosing.[35] For patients presenting with bleeding issues, heparin anti-Xa levels can be used to identify the presence of apixaban, rivaroxaban, or edoxaban, and agent-specific Xa-levels can be used in quantification.[36] Dabigatran activity can be monitored by assaying thrombin time, dilute thrombin time, or ecarin clotting time.[35,37]

## ESTABLISHED INDICATIONS FOR DOACs

### Primary prevention of thrombotic events in patients with AF

AF may pose an increased risk of stroke according to underlying clinical risk factors. To determine candidacy for anticoagulation, several risk scores have been developed over the years, the $CHA_2DS_2$-VASc being the most used and validated. European Society of Cardiology guidelines recommend anticoagulation based on $CHA_2DS_2$-VASc score, with a score ≥2 receiving a Class 1 indication, and Class 2a indication for those with scores of 1.[38] However, the 2023 ACC/AHA/Multisociety Guideline for the Diagnosis and Management of AF acknowledged that absolute risk, especially at lower risk levels, can vary widely across populations (**Table 2**).[17] Quinn et al[39] analyzed 34 different cohorts and demonstrated that at a $CHA_2DS_2$-VASc score of 1, 76% of cohorts reported ischemic stroke rates <1% per year, whereas at a $CHA_2DS_2$-VASc score of 2, 27% of cohorts reported stroke rates below 1% per year, and 40% reported stroke rates between 1% and 2% per year. Therefore, in contrast to the European Society of Cardiology guidelines, the 2023 ACC/AHA/Multisociety AF guideline recommendations on anticoagulation are based on magnitude of risk, as opposed to a traditional risk score. By acknowledging the concept of absolute risk, the 2023 ACC/AHA/Multisociety AF guideline opens the door to other risk scores that may modestly improve risk discrimination (C index) compared with $CHA_2DS_2$-VASc and may offer advantages in specific populations, such as the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) and GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation) scores,[40,41] which incorporate renal function as a risk factor. A stroke and systemic embolism risk threshold of ≥2% per year receives a Class 1 recommendation for anticoagulation, whereas those with an estimated risk of 1% to 2% receive a Class 2a recommendation.[17] Also, female sex is now considered a risk modifier rather than a risk factor, as female sex accentuates stroke risk in women who were already deemed candidates for anticoagulation based on additional risk factors.[42]

Hypertension is the risk factor with the highest attributable risk for AF; degree of blood pressure control may affect the risk of stroke, and is thus an important consideration.[17,43,44] Among patients with a $CHA_2DS_2$-VASc score of 1, because the magnitude of risk for each factor is heterogeneous, the 2023 ACC/AHA/Multisociety AF guideline gives a Class 2a recommendation for shared decision making for patients who remain uncertain about anticoagulation such that additional risk factors not incorporated in the traditional scores can be considered, such as type of AF, or the presence of other cardiac conditions associated with higher risk of stroke, such as hypertrophic cardiomyopathy.[45] For all patients with AF, DOACs are recommended over warfarin, except in patients with moderate to severe rheumatic mitral stenosis or those with mechanical heart valves.[17]

Three other scenarios warrant special comment. AF after cardiac surgery is common, observed in about 25% of patients, and associated with longer hospital stay and increased morbidity and mortality.[46] It is generally attributed to surgical factors, thus tends to be time-limited, resolving by about 2 months postoperatively, and its recurrence rate is lower than in patients with clinical AF.[47] The 2023 ACC/AHA/Multisociety AF guideline gives a Class 2a recommendation for patients with AF after cardiac surgery to receive anticoagulation when deemed safe in regard to surgical bleeding for 60 days after surgery and to reevaluate the need for longer-term anticoagulation at that time.[17] Secondly, recent clinical trials have questioned the role of anticoagulation for stroke prevention following catheter ablation of AF. The OCEAN (Optimal Anticoagulation for Enhanced Risk Patients Post-Catheter Ablation for Atrial Fibrillation) trial randomized 1,284 patients who were ≥1 year from a successful AF ablation procedure to rivaroxaban or aspirin. There was no difference in the primary outcome of stroke, systemic embolism, or new covert embolic stroke identified on brain magnetic resonance imaging between the 2 groups, with no statistical difference in the primary safety outcome of fatal or major bleeding.[48] In the ALONE-AF (Anticoagulation One Year After Ablation of Atrial Fibrillation in Patients With Atrial Fibrillation) trial, 840 patients in South Korea without documented

**TABLE 2 Changes in the 2023 ACC/AHA/Multisociety Guideline for Management of AF**

| |
|---|
| Recommendations for anticoagulation are now made based on yearly thromboembolic event risk using a validated clinical risk score, such as $CHA_2DS_2$-VASc, but other scores can be used when clinically useful. |
| Initiation of anticoagulation in patients with an estimated stroke and systemic embolism risk threshold of ≥2% per year (eg, $CHA_2DS_2$-VASc score of ≥2 in men and ≥3 in women) receives a Class 1 recommendation; those with an estimated risk of 1%–2% receive a Class 2a recommendation. |
| Patients with AF at intermediate to low (1%–2%) annual risk of ischemic stroke (eg, equivalent to $CHA_2DS_2$-VASc score of 1 in men or 2 in women) can benefit from consideration of factors that might modify their risk of stroke, such as the type of AF (eg, permanent vs paroxysmal), or the presence of an underlying cardiac substrate perceived to be of greater risk. |
| In terms of preferred agents, DOACs are recommended over warfarin, except in patients with moderate to severe rheumatic mitral stenosis and those with mechanical heart valves.[17] |

AF = atrial fibrillation; DOAC = direct oral anticoagulant.

AF recurrence ≥1 year following an AF ablation were randomized to continued DOAC therapy or discontinuation of DOAC.[49] The primary outcome of stroke, systemic embolism, and major bleeding occurred more frequently in the DOAC group, driven primarily from an increased bleeding risk. Further studies are needed to understand the optimal strategy of monitoring patients following AF ablation and determine when anticoagulation can be safely discontinued or reinitiated. The REACT-AF (NCT05836987, Rhythm Evaluation for Anticoagulation With Continuous Monitoring of Atrial Fibrillation) clinical trial will further attempt to address this issue.

Another area of uncertainty is how to manage subclinical device-detected AF, as observational studies have shown lower risk of stroke than in clinical AF. Two similar studies were recently published: ARTESIA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) showed that apixaban reduced stroke/systemic embolism risk by about one-third as compared to aspirin in patients with subclinical AF, but increased major bleeding,[50] whereas NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) trial found no significant difference in efficacy compared to no anticoagulation (aspirin/placebo), while also showing increased bleeding.[51] Thus, decisions on treating these patients require balancing a 1% to 1.2% annual stroke risk against a 1.6% to 2.5% increase in major bleeding. A subanalysis from the ARTESIA trial suggests that the benefit seems to exceed the risk of bleeding in patients with $CHA_2DS_2$-VASc score >4 (annual stroke/systemic embolism risk ~2.2%).[52]

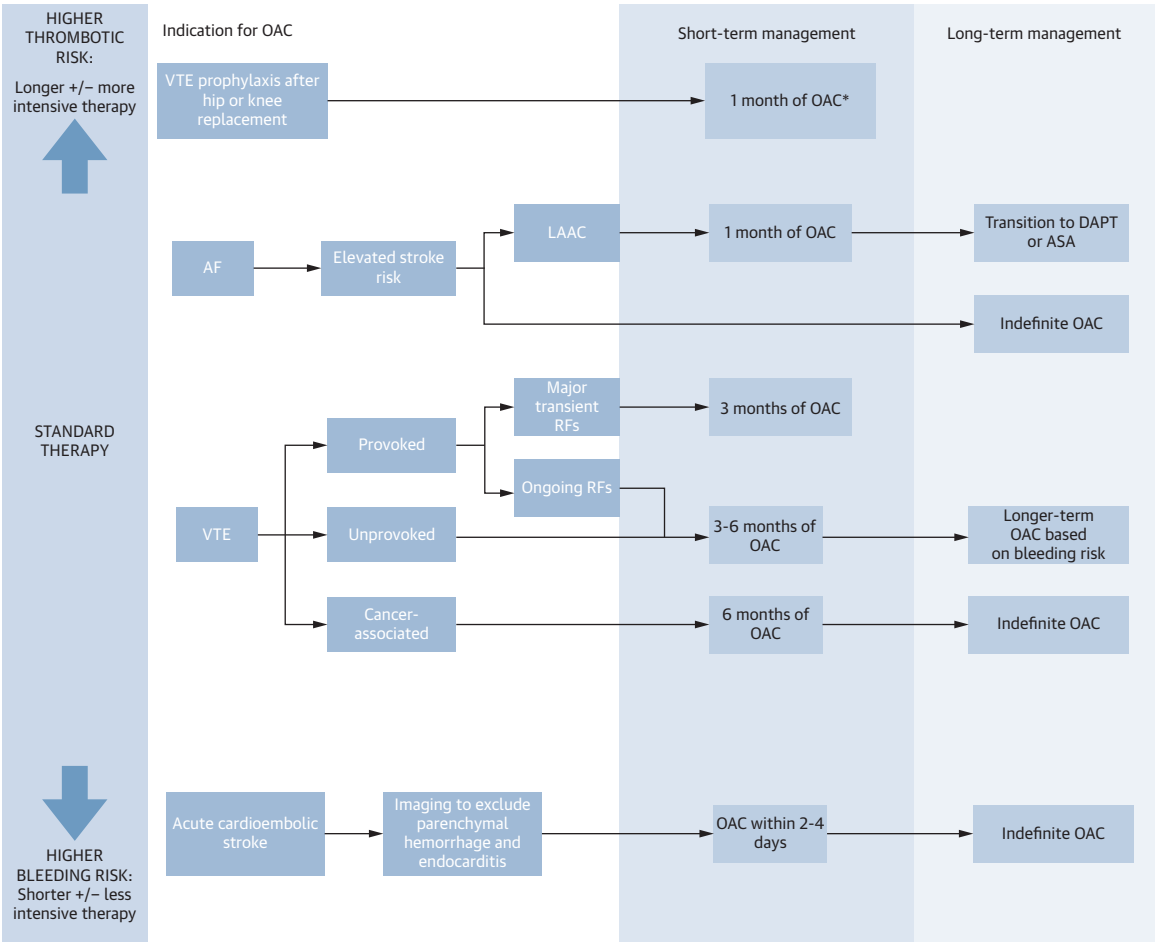
Less is known about the optimal approach for patients with atrial myopathy. This has also been identified as a risk factor for stroke, and typically refers to various structural detrimental changes within the atria, such as dilatation, scar, and fibrosis, which can potentially lead to stasis, endothelial dysfunction, and a hypercoagulable state. In view of structural changes, this process seems to be an important cause of stroke. Markers of atrial myopathy such as natriuretic peptides (eg, pro-B-type natriuretic peptide, midregional-pro-atrial natriuretic peptide), or markers of left atrial appendage dysfunction, have also been identified as markers of stroke; yet, the term remains poorly defined, and it remains unclear how to incorporate these findings into clinical practice or patient discussions.[17] This is an area of intense research because it could be that AF is an indirect marker of atrial myopathy, the causative substrate for stroke. Trials are ongoing to evaluate whether people with imaging and other biomarkers of AF will derive benefit from secondary prevention with DOACs compared to standard therapy with antiplatelets.[53,54]

### Primary prevention of VTE in patients undergoing surgery

Patients undergoing surgery resulting in immobility are at increased risk for the development of VTE. The risk of thromboembolism depends on both patient-level risk factors (history of prior thromboembolism, malignancy, increased age, obesity, heart failure, and use of hormonal drugs) and procedure-related factors (extent and duration of surgery, type of anesthesia, and postoperative mobility). For patients undergoing nonorthopedic surgery, the modified Caprini risk score,[55] which includes multiple variables such as age, type of surgery, immobility, prior VTE, cancer, or other thrombophilic states, can be used to stratify patients into very low (<0.5%), low (1.5%), moderate (3.0%), and high (6.0%) risk for VTE. For patients at moderate to high risk for VTE and low risk for bleeding, pharmacological antithrombotic therapy can be considered with fondaparinux or low molecular weight heparin (LMWH). The use of DOACs for the primary prevention of VTE in nonorthopedic surgeries has not been adequately studied.[56,57]

Patients undergoing lower extremity orthopedic surgery resulting in postsurgical immobility are at a higher risk for postoperative VTE, particularly in the setting of a fracture. Several large, randomized controlled trials (RCTs) have shown the safety and efficacy of reducing postoperative VTE with DOAC following total hip arthroplasty (THA) and total knee arthroplasty (TKA) surgery. The RECORD1 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism 1) trial randomized patients undergoing THA to rivaroxaban 10 mg daily for 35 days or enoxaparin 40 mg daily and found a significant reduction in VTE (as detected by bilateral venography), nonfatal PE, and death with rivaroxaban, with similar rates of bleeding.[58] Similarly, in the RECORD4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism 4) trial of patients undergoing TKA, rivaroxaban 10 mg daily for 10 to 14 days was superior to enoxaparin 30 mg twice daily for the prevention of VTE.[59] Further, apixaban 2.5 mg twice daily was found to be more effective than enoxaparin 40 mg daily for the reduction of VTE in THA and TKA.[60] Dabigatran (150 or 220 mg) daily was as effective as enoxaparin 40 mg daily in reducing postoperative VTE in THA[58] and TKA.[61] In contrast, ≥2 trials failed to demonstrate noninferiority of apixaban 2.5 mg twice daily or dabigatran 150 or 220 mg daily compared with enoxaparin 30 mg twice daily for thromboprophylaxis after TKA.[62,63] Overall, the evidence supports that both DOAC and LMWH are appropriate for VTE prophylaxis post-THA or TKA (**Central Illustration**). The American Society of Hematology 2019 Guidelines for Management of VTE recommend a DOAC over LMWH for patients undergoing TKA or THA to prevent VTE,[64] primarily due to easier

**CENTRAL ILLUSTRATION** **Duration of Anticoagulation in Clinical Scenarios**




**Kumbhani DJ, et al. JACC. 2026;88(11):1255–1283.**

*exact duration depends upon type of surgery. AF = atrial fibrillation; ASA = aspirin; DAPT = dual antiplatelet therapy; LAAC = left atrial appendage closure; OAC = oral anticoagulant; RF = risk factor; VTE = venous thromboembolism.

logistics and potentially better cost-effectiveness. The use of DOACs in patients undergoing hip fracture surgery has not been well evaluated, and LMWH is still preferred for thromboprophylaxis when indicated.[64] The use of aspirin has also shown efficacy to prevent VTE in patients post-THA or -TKA. The ongoing PEPPER (Pulmonary Embolism Prevention After Hip and Knee Replacement) trial is evaluating the efficacy of aspirin (81 mg twice a day), low-intensity warfarin (target international normalized ratio [INR] 1.7-2.2), and rivaroxaban (10 mg daily) for thromboprophylaxis in patients undergoing elective total hip and knee replacements.[65]

### Valvular heart disease

Valvular heart disease is associated with an increased risk for AF and VTE. Systemic anticoagulation is not routinely recommended for native heart valve stenosis or regurgitation. However, patients with rheumatic heart disease and AF are at significantly elevated risk for strokes, and thus anticoagulation to reduce the risk of AF-related stroke is recommended.[6] RCTs of DOACs for the prevention of VTE in AF have largely excluded patients with valvular heart disease (defined as moderate to severe mitral stenosis or presence of a mechanical valve). The INVICTUS (Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban, or Aspirin Studies) trial[66] randomized patients with moderate to severe mitral stenosis in the setting of rheumatic heart disease and AF to rivaroxaban or a VKA. Patients randomized to a VKA had lower rates of the composite outcome of stroke, systemic embolism, MI, or death with similar rates of bleeding.[66]

Accordingly, DOACs should not be used in this clinical situation.

Two high-quality RCTs have evaluated the safety and efficacy of DOACs in patients with mechanical valves. RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement) randomized patients with mechanical heart valves to dabigatran or warfarin. The trial was terminated early due to harm, with both higher thromboembolic and bleeding rates in the dabigatran arm.[67] The PROACT Xa (Prospective Randomized On-X Anticoagulation Clinical Trial) trial randomized patients with an On-X mechanical aortic valve (Artivion, Austin, Texas) to apixaban or warfarin. While bleeding rates were similar, patients randomized to apixaban had higher rates of valve thrombosis and valve-related thromboembolic events.[68] Based on these trials, a DOAC should not be used in patients with a mechanical valve. For surgical bioprosthetic valves, the 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease recommends warfarin (INR ~2.5) as a reasonable option (Class 2a) for the first 3 to 6 months after surgical bioprosthetic aortic or mitral valve replacement to reduce risk of valve thrombosis; aspirin 75 to 100 mg daily is also proposed for those who have no other indications for OAC (Class 2a). Although this is not universally practiced, VKA use is often considered in particular for bioprosthetic mitral valves, which have higher thrombotic risk; DOACs have not been well studied in this setting. For patients undergoing transcatheter aortic valve implantation, DOACs reduce subclinical leaflet motion abnormalities, such as hypoattenuated leaflet thickening and restricted leaflet motion on cardiac computed tomography angiography, compared with antiplatelet therapy, but without a demonstrated clinical benefit and with potential for harm.[69,70] Accordingly, routine OAC in people undergoing transcatheter aortic valve implantation without another indication for anticoagulation is not currently recommended. Patients who develop hypoattenuated leaflet thickening or clinical valve thrombosis can be treated successfully with DOACs, although this has not been studied in clinical trials.[71] OAC is generally recommended after transcatheter mitral or tricuspid valve replacement, though bleeding risk is often substantial given the advanced age and frailty of these patients.[72-74]

### Secondary prevention of thrombotic events in patients with atherosclerotic cardiovascular disease

In patients with chronic coronary disease who require anticoagulation, such as those with concomitant AF, it is critical to routinely assess bleeding and thrombotic risk. Due to elevated bleeding risk, combining DOACs with antiplatelet therapy should be limited to patients with a recent ACS or percutaneous coronary intervention (PCI), or high thrombotic risk. Following PCI, aspirin should be discontinued within 1 to 4 weeks to limit the duration of triple antithrombotic therapy. Dual antithrombotic therapy is indicated for 6 to 12 months following ACS or PCI. Clopidogrel is typically recommended as the $P2Y_{12}$ inhibitor of choice in this scenario due to a lower risk of bleeding. An important consideration is the DOAC dose used in this setting. While all DOACs have been evaluated in large trials, rivaroxaban is the only agent studied at a reduced dose (15 mg daily, or 10 mg with renal dysfunction) when combined with antiplatelet therapy, based on PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), whereas standard dosing was generally used for other DOACs.[75-80] In patients without an ACS or PCI in the past year, DOAC monotherapy at regular dosing without concomitant antiplatelet use can be considered.[81] Those with complex multivessel disease, previous stent thrombosis, or high-risk features related to the vessel or intervention can be considered for prolonged dual antithrombotic therapy. Use of a proton pump inhibitor with this combination has been associated with a decrease in gastrointestinal bleeding.[82]

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial[83] demonstrated that adding rivaroxaban 2.5 mg twice daily to low-dose aspirin significantly reduced MACE and total mortality in patients with stable CAD or peripheral artery disease (PAD), despite a higher risk of major nonfatal bleeding. Important exclusion criteria were patients with prior stroke or prior major bleeding. The COMPASS trial also demonstrated that rivaroxaban 5 mg twice daily alone did not significantly reduce MACE versus aspirin alone and increased major bleeding, arguing against oral full-dose DOAC alone as a substitute for aspirin beyond 1 year.[83] The 2023 AHA/ACC/Multisociety Guideline for the Management of Patients With Chronic Coronary Disease supports the addition of low-dose rivaroxaban (2.5 mg twice daily) to aspirin in patients without an indication for full-dose anticoagulation or dual antiplatelet therapy (DAPT) who have high ischemic risk and low to moderate bleeding risk, as a reasonable strategy to reduce long-term MACE (Class 2b recommendation).[81] Similarly, rivaroxaban 2.5 mg twice daily along with low-dose aspirin demonstrated a benefit in patients with PAD undergoing revascularization in the VOYAGER PAD (Vascular Outcomes Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) trial; this strategy is recommended in the 2024 ACC/AHA/

Multisociety Guideline for the Management of Lower Extremity PAD.[84]

### Consensus recommendations: DOACs for primary prevention of VTE and stroke

- Both DOACs and LMWH are appropriate for VTE prophylaxis post-THA or TKA; DOACs are preferred when possible.
- DOACs are appropriate for use in most patients with valvular heart disease and AF, except those with rheumatic mitral stenosis. In addition, they are inferior to VKAs for patients with mechanical valves in preventing thromboembolic events.
- Routine OAC with a DOAC in patients who undergo transcatheter aortic valve implantation without another indication for anticoagulation is not currently recommended.
- For many patients with chronic coronary disease and need for anticoagulation, DOAC monotherapy at regular dosing is a reasonable long-term strategy. In addition, rivaroxaban 2.5 mg twice daily can be considered in conjunction with low-dose aspirin therapy among high-risk patients with CAD or PAD to reduce risk of myocardial infarction, stroke, and cardiovascular death.

### VTE management

Analysis of risk factors for VTE, such as cancer, surgery, prior episodes of VTE, immobilization, and thrombophilic states, allow for estimation of clinical probability, which is needed to support diagnosis and treatment. Validated clinical prediction tools include Wells' criteria,[85] PE Rule Out Criteria (PERC),[86] and the Revised Geneva Score.[87] They also drive the dosing and duration of treatment. For specific considerations of VTE management in individuals with cancer, refer to the "Special considerations: cancer and VTE" section in the following text.

### Initial treatment in the acute phase

Treatment in the acute phase is used to prevent recurrence, especially for PE, which can be lethal; therefore, higher dosing is used in the initial days of treatment for PE and DVT. Acute-phase mortality due to PE varies depending on clinical presentation. The 2026 AHA/ACC/Multisociety Guideline for the Evaluation and Management of Acute PE in Adults recommends the use of an algorithm to determine the level of acute care for hospitalization and type of treatment depending on clinical severity. Patients with subclinical PE or symptomatic PE with a low clinical severity score (simplified Pulmonary Embolism Severity Index [sPESI] or Hestia scores) can be managed in outpatient settings, but those with symptomatic PE with an elevated clinical severity score, PE with incipient normotensive shock, and PE with cardiopulmonary failure will be hospitalized.[88] DVT is mostly treated in an outpatient setting, except in scenarios such as proximal acute DVT resulting in phlegmasia cerulea dolens or patients with cardiopulmonary or renal failure.[88]

**TABLE 3 DOAC Dosing Strategy for Initial Management and Treatment of VTE**

| Initial Management | Primary Treatment |
|---|---|
| Heparin (UFH or LMWH) ≥5 days | Dabigatran 150 mg twice daily (up to 6 months)[96] |
| Heparin (UFH or LMWH) ≥5 days | Edoxaban 60 mg daily (up to 6 months)[97] |
| Rivaroxaban 15 mg twice daily for 21 days | Rivaroxaban 20 mg daily (up to 6 months)[90,91] |
| Apixaban 10 mg twice daily for 7 days | Apixaban 5 mg twice daily (up to 6 months)[92] |

LMWH = low molecular weight heparin; UFH = unfractionated heparin.

All pivotal trials testing DOACs versus VKAs and heparin reached noninferiority for VTE recurrence and superiority for major bleeding, especially intracranial and fatal bleeding.[89-94] A subsequent meta-analysis confirmed the efficacy and safety of DOACs to treat VTE. In 24,390 patients, recurrence occurred in 2.0% of patients treated with DOACs versus 2.2% among patients treated with VKA (RR, 0.88 [95% CI: 0.74-1.05]). Mortality was the same in both groups: 2.4% with DOACs versus 2.4% with VKA. Major bleeding complications were lower: 1.1% with DOACs versus 1.7% with VKA (RR, 0.60 [95% CI: 0.41-0.88]; P = 0.03). DOACs are now first-line treatment for VTE according to American Society of Hematology guidelines.[95] For initial treatment, different strategies exist, depending on trial design and medications as shown in Table 3. Rivaroxaban and apixaban are preferred, as concomitant heparin use is not required. Dose adaptations are not allowed as in AF (eg, rivaroxaban 15 mg daily is not a validated dosage possible in VTE). VKA is no longer prescribed except in cases of severe renal insufficiency with creatinine clearance <30 mL/min, moderate to severe liver disease, or antiphospholipid syndrome (APS). For most patients with acute VTE planned to receive a DOAC, apixaban should be considered as the treatment of choice. This is supported by the recent results of the Comparison of Bleeding Risk Between Rivaroxaban and Apixaban (COBRRA) trial, in addition to earlier observational studies[98] and a network meta-analysis.[99] In the COBRRA trial, among patients with acute VTE randomized to apixaban or rivaroxaban,

**TABLE 4 Considerations for DOAC Use in Increased Risk Cohorts**

| | Direct Thrombin Inhibitor | Factor Xa Inhibitor | | |
|---|---|---|---|---|
| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
| **CKD** | | | | |
| • **Stage 4** | Outcomes similar to warfarin<br>FDA: 75 mg twice daily<br>EMA: Contraindicated | Preferred; ↓ stroke/bleeding vs warfarin<br>FDA: 5 or 2.5 mg twice daily*<br>EMA: 2.5 mg twice daily | Limited data<br>FDA: 30 mg once daily<br>EMA: 30 mg once daily | Outcomes similar to warfarin<br>FDA: 15 mg once daily<br>EMA: 15 mg once daily |
| • **Stage 5/ Dialysis** | Removed with dialysis<br>FDA: Contraindicated<br>EMA: Contraindicated | Limited PK data<br>FDA: 5 or 2.5 mg twice daily*<br>EMA: Contraindicated | FDA: Contraindicated<br>EMA: Contraindicated | FDA: 15 mg once daily<br>EMA: Contraindicated |
| **Liver Disease** | | | | |
| • **Child-Pugh A** | Reasonable, no dose adjustment | | | |
| • **Child-Pugh B** | Use with caution | Use with caution | Use with caution | Avoid use |
| • **Child-Pugh C** | Avoid use; insufficient data | | | |
| **Frailty/Advanced Age** | Benefit over VKA mostly in nonfrail | Best safety profile of DOACs in retrospective data | Consider low-dose (15 mg) option in individuals where OAC is typically not recommended | Benefit over VKA mostly in nonfrail |
| **Class 3 Obesity (BMI ≥40 kg/m$^2$)** | Not recommended | Preferred | Not recommended | Preferred |
| **Post-Bariatric Surgery** | Absorption concerns; consider warfarin instead of DOAC | | | |
| **Prior Bleeding/ HBR** | Consider low dose (110 mg twice daily) if available | Preferred (↓ICH, ↓GI bleed compared with VKA) | Consider low-dose (15 mg) option in individuals where OAC is typically not recommended | Not preferred |

*2.5 mg twice daily for nonvalvular AF if 2 of the following are present: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg).

AF = atrial fibrillation; BMI = body mass index; CKD = chronic kidney disease; DOAC = direct oral anticoagulant; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HBR = high bleeding risk; ICH = intracerebral hemorrhage; OAC = oral anticoagulant; PK = pharmacokinetic; VKA = vitamin K antagonist.

clinically relevant bleeding was less frequent with apixaban (3.3%) compared to rivaroxaban (7.1%) (relative risk 0.46 (0.3-0.65) during the 3 month treatment duration. Both GU and GI bleeding were lower among apixaban-treated patients.[100]

### Maintenance dosing

After 5 to 21 days of initial management, maintenance dosing with a DOAC is continued for 3 to 6 months, as outlined in Table 3. After primary treatment, therapy may be extended, as studies have shown that recurrence may occur; this depends on the ratio between bleeding risk over recurrence. Several calculators are available to estimate bleeding risk with DOACs. Further, high bleeding-risk cohorts require careful considerations (Tables 4 and 5). In addition, risk stratification tools such as HERDOO2 (Hyperpigmentation, Edema, or Redness; D-dimer; Obesity; Older age) can help identify patients at lowest risk of recurrence.[101] When VTE is provoked, that is, occurrence in the setting of a major transient risk factor, such as surgery or immobilization, the risk of recurrence is low (~2%/y), and generally does not require long-term anticoagulation. When VTE occurs in the absence of identifiable provoking risk factors, the risk of recurrence is higher, approximately 10% per year; the benefit of continuing therapy is likely, as shown in the PADIS-PE (Prolonged Anticoagulation During Eighteen Months vs. Placebo After Initial Six-Month Treatment for a First Episode of Idiopathic Pulmonary Embolism) study 42 months after inclusion.[102] Regardless of treatment duration in those with unprovoked VTE, recurrence occurs when treatment is stopped and follows the initial form of VTE in 80% of cases. PE recurrence is fatal in 10% of cases. Bleeding complications occur at a rate of approximately 5% annually.

### Secondary prevention: indications, duration, dosing

As bleeding complications are less frequent with DOACs, several trials have tested the benefit of continuing DOACs for extended therapy after VTE with reduced doses to avoid bleeding complications.[95,103,104] Extended therapy can be pursued with apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily, or dabigatran 150 mg twice daily. Edoxaban can also be prescribed for long-term use, as data from the RIETE (Registro Informatizado de Enfermedad TromboEmbólica) registry show good efficacy and tolerance, but this has not been tested in a trial.[105]

For apixaban, the AMPLIFY-EXT (Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis With First-Line Therapy-Extended Treatment) study demonstrated a better antithrombotic profile with lower bleeding risk, using 2.5 mg twice daily compared with 5 mg twice daily. Importantly, apixaban 2.5 mg twice daily has not been directly compared with 5 mg twice daily, but each dosage was compared with the placebo. For patients presenting with VTE occurring after a transient provoking factor and a persistent risk factor (such as inflammatory disease, arterial disease, body

mass index [BMI] >30 kg/m$^2$), the HI-PRO (Extended-Duration Low-Intensity Apixaban to Prevent Recurrence in High-Risk Patients With Provoked Venous Thromboembolism) study showed that extended therapy with apixaban 2.5 mg twice daily for 12 months is superior to placebo due to a low risk of VTE recurrence and low risk of bleeding.[106]

Rivaroxaban 10 mg daily was compared with placebo and aspirin 100 mg daily in the EINSTEIN CHOICE (Reduced-Dosed Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism) trial and was found to be superior to both aspirin and placebo to prevent recurrence.[103] The efficacy and safety profile of apixaban and rivaroxaban, comparing full and reduced doses for long-term extended therapy, was tested in the RENOVE (Reduced Dose Versus Full-Dose of Direct Oral Anticoagulant After Unprovoked Venous Thromboembolism) trial with a long follow-up of 5 years; although the reduced dose did not meet the noninferiority criteria, the low recurrence rates in both groups and a substantial reduction of clinically relevant bleeding with the reduced dose support the consideration of this regimen as an option.[107] Low-dose aspirin monotherapy provides modest benefit for secondary prevention of recurrent VTE after completion of anticoagulation, reducing recurrence risk by approximately 30% to 40%; however, it is substantially less effective than extended anticoagulation with DOACs.[103,104,108-110]

## Consensus recommendations: management and secondary prevention of VTE

- DOACs are recommended as initial treatment for VTE in most patients, except in select populations (eg, mechanical valves, severe renal dysfunction). Loading doses are different from maintenance dosing. Recent data suggest that an apixaban strategy may be superior to a rivaroxaban strategy due to lower bleeding and may be the agent of choice in this setting.
- Extended treatment (beyond 6 months) to prevent VTE should be considered for patients presenting with unprovoked VTE, those with recurrent episodes, and for those with a high risk profile of recurrence including multiple permanent risk factors. The treatment duration is typically indefinite, but bleeding risk should be reevaluated regularly. DOACs are superior to VKAs for this indication in view of superior efficacy and lower risk of major bleeding compared to warfarin. Aspirin monotherapy has limited benefits for extended treatment of VTE.
- Apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or rivaroxaban 10 mg daily can be used if extended anticoagulant treatment is indicated. Apixaban 2.5 mg twice daily has comparable efficacy to apixaban 5 mg twice daily with lower major bleeding. Dabigatran 150 mg twice daily can be prescribed for extended treatment; no dose reduction has been tested. Edoxaban has not been tested for extended treatment, but real-life studies suggest good tolerance and efficacy.

## Thrombophilic states: coagulation inhibitor deficiency and APS

### Coagulation inhibitor deficiency

RCTs of DOAC efficacy in patients with coagulation inhibitor deficiencies such as antithrombin, protein C, or protein S have not been performed, but DOACs are routinely used in this scenario. They interfere with antithrombin, protein C, and protein S dosage, with all published data suggesting reduced bleeding events and a low overall VTE recurrence.[111,112] As each patient may have individualized risk of thrombosis, depending on the type of inherited thrombophilia, it is difficult to formulate blanket recommendations for these patients. Overall, DOACs are a good option for most patients with thrombophilia when anticoagulant therapy is indicated, as DOACs have few drug-drug interactions, oral route of administration, and allow for rapid treatment.

### APS

Patients with high-risk APS should be treated with VKA. This includes patients with triple positive antibodies (anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies, lupus anticoagulant), arterial thrombosis, small vessel or organ involvement, or concomitant valve disease.[113,114] For patients with VTE and 1 positive antibody, VKAs are again preferred because data are lacking to support the use of DOACs for this indication; series studying their use have been small and inconclusive. Use of DOACs in APS may be followed by arterial thrombosis over time, and VKAs have a clear advantage. Reasons for the lack of efficacy of DOACs in APS are still unknown. Further, the roles of a higher dosage of DOACs, type of thrombosis, and involvement of microcirculation are unresolved questions.

## Secondary prevention in patients with history of stroke and AF

### Timing of anticoagulation initiation in people with AF-related acute ischemic stroke

In individuals with AF, starting anticoagulation early after an acute ischemic stroke may reduce the risk of recurrent stroke; on the other hand, early anticoagulation may increase hemorrhagic transformation of infarcted brain tissue resulting in additional neurological disability and death.[115] Four RCTs investigated the safety and efficacy of early versus later DOAC initiation by comparing composite endpoints. These comprised various combinations of ischemic and hemorrhagic outcomes, both cerebrovascular (ie, recurrent ischemic stroke and

intracerebral hemorrhage [ICH]), and other vascular outcomes (ie, systemic embolism and major extracranial bleeding).[116-119] CATALYST (Collaboration on the Optimal Timing of Anticoagulation After Ischaemic Stroke and Atrial Fibrillation), an individual participant-level meta-analysis of 4 RCTs (n=5,441; median National Institutes of Health Stroke Score of 5) compared early (≤4 days) versus later (≥5 days) DOAC initiation after stroke.[120] Early initiation was associated with a lower risk of the 30-day composite outcome of recurrent ischemic stroke, symptomatic intracranial hemorrhage, or unclassified stroke (odds ratio, 0.70; 95% CI: 0.50-0.98; P=0.04). These benefits were consistent across key prespecified subgroups including initial clinical stroke severity, reperfusion treatment, and previous use of OACs. Most of these benefits were due to reduced risk of recurrent ischemic stroke at day 30. The symptomatic ICH event rate was low (<0.5%) and did not differ between groups at days 30 or 90. Based on these studies, the 2026 AHA/American Stroke Association Guideline for the Early Management of Patients With Acute Ischemic Stroke provides a Class 2a recommendation for early initiation of anticoagulation among patients with milder severity acute ischemic stroke and known AF. This guideline also advises against routine early anticoagulation (within 48 hours) among unselected patients with acute ischemic stroke due to unclear benefit and potential for harm (Class 3).[121]

### Consensus recommendations: secondary prevention after acute stroke

- For people with acute ischemic stroke and AF, DOAC initiation within 4 days reduces the risk of the composite outcome of recurrent ischemic stroke, symptomatic ICH, or unclassified stroke within 30 days. This assumes exclusion of people with very severe stroke, severe space occupying hemorrhagic transformation, and endocarditis.

### Management of people with "breakthrough" stroke

It is not uncommon in clinical practice to encounter patients with AF who have experienced cerebrovascular events despite being on DOAC, and these cases are linked to a poor prognosis. The mechanism underlying DOAC failure is not yet fully understood, which complicates the prevention of recurrent events. The main focus in secondary prevention should be on excluding alternative reasons for stroke and those cases where OAC was insufficient. In breakthrough strokes with no evidence of underdosing or nonadherence, many clinicians change OAC type; however, available observational studies do not support this practice.[115] Addition of antiplatelet therapy to anticoagulation in people with a risk of cardiovascular disease increases the risk of hemorrhage without decreasing the risk of ischemic events and is therefore not recommended, although RCTs in people with breakthrough stroke are lacking. Left atrial appendage closure (LAAC) for patients with AF and a breakthrough stroke is a promising alternative to pharmacological approaches and is currently being tested in RCTs.[122,123]

### Reinitiation of OAC in people with AF and ICH

Patients with prior ICH have historically been excluded from pivotal RCTs evaluating anticoagulation in AF, leaving significant uncertainty regarding the net clinical benefit of restarting anticoagulation in this population. A recent meta-analysis of 798 patients with spontaneous ICH from 6 RCTs (median time from ICH ~3 months; mean $CHA_2DS_2$-VASc score 4.2) found that, compared with avoiding anticoagulation, resuming anticoagulation reduced the rates of new ischemic stroke (RR, 0.20; 95% CI: 0.06-0.72) and ischemic MACE (RR, 0.41; 95% CI: 0.23-0.75), but with a higher rate of recurrent ICH (RR, 3.14; 95% CI: 1.41-7.01) and hemorrhagic MACE (RR, 2.35; 95% CI: 1.32-4.21). All-cause mortality and cardiovascular death at 90 days did not differ between the 2 groups. The optimal timing and strategy remain unclear.[124] The 2023 ACC/AHA/Multisociety AF guideline recommends waiting at least 4 to 8 weeks before considering resumption of OAC in these patients, carefully balancing ischemic risk against the risk of recurrent ICH or other bleeding events (Class 2b).[17]

### Consensus recommendations: OAC in ICH

- Restarting anticoagulation in people with AF and ICH lowers ischemic events but raises risks of recurrent ICH and major bleeding, without a clear early mortality difference. For most patients, waiting 4-8 weeks is prudent. The net long-term benefit remains uncertain.
- LAAC may be considered to reduce thromboembolic events in people with prior ICH and AF who are considered unsuitable for long-term OAC therapy (eg, people with imaging or pathological evidence of cerebral amyloid angiopathy).

## SPECIAL CONSIDERATIONS FOR USE OF DOACs

### Chronic kidney disease stage IV to V and end-stage kidney disease

While chronic kidney disease (CKD) is itself an independent risk factor for stroke and thrombosis,[125] data specific to patients with advanced kidney disease remain limited because these patients were excluded from most clinical trials. An important consideration is that many pivotal DOAC trials used creatinine clearance thresholds for enrollment rather than estimated glomerular filtration rate, and creatinine clearance can overestimate[17] renal function.

For CKD stage 4 (creatinine clearance 15-30 mL/m$^2$/min), data are derived largely from observational studies. The ACC/AHA/Multisociety AF guideline provides a Class 2a recommendation for warfarin or labeled doses of DOACs to reduce the risk of stroke in this cohort.[17] Overall, the totality of data[126] suggest relative safety and efficacy of the DOACs compared with warfarin across a range of renal function. In a large Medicare analysis including patients with CKD stages 3 to 5,[127] apixaban was associated with decreased risk of stroke, systemic embolism, and bleeding compared with warfarin. In contrast, outcomes with rivaroxaban and dabigatran did not differ from warfarin. Dosing considerations were not reported in this study. Consistent with these findings, the 2024 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline[128] supports the use of DOACs in stage 4 CKD.

Most pivotal DOAC trials excluded individuals with end stage kidney disease (ESKD) receiving dialysis so there are limited data to guide anticoagulation in this population. A small pharmacokinetic study[129] in 7 hemodialysis patients demonstrated that apixaban 2.5 mg twice daily resulted in drug exposure comparable to that of 5 mg twice daily in individuals with normal renal function. However, there are no high-quality clinical data supporting the use of apixaban 2.5 mg. A small RCT comparing apixaban 2.5 mg twice daily with the VKA phenprocoumon in patients with AF on hemodialysis suggested no differences in efficacy or safety, but this study did not meet its prespecified noninferiority criteria due to slow enrollment. A retrospective cohort study using Medicare data between 2010 and 2015 compared OAC in patients with ESKD and AF, finding that apixaban use may be associated with a lower risk of bleeding compared with warfarin, and that apixaban 5 mg twice daily appeared to be associated with reductions in thromboembolic and mortality risk. Similarly, an analysis of patients with ESKD in the U.S. Renal Data System found that in patients with nonvalvular AF undergoing dialysis, label-concordant apixaban dosing was associated with a lower risk of bleeding and a mortality benefit compared with warfarin, while below-label apixaban dosing was not associated with less bleeding than label-concordant dosing, suggesting that label-concordant dosing may offer the most favorable benefit-to-risk profile.

Dabigatran is the only DOAC that is substantially removed by dialysis,[130,131] and is therefore not recommended in this setting. The ACC/AHA/Multisociety AF guideline[17] provides a Class 2b recommendation for warfarin or an evidence-based dose of apixaban in those with end-stage CKD. A recent meta-analysis[132] found no significant differences in rates of thromboembolic events and major bleeding between DOACs and VKAs in individuals with AF and ESKD. The U.S. Food and Drug Administration (FDA) and European Medicines Agency recommended doses for DOACs in CKD stages 4 to 5 are shown in **Table 4**.

### Consensus recommendation: DOACs in patients with CKD/ESKD

- In CKD stage 4/5 and on dialysis with risk for thromboembolism, there are limited data to guide DOAC use. Apixaban can be considered for nonvalvular AF (with label-concordant dosing). Dabigatran should be avoided in dialysis patients due to significant renal clearance.

### Liver disease

Retrospective, observational data[134-136] suggest that compared with no OAC, anticoagulant therapy is associated with lower risks of stroke and thromboembolism but higher risks of major bleeding and ICH in patients with liver disease. The American Gastroenterological Association[137] notes that anticoagulation is generally well tolerated and reduces stroke risk in patients with well-compensated cirrhosis. In practice, anticoagulation should be avoided with severe thrombocytopenia (platelet count <50,000/uL), and screening for varices should be performed.[133]

Meta-analyses comparing DOACs with VKA[138-140] demonstrate lower risks of major bleeding and ICH with DOAC therapy in those with liver dysfunction. Accordingly, the 2023 ACC/AHA/Multisociety AF guideline recommends preferential use of DOACs over warfarin in patients with Child-Pugh class A or B liver disease. Given hepatic metabolism of factor Xa inhibitors, especially apixaban and rivaroxaban, liver dysfunction may increase plasma concentrations. A systematic review evaluating DOACs[141] suggests that all DOACs appear safe in Child-Pugh class A disease. In Child-Pugh class B, apixaban, dabigatran, and edoxaban are reasonable options, whereas rivaroxaban generally should be avoided. There is insufficient evidence to support DOAC use in Child-Pugh class C cirrhosis.

### Consensus recommendation: DOACs in patients with liver disease

- In individuals with liver disease, the use of OAC is based on Child-Pugh class stages. All DOACs appear safe with Child-Pugh class A. For Child-Pugh class B, apixaban, dabigatran, and edoxaban can be used, whereas rivaroxaban should be avoided. For Child-Pugh class C, there is insufficient evidence to support DOAC use.

### Frailty and advanced age

Frailty is common in older adults and reflects diminished physiologic reserve across physical, cognitive, and social domains. Assessment is multidimensional, with most

tools capturing 1 or more core phenotype features: slowness, weakness, low activity, exhaustion, and unintentional weight loss.[142] One of the greatest concerns in frail patients is fall risk, with a consequent increase in major bleeding, including intracranial hemorrhage, among those receiving OAC. Despite this, frailty alone should not be considered a contraindication to OAC because observational studies consistently demonstrate benefit in elderly and frail patients. A retrospective study of individuals ≥90 years of age[143] with AF found that OAC use was associated with lower stroke risk with no difference in ICH compared with no treatment. DOAC was associated with a lower risk of ICH compared with warfarin. In a large propensity-matched cohort study[144] of frail patients aged ≥65 years with AF, OAC was associated with reduced ischemic stroke and cardiovascular death without increased major bleeding, with DOACs demonstrating favorable outcomes compared with warfarin, particularly in patients with $CHA_2DS_2$-VASc scores of ≥3. A registry-based analysis[145] similarly showed lower mortality and cardiovascular events with DOACs in patients aged ≥80 years.

Among the DOACs, apixaban has demonstrated a consistent benefit[144] across a range of nonfrail, prefrail, and frail populations, with lower risks of death, stroke, and major bleeding compared with warfarin. In contrast, dabigatran and rivaroxaban appeared to confer benefit primarily in nonfrail patients compared with warfarin. The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial[146] enrolled patients aged ≥80 years with nonvalvular AF (mean $CHA_2D_2$-VASc score 3.1) in whom OAC was considered unsuitable because of bleeding risk, including nearly one-third with a fall in the year prior to enrollment. Participants were randomized to low-dose edoxaban (15 mg daily) or placebo. Regardless of frailty status, edoxaban was associated with lower rates for stroke or systemic embolism. Major bleeding events (primarily gastrointestinal) were numerically higher with edoxaban with no interaction by frailty status.

COMBINE-AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation)[147] included patient-level data from 5 clinical trials and specifically examined outcomes in frail, elderly individuals switching from warfarin to DOAC. It found that stroke, systemic embolism, and death were reduced with DOACs, with similar rates of major bleeding (although higher gastrointestinal bleeding). In contrast, the FRAIL-AF (Frailty and Atrial Fibrillation) study[148] found higher bleeding rates without thromboembolic benefit when older (aged ≥75 y), frail patients stable on VKA therapy were switched to a DOAC, likely reflecting differences in baseline stability on VKA and frailty definitions.

### Consensus recommendation: DOAC in patients with frailty

- In frail individuals at risk for thromboembolism, apixaban is preferred because it shows consistent benefit across the range of frailty status and poses a lower risk of bleeding.
- In elderly, frail patients in whom standard dose anticoagulation is typically not recommended despite thromboembolism risk, low-dose edoxaban (15 mg daily) can be considered.

## Obesity

While individuals with class 3 obesity (BMI ≥40 kg/m$^2$) have been underrepresented in major clinical trials for DOACs, post hoc analyses[149-151] suggest comparable efficacy and safety of DOACs and VKAs. Several meta-analyses[152-154] have shown that DOACs are associated with favorable outcomes compared with warfarin for thromboembolic events, major bleeding, and mortality in patients with obesity. In a study focusing specifically on patients with BMI ≥40 kg/m$^2$, DOAC therapy was associated with similar risks of stroke and systemic embolism, but lower rates of recurrent VTE and major bleeding events compared with VKA use.[154]

Guidance from the International Society on Thrombosis and Haemostasis[155] recommends that any DOAC is appropriate for patients with BMI up to 40 kg/m$^2$. For BMI ≥40 kg/m$^2$, rivaroxaban or apixaban are appropriate options, whereas dabigatran and edoxaban are not recommended due to insufficient data. Further, monitoring of peak or trough DOAC levels is not supported by available evidence.

In patients who have undergone bariatric surgery, concerns exist regarding impaired drug absorption. A meta-analysis found that the pooled proportion of peak DOAC levels within the expected range was 58%.[156] Accordingly, the 2023 ACC/ACC/Multisociety AF guideline provides a Class 2b recommendation for the use of warfarin as a reasonable alternative over DOAC in patients with prior bariatric surgery.[17]

### Consensus recommendation: DOACs in patients with obesity

- In individuals with class 3 obesity (BMI ≥40 kg/m$^2$) and at risk for thromboembolism, rivaroxaban or apixaban are appropriate options.

## Prior bleeding or high risk for bleeding

Across studies, the net clinical benefit of stroke prevention generally outweighed risks of bleeding, even in patients at increased risk of bleeding.[156-159] A meta-analysis[160] suggested that restarting OAC after a major bleeding event in AF may be associated with clinical benefit due to a reduction in thromboembolism and mortality, despite a recurrent bleeding risk. Following a bleeding event, a review of modifiable bleeding risk

factors should be performed. In addition, the determination to restart therapy after a bleeding event is dependent on bleeding location, severity, and patient characteristics. Those patients with lower stroke risk, remote VTE, or remote bioprosthetic valve placement may consider discontinuation of anticoagulation. In patients who have experienced a gastrointestinal bleed, resumption of anticoagulation 7 to 14 days following hemostasis can be considered.

The CHEST antithrombotic therapy[161] and ACC/AHA/Multisociety 2023 AF Guideline[17] favor DOACs over warfarin in patients with prior unprovoked bleeding or elevated bleeding risk, given the lower risk of ICH with DOACs. In particular, apixaban or low-dose dabigatran (110 mg twice daily) are preferred because they are not associated with increased gastrointestinal bleeding compared with warfarin.

Patients with cerebral amyloid angiopathy on OAC represent another high-risk subset from a bleeding perspective. Data specific to DOAC use in these patients are limited, and the decision regarding anticoagulation may depend on location, burden, and individualized risk assessment. Patients with cortical superficial siderosis or a prior lobar ICH may have the highest risk of future hemorrhage.[162] An individual patient-level meta-analysis found that OAC had uncertain effects[163] on most outcomes in patients with a history of AF and intracranial hemorrhage, underscoring the need for additional data. LAAC is a reasonable alternative to long-term OAC in these patients[164] and carries a Class 2a recommendation in the 2023 ACC/AHA/Multisociety AF Guideline.[17]

Commonly used risk scores including HAS-BLED (Hypertension, Abnormal renal function, Stroke history, Bleeding history or disposition, Labile INR, Elderly, Drugs),[165] ATRIA,[40] and GARFIELD-AF have modest discriminatory ability for predicting bleeding events.[166-168] The components of these scores incorporate clinical factors that may increase both the risk of stroke and bleeding, making it difficult to balance the risks and benefits of anticoagulation. The DOAC score was developed specifically for DOAC use and showed a C statistic ranging from 0.65 to 0.71 in validation cohorts.[169] Subsequent comparison of the HAS-BLED and DOAC scores showed similar performance of the 2 models.[170]

### Consensus recommendation: DOACs in patients with prior bleeding or elevated bleeding risk

- In patients with a history of prior bleeding or elevated bleeding risk who require anticoagulation, apixaban or low-dose dabigatran (110 mg twice daily) are preferred.

## Cancer and VTE

VTE is a frequent complication of cancer, with up to a 23-fold higher risk in patients receiving chemotherapy compared with individuals without cancer.[171] As cancer survival improves, the cumulative burden of CAT increases, underscoring the need for adequate treatment, considering that CAT can be life-threatening. A personalized strategy should be proposed to the patient that accounts for patient-specific risk factors, anticancer therapy, drug-drug interactions, and patient preferences. In patients with cancer, routine thromboprophylaxis is not recommended because the absolute risk reduction is modest and must be balanced against bleeding risk. In select high-risk ambulatory patients with cancer (excluding multiple myeloma, acute leukemia, myeloproliferative neoplasms, and patients with primary/metastatic brain tumors), such as those initiating systemic chemotherapy and identified using dedicated risk stratification tools such as the Khorana score,[172] prophylactic anticoagulation with a DOAC (apixaban or rivaroxaban) or LMWH (dalteparin or enoxaparin) may be considered, provided there are no significant bleeding risks or drug-drug interactions.[173-175]

### Initial treatment

Patients with CAT and active cancer should be treated with anticoagulation. Active cancer is defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment has been administered within the past 6 months; or hematological disease that is not in complete remission.[176] CAT includes proximal DVT and PE, with incidental PE treated as equivalent to symptomatic PE given similar prognosis.[177] Isolated distal DVT may be treated similarly to proximal DVT considering the risk of recurrence, to be balanced with the bleeding risk.[178,179]

For the first 6 months, DOACs or LMWH are the best options to treat CAT, based on the results of prospective trials. Overall, DOACs are generally preferred over LMWH for the treatment of CAT because they are associated with a lower risk of VTE recurrence and a similar overall risk of major bleeding.[180,181] Apixaban is best supported by the Caravaggio (Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer) trial, where no difference in major bleeding or clinically relevant nonmajor bleeding was found between LMWH and apixaban among patients with CAT.[182] Rivaroxaban and edoxaban are also acceptable options for CAT except in urologic cancers, luminal gastrointestinal tract cancers (especially before surgery if intraluminal tumor is present), and gynecological cancers (especially cervical cancer). Dabigatran has not been evaluated in patients with CAT and therefore is not recommended in this setting.[180,183,184] Switching anticoagulant therapy during the first 6 months is appropriate when clinically indicated, including in cases of intercurrent events, drug-drug interactions, or changes in patient profile.

LMWH may be preferred in the following clinical scenarios:

- Renal insufficiency, with creatinine clearance <30 mL/min
- High bleeding-risk tumor types or locations, including esogastric tumor or nonresected colorectal tumor, nonresected urothelial or gynecological tumor (especially cervical cancer), metastatic renal cell carcinoma, melanoma, primary or secondary tumors adjacent to pulmonary vessels, inoperable breast cancer with skin involvement
- Drug-drug interactions with OACs
- Malabsorption
- Poor general condition or frailty (patients with cancer and ECOG (Eastern Cooperative Oncology Group) 3 or 4 were excluded from trials on DOAC use in CAT)
- Low body weight (<50 kg)
- Anemia, thrombocytopenia, anorexia, and vomiting (risk for bleeding is slightly higher with DOACs compared with LMWH)

### Long-term anticoagulation for CAT

Long-term, sometimes indefinite anticoagulation should be considered in patients with active cancer after the initial 6 months of treatment using either a DOAC or LMWH. The following should be considered when deciding on extended therapy:

- Risk for VTE recurrence
- Tolerability of treatment and risk for drug-drug interactions
- Severity of index event
- Patient's preference
- Bleeding risk[185]

In the API-CAT (Apixaban for Cancer-Associated Thrombosis) trial, after 6 months of anticoagulation, apixaban at a reduced dose (2.5 mg twice daily) was noninferior to 5 mg twice daily for prevention of VTE, with a 25% relative reduction in bleeding risk.[186] Other DOACs have not been tested with a reduced dose strategy for this indication.

### Consensus recommendations: CAT

- In selected high-risk ambulatory patients with cancer, prophylactic anticoagulation with a DOAC (apixaban or rivaroxaban) or LMWH (dalteparin or enoxaparin) may be considered.
- DOACs or LMWH can be used to treat CAT. DOACs are generally preferred over LMWH for the treatment of CAT because they are associated with a lower risk of VTE recurrence and a similar overall risk of major bleeding. Among DOACs, the evidence base is strongest for apixaban. Rivaroxaban and edoxaban are also acceptable options for CAT except in urologic, gastrointestinal, and gynecological cancers.
- Long-term, sometimes indefinite anticoagulation should be considered in patients with active cancer after the initial 6 months of treatment. Apixaban 2.5 mg twice daily has similar efficacy to 5 mg twice daily with a lower bleeding risk. Other DOACs have not been tested with a reduced dose strategy for this indication. LMWH can also be considered.

### Central venous catheter DVT

In critically ill patients undergoing surgery, catheter-related thrombosis occurred in 37% to 64% of central venous catheters within 1 day of insertion and in 64% to 100% within 1 week.[187] However, no prophylactic strategy has so far been associated with sufficient efficacy to support routine use. Despite the absence of comparative trials, catheter-related thrombosis may be treated with DOACs or LMWH for a minimum duration of 3 months, including ≥1 month following catheter removal.[188]

### Left ventricular thrombus

Patients with low ejection fraction and/or anterior wall MI have a higher risk of developing left ventricular thrombi. Anticoagulation is typically pursued for ≥3 months in patients with established left ventricular thrombus, although some patients may need it longer. Limited randomized data such as the No-LVT (Comparative Study of Oral Anticoagulation in Left Ventricular Thrombi) trial[189] and multiple observational studies suggest that DOACs, particularly rivaroxaban and apixaban, are comparable to VKAs in terms of thrombus resolution and thromboembolic outcomes, with a similar or potentially lower risk of bleeding;[190] however, definitive large randomized trials are lacking.

### Management of anticoagulation during noncardiac surgery

In general, current recommendations are to hold OAC without heparin bridging, with the duration of the hold dictated by the type of surgery, drug pharmacokinetics, and patient-specific factors such as renal function.[17,191] Procedures such as endoscopies, dental procedures, and cardiac catheterization laboratory procedures are considered to have a low bleeding risk. In contrast, intermediate- or high-risk surgeries include intra-abdominal and orthopedic procedures, among others.[191] Several studies support this strategy. In a meta-analysis of 32 studies of patients receiving VKAs, in which 7,118 patients were bridged, and 5,160 were not, there was no difference in thromboembolic events. Yet, heparin bridging was associated with an increased risk of overall and major bleeding.[191] The PAUSE (Perioperative Anticoagulation Use for Surgery Evaluation) cohort study,

which enrolled 3,007 patients with a mean $CHA_2DS_2$-VASc score of 3.5, found a low incidence of thromboembolic events when DOAC was briefly interrupted without bridging.[192] An exception to this would be patients considered to be at high risk of stroke, such as those with mechanical valves, recent stroke/transient ischemic attack, or other high-risk markers, who may still require bridging anticoagulation,[17] as these patients generally have been deemed high risk, thus not included in the aforementioned trials.

For patients undergoing pacemaker or defibrillator implantation or generator replacement who are deemed at high risk of stroke with an estimated annual stroke risk of ≥5%, continued anticoagulation is recommended in preference to interruption of warfarin and bridging anticoagulation based on the results of the BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) study, in which the incidence of clinically significant pocket hematoma was significantly higher in the bridging group.[193] Similarly, in patients on DOACs, interruption is preferred, but for those deemed at higher risk, DOAC continuation is preferred over bridging with parenteral anticoagulation.[194]

### Anticoagulation considerations after LAAC

LAAC devices were developed as an alternative to anticoagulation for stroke mitigation in patients with AF. This has been validated in a study that examined 5-year outcomes of the combined PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) and PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trials, demonstrating that LAAC with the Watchman device (Boston Scientific, Marlborough, Massachusetts) provided stroke prevention in nonvalvular AF comparable to warfarin, with additional reductions in late postprocedure bleeding, particularly hemorrhagic stroke, and mortality.[195] Yet, the two pivotal trials that led the FDA to approve the Watchman device enrolled patients without contraindications to chronic anticoagulation. Thus, the optimal antithrombotic treatment, either short- or long-term after device implantation, remains uncertain because many patients being considered for this procedure have contraindications to anticoagulation. Accordingly, a wide variety of postprocedure regimens have been used according to patients' bleeding risks.[196] Furthermore, the evidence suggests that newer LAAC devices carry a lower risk of thrombosis than earlier generations. In addition, there are 2 important procedural considerations that may have additional bearing on long-term anticoagulation after LAAC. These include peridevice leaks (especially those ≥5 mm) and device-related thrombus, both of which may independently increase long-term thromboembolic risk despite LAAC and require consideration for longer-term OAC.[197-199]

The original regimen approved by the FDA after Watchman device implantation was a combination of warfarin and aspirin (81 mg daily) for 45 days, followed by DAPT with aspirin (325 mg daily) and clopidogrel (75 mg daily) up to 6 months and lifelong aspirin (325 mg daily) thereafter.[197] However, more recently, regimens such as DAPT or DOACs have been adopted due to a more favorable safety profile.[200] DOACs have replaced warfarin for short-term anticoagulation, whereas DAPT regimens have been increasingly adopted and have even received FDA approval for a 45-day DAPT label for the Watchman FLX as an alternative to 45-day OAC plus aspirin. The ADALA (Apixaban vs Dual Antiplatelet Therapy Study After Left Atrial Appendage Occlusion) trial comparing low-dose apixaban (2.5 mg twice daily) versus DAPT with clopidogrel 75 mg daily and aspirin 100 mg daily for 3 months post-LAAC was terminated after enrolling 90 patients but showed a reduction in device-related thrombosis and bleeding events with low-dose DOAC.[201] Single antiplatelet or even no antithrombotic treatment after LAAC has also been used effectively in patients at particularly high risk of severe bleeding.[202] Several trials on the optimal regimen after LAAC are underway, including the possibility of long-term discontinuation of antithrombotic agents, but for now, a tailored approach to antithrombotic regimens based on the patient's specific risks can be considered.

### Considerations after AF ablation

For those with a $CHA_2DS_2$-VASc score ≥2 in men and ≥3 in women,[203] the 2023 ACC/AHA/Multisociety AF guideline mandates anticoagulation for at least 2 to 3 months post-catheter ablation and continued indefinitely, regardless of procedural success.[17] This strategy has recently been put into question. Evidence from observational studies suggested the safety of discontinuing anticoagulation, especially in patients deemed at intermediate risk of stroke.[204] Subsequently, 2 randomized trials with a similar design, the ALONE-AF and OCEAN trials, both demonstrated the safety of discontinuing anticoagulation 1 year after successful ablation.[48,49] Of note, patients were generally low risk; in OCEAN, the mean age was 66 years, and the mean $CHA_2DS_2$-VASc score was 2.2, whereas in ALONE-AF, the mean age was 64 years and the $CHA_2DS_2$-VASc score was 2.1; most had normal or minimally abnormal left atrial enlargement. Still, these findings suggest that, in carefully selected low-to-intermediate-risk individuals ($CHA_2DS_2$-VASc score ≤3), who maintain sinus rhythm after ablation, discontinuation of OAC 1-year postablation is a reasonable approach in the absence of additional markers of risk

such as extensive atrial myopathy or high-risk conditions.

An alternative approach for patients at high stroke risk who are unable to tolerate anticoagulation was defined by the OPTION (Comparison of Anticoagulation With Left Atrial Appendage Closure After Atrial Fibrillation Ablation) trial. Patients who underwent concomitant AF ablation and percutaneous LAAC had a lower risk of major bleeding at 36 months after ablation compared with remaining on anticoagulation.[205]

### Consensus recommendations: anticoagulation after LAAC or AF ablation

- The optimal regimen for anticoagulation post-LAAC remains uncertain because clinical decisions are driven by individual bleeding risk.
- For individuals with low to intermediate risk for stroke ($CHA_2DS_2$-VASc score ≤3), who maintain sinus rhythm after catheter ablation of AF, discontinuation of OAC 1 year post-AF ablation is a reasonable approach in the absence of other high-risk conditions warranting continued OAC use.

## MONITORING AND FOLLOW-UP

### When and how to monitor for bleeding

All patients receiving OAC therapy require monitoring for bleeding, and the signs and symptoms of hemorrhage requiring attention are an essential item of patient education. The potential for bleeding with warfarin therapy is reflected by the INR; DOACs have no similar marker and clinical vigilance is paramount.

Many prediction rules for bleeding in patients taking OACs have been developed to assist monitoring—most including anemia, renal or liver disease, thrombocytopenia, cancer, history of major bleeding, older age, and coadministration of other medications associated with bleeding (aspirin, nonsteroidal anti-inflammatory drugs, etc) (Table 5).[206] While they remind clinicians of potentially reversible factors to address, none is sufficiently robust to predict individual risk over time for OAC users.[207,208] Bleeding risk scores are also useful to identify high-risk patients whose bleeding risk should be reviewed more frequently. There is limited evidence on sequential monitoring of patients with a bleeding risk tool; however, the mAFA-II (Mobile Health Technology for Improved Screening and Optimized Integrated Care in Atrial Fibrillation) randomized trial involving patients with AF in China found that HAS-BLED score monitoring at 4 intervals over a year reduced bleeding events compared with control (2.1% vs 4.3%; P=0.004).[209] In general, DOACs have lower rates of major bleeding than warfarin and are preferred where indicated and where affordable, particularly in the elderly.[210,211] Apixaban, in particular, appears to be a safe alternative to VKAs at all levels of CKD, even to the point of renal replacement therapy.[212] At present, there is no good evidence for any specific renal monitoring program or frequency to prevent DOAC-related bleeding or other outcome.[213]

### Definitions of major bleeding

Major bleeding is generally defined as bleeding sufficiently severe to require blood transfusion, or bleeding into a critical closed space (eg, intracranial or intraocular or retroperitoneal bleeding, compartment syndrome), or requiring an intervention for management (eg, surgery, interventional radiology, or endoscopic treatments). Major bleeding has a significant risk of immediate morbidity and mortality related to the bleeding, and thus necessitates discontinuation of the OAC. Clinically relevant nonmajor bleeding requires a face-to-face health care assessment but does not require interruption of OAC therapy.

### How to address nonadherence

Warfarin represents the gold standard drug for adherence assessment because of the availability of a valid, widely available, and easily measured pharmacodynamic marker: the INR. A systematic review of RCTs involving >100,000 patients concluded that adherence to DOACs is similar to adherence to warfarin. Estimates vary but nonadherence rates can be as high as 30% among patients taking long-term OAC.[216-220] Of note, nonadherent or partially adherent patients on a DOAC may have a greater amount of time during which they are not therapeutically anticoagulated compared with patients who miss occasional doses of warfarin. Identifying DOAC nonadherence is much more difficult[221] and relies on targeted history-taking and examination of prescription refills at the appropriate time. Although patient education, supportive supervision, and daily versus twice daily administration have all been promoted as improving adherence and OAC-related clinical outcomes, these are not yet supported by randomized trials and raise issues of cost-effectiveness.[222,223] The role of heparin anti-Xa or agent-specific Xa levels for DOACs other than dabigatran in monitoring compliance is unclear.

### Polypharmacy and drug-drug interactions

Major polypharmacy, defined as >10 prescription medications consumed at least once daily, is a common finding in patients taking OACs, particularly in older adults with AF. Drug interactions are therefore a common concern, but are rarely the subject of randomized trials, leaving guidance that is based on low-quality evidence at risk of confounding. With that caveat, warfarin drug interactions have been well characterized, based on studies involving nearly 4 million patients, and in terms of impact on clinical outcomes rather than just INR.[224]

**TABLE 5 Comparison of Bleeding Risk Models**

| Tool | Year of Release | Data Source | Factors Considered | Drug Used | Condition Warranting OAC |
|---|---|---|---|---|---|
| HAS-BLED[165] | 2010 | Subanalysis of EuroHeart Survey | ■ Hypertension<br>■ Abnormal renal/liver function<br>■ Stroke<br>■ Bleeding history or predisposition<br>■ Labile INR<br>■ Age ≥65 years<br>■ Alcohol use | Warfarin | ■ AF without mitral valve stenosis or valve surgery<br>■ Subsequently validated in VTE and ACS |
| $HEMORR_2HAGES$[214] | 2006 | Subanalysis of National Registry of Atrial Fibrillation | ■ Hepatic or renal disease<br>■ Alcohol abuse<br>■ History of malignancy<br>■ Age >75 years<br>■ Reduced platelet count or function (incl. aspirin use)<br>■ Bleeding history (+2)<br>■ Uncontrolled hypertension<br>■ Anemia<br>■ Genetic factors<br>■ Excessive fall risk<br>■ Stroke history | Warfarin | AF |
| RIETE[215] | 2008 | Patient registry | ■ Recent major bleeding (+2)<br>■ Creatinine >1.2<br>■ Anemia (+1.5)<br>■ Malignancy history (+1.5)<br>■ Clinically overt PE<br>■ Age >75 years | Warfarin, LMWH, or DOACs | ■ Acute symptomatic VTE (PE, DVT, or both)<br>■ Subsequently included superficial thrombosis; splanchnic, retinal, or cerebral |
| DOAC[169] | 2023 | Secondary analysis of RE-LY trial, further developed using GARFIELD-AF registry | ■ Stratified age, ranging from <65 years (0 points) to ≥80 years (+5 points)<br>■ Stratified renal function<br>■ Underweight (BMI ≤18.5 kg/$m^2$)<br>■ Stroke/TIA/embolism history<br>■ Diabetes<br>■ Hypertension<br>■ Antiplatelet use (aspirin +1, DAPT +2)<br>■ NSAID use<br>■ Bleeding history (+3)<br>■ Liver disease (+2) | ■ Dabigatran<br>■ Edoxaban<br>■ Rivaroxaban<br>■ Apixaban | AF |
| ATRIA[40] | 2011 | Medical records from a single health system | ■ Anemia (+3)<br>■ Severe renal disease (eGFR <30) (+3)<br>■ Age ≥75 years (+2)<br>■ Any prior hemorrhage<br>■ Hypertension history | Warfarin | AF |

*Continued on the next page*

These largely concentrate on bleeding risk that is most reliably affected by concomitant medications, which also independently contribute to bleeding: antiplatelet agents, nonsteroidal inti-inflammatory drugs, selective serotonin reuptake inhibitors, but also antimicrobials. DOACs are also susceptible to pharmacodynamic interactions with other medications that promote bleeding. Despite theoretical concerns based on their P-glycoprotein alone (all DOACs) or P-glycoprotein plus CYP3A4 substrate (small amount for apixaban and rivaroxaban) status, there has been surprisingly little high-quality evidence proving clinically important drug interactions[225] based on metabolic inhibition or induction. There does seem to be increased risk of bleeding outcomes related to factor Xa inhibitors when coprescribed with diltiazem. Proton pump inhibitors, based largely on observational studies, appear to protect against bleeding for all OACs.[226-228]

**TABLE 5 Continued**

| Tool | Year of Release | Data Source | Factors Considered | Drug Used | Condition Warranting OAC |
|---|---|---|---|---|---|
| GARFIELD-AF[41] | 2017 | Data from prospective GARFIELD-AF registry | ■ Age<br>■ Weight<br>■ Pulse rate<br>■ Diastolic blood pressure<br>■ Race/ethnicity<br>■ Sex<br>■ History of bleeding<br>■ Heart failure, LVEF <40%, or both<br>■ History of stroke<br>■ CKD class III-V<br>■ CAD or PAD<br>■ Diabetes<br>■ Smoker<br>■ Dementia<br>■ Current use of antiplatelet<br>■ Occlusive carotid disease | ■ VKA<br>■ DOAC<br>■ No medication | ■ AF<br>■ Allows risk comparison for rates of mortality, ischemic stroke or systemic embolism, and major bleeding including hemorrhagic stroke over time (6 months, 1 year, 2 years) with no OAC vs VKA vs DOAC |
| VTE-BLEED[186] | 2017 | Post hoc analysis of pooled RE-COVER trials | ■ Age ≥60 years (+1.5)<br>■ Active cancer (+2)<br>■ Male patient with uncontrolled hypertension<br>■ Anemia (+1.5)<br>■ History of bleeding (+1.5)<br>■ Renal dysfunction (patients with significant renal dysfunction excluded) (+1.5) | ■ Warfarin or dabigatran<br>■ Subsequently validated with apixaban, edoxaban, and rivaroxaban | ■ Post-VTE |

ACS = acute coronary syndrome; AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; GARFIELD-AF = Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; HAS-BLED = Hypertension, Abnormal renal function, Stroke history, Bleeding history or disposition, Labile INR, Elderly, Drugs; $HEMORR_2HAGES$ = Hepatic or renal disease, Ethanol, Malignancy, Older age, Reduced platelets, Re-bleeding risk, Hypertension, Anemia, Genetic factors, Excessive fall risk, Stroke history; INR = international normalized ratio; LMWH = low molecular weight heparin; NSAID = nonsteroidal inti-inflammatory drug; LVEF = left ventricular ejection fraction; OAC = oral anticoagulation; PAD = peripheral artery disease; PE = pulmonary embolism; RE-COVER = Randomized Evaluation of dabigatran versus warfarin in the Coverage of Acute venous Thromboembolism; RIETE = Registro Informatizado de Enfermedad TromboEmbólica; TIA = transient ischemic attack; VKA = vitamin K antagonist; VTE = venous thromboembolism.

### Complications and barriers to use

Cost remains a significant barrier to utilization of DOACs in certain patients. Although many cost-effectiveness analyses demonstrate that DOACs are economically favorable long term because of reduced stroke and bleeding events, the higher upfront drug cost remains a practical obstacle for individual patients. Out-of-pocket costs greater than $100 have been associated with prescription abandonment. Consequently, financial barriers can lead to suboptimal anticoagulation and delays in treatment. Efforts should be made to confirm affordability for patients and provide education related to the importance of adherence to DOAC therapy.

### Bleeding management

Due to their relatively short half-lives, many bleeding events with DOACs can be managed conservatively by holding the anticoagulant and providing supportive care. Rapid reversal is generally reserved for life-threatening bleeding, bleeding in critical organs, or urgent surgical situations. As of December 2025, andexanet alfa has been withdrawn from the U.S. market due to increased thrombotic events in the ANNEXA-I (Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage) trial.[229] This leaves 4-factor prothrombin complex concentrate (4F-PCC) or activated PCC as the primary reversal agent for factor Xa inhibitors. For dabigatran-associated ICH, idarucizumab remains the preferred reversal agent, with PCC, activated PCC, or renal replacement therapy as alternatives when needed. Laboratory assessment of DOAC activity remains challenging, and the high cost of reversal agents continues to be an important consideration in clinical management of bleeding.

### Consensus recommendations: monitoring and follow-up

- Patients receiving DOAC therapy should undergo periodic reassessment of bleeding risk, renal and hepatic function, concomitant medications, and adherence,

with closer surveillance in those at higher risk for bleeding or drug accumulation.

- Bleeding risk scores may be used to identify patients who warrant more frequent follow-up but should not be used in isolation to withhold anticoagulation; instead, clinicians should focus on mitigating modifiable bleeding risk factors and reinforcing patient education on signs and symptoms of bleeding.
- At follow-up visits, clinicians should reassess adherence, affordability, drug-drug interactions, interval clinical events, and patient-specific factors to determine whether the selected DOAC and dose remain appropriate.

### Evidence gaps and future directions

Despite a better safety profile than VKA, bleeding remains one of the biggest limitations of DOAC use. Adherence is another important consideration. A variety of novel agents are under investigation to address these issues. Factor XI plays a relatively minor role in hemostasis but contributes substantially to thrombus propagation. Factor XI inhibitors aim to uncouple hemostasis from thrombosis, representing a novel anticoagulant strategy with the potential for reduced bleeding risk compared with traditional agents, while preserving antithrombotic efficacy. Several classes of agent have been developed or are under consideration to target factor XI and/or factor XIa, including antisense oligonucleotides, monoclonal antibodies, small molecules, natural inhibitors, aptamers, and small interfering RNAs.[34] Antisense oligonucleotides[230] (eg, IONIS-FXIRx, fesomersen) and monoclonal antibodies[231-234] (eg, osocimab, abelacimab, gruticibart) require parenteral administration and allow infrequent dosing (eg, every 2-4 weeks). However, the risk of intercurrent and periprocedural bleeding requires further evaluation. Asundexian and milvexian are orally acting small molecule anti-XIa drugs. A number of these agents have been tested in phase 2 trials for thromboprophylaxis in patients undergoing orthopedic surgery[235-237] with promising results; phase 3 trials are ongoing. Another indication where they are being extensively tested is for stroke prevention among patients with AF. In the phase 2 AZALEA-TIMI 71 (A Multicenter, Randomized, Active-Controlled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared With Open-Label Rivaroxaban in Patients With Atrial Fibrillation) trial, abelacimab was evaluated in a 1:1:1 randomized design (150 or 90 mg once monthly vs rivaroxaban 20 mg daily) in patients with AF (median $CHA_2DS_2$-VASc score 5). The trial was stopped early due to a marked reduction in bleeding with abelacimab, with approximately 60% to 70% lower major bleeding compared with rivaroxaban at both doses, whereas rates of stroke and systemic embolism were similar during follow-up. In the phase 3 OCEANIC-AF (Oral Factor XIa Inhibition Compared to Standard Therapy in Patients With Atrial Fibrillation) trial comparing asundexian 50 mg once daily to apixaban (mean $CHA_2DS_2$-VASc score 4.3), major bleeding was similarly lower with asundexian but stroke or systemic embolism rates were higher, requiring premature cessation of the trial.[238] Several other trials in this patient population are ongoing.[239] In addition, these agents are being tested for a variety of other indications, including noncardioembolic stroke, post-MI, etc. Most recently, asundexian 50 mg daily in addition to antiplatelet therapy among patients with noncardioembolic ischemic stroke or high-risk transient ischemic attack was found to be superior to antiplatelet therapy alone in reducing ischemic strokes with similar bleeding rates in the phase 3 OCEANIC-STROKE (Oral Factor Eleven A Inhibitor Asundexian as Novel Antithrombotic Stroke) trial.[240] Beyond factor XI/XIa inhibition, anticoagulant development is expanding toward upstream contact pathway targets (factor XII), newer direct thrombin inhibitor and anti-Xa agents,[241,242] and pharmacologic reversal systems such as ciraparantag,[243] all aimed at improving the therapeutic index by minimizing bleeding while preserving antithrombotic efficacy.

## PRESIDENT AND STAFF

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Bonnie Ky, MD, MSCE, FACC

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**KEY WORDS** ACC Scientific Statement, atrial fibrillation, bleeding, cancer-associated thrombosis, device-detected atrial fibrillation, direct oral anticoagulant, left atrial appendage closure, venous thromboembolism

## APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT): ORAL ANTICOAGULANTS IN THE PRIMARY AND SECONDARY PREVENTION OF THROMBOTIC EVENTS: 2026 ACC SCIENTIFIC STATEMENT

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Dharam J. Kumbhani, *Chair* | Section Chief, Director of Interventional Cardiology; Jim and Norma Smith Distinguished Chair for Interventional Cardiology, UT Southwestern Medical Center | None | None | None | None | None | None |
| Anastasia L. Armbruster | Associate Professor of Pharmacy Practice, Washington University in St. Louis | None | None | None | None | None | None |
| Richard K. Cheng | Professor of Medicine; Section Chief, Advanced Heart Failure, and Transplant, MCS, and Cardio-oncology Cardiology, University of Washington | None | None | None | None | None | None |
| Jonathan Chrispin | Associate Professor of Medicine, Johns Hopkins University | ■ Abbott*<br>■ AtriCure<br>■ Biosense Webster<br>■ Boston Scientific | None | None | None | None | None |
| Urs Fischer | Director and Chairman, Department of Neurology University Hospital, Bern, Switzerland | None | None | None | ■ Boehringer Ingelheim*<br>■ Medtronic*<br>■ Penumbra*<br>■ Phenox*<br>■ Rapid Medical*<br>■ Stryker* | ■ AbbVie<br>■ AstraZeneca<br>■ Auzone<br>■ Bayer<br>■ Biogen<br>■ Boehringer Ingelheim<br>■ Boston Scientific<br>■ Corxel<br>■ CSL Behring<br>■ Medtronic*<br>■ Merck<br>■ Phenox*<br>■ Siemens<br>■ Takeda | None |
| Anne Marie Holbrook | Professor of Medicine, Division Director, Clinical Pharmacology and Toxicology McMaster University | None | None | None | None | None | None |
| Jose Joglar | Program Director, Clinical Cardiac Electrophysiology Fellowship Program UT Southwestern | None | None | None | None | None | None |
| Marie-Antoinette Sevestre | Program Coordinator, Specialty Diploma in Vascular Medicine Centre Hospitalier Universitaire d'Amiens | ■ BMS<br>■ Pfizer<br>■ Viatris | None | None | None | None | None |

*Significant relationship.

## APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE): ORAL ANTICOAGULANTS IN THE PRIMARY AND SECONDARY PREVENTION OF THROMBOTIC EVENTS: 2026 ACC SCIENTIFIC STATEMENT

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Dominick J. Angiolillo | Distinguished Professor of Medicine; Chief, Division of Cardiology; Medical Director, UF Health Cardiovascular Center; Director, Cardiovascular Research; Program Director, Interventional Cardiology Fellowship, University of Florida College of Medicine-Jacksonville | ■ Anthos*<br>■ Bayer<br>■ Boehringer Ingelheim*<br>■ Bristol-Myers Squibb*<br>■ Chiesi*<br>■ Faraday<br>■ Idorsia<br>■ Johnson & Johnson<br>■ Novartis*<br>■ Novo Nordisk*<br>■ PLx Pharma*<br>■ Sanofi*<br>■ SFJ Pharmaceuticals<br>■ Vectura*<br>■ Werfen | None | None | None | ■ Abbott*<br>■ Amgen*<br>■ AstraZeneca*<br>■ Bayer*<br>■ Chiesi*<br>■ CSL Behring*<br>■ DalCor Pharmaceuticals*<br>■ Daiichi Sankyo*<br>■ Edwards*<br>■ Eli Lilly*<br>■ Faraday*<br>■ Janssen*<br>■ Hikari DX*<br>■ Novartis*<br>■ Prolocor*<br>■ Vertex* | None |
| Julia H. Indik | Professor of Medicine, University of Arizona | None | None | None | None | None | None |
| Gregory Piazza | Director, Vascular Medicine, Mass General Brigham Heart and Vascular Institute; Associate Professor of Medicine, Harvard Medical School | ■ Penumbra<br>■ Pfizer<br>■ Thrombolex | None | None | ■ Amgen*<br>■ Bayer*<br>■ Bristol-Myers Squibb*<br>■ Boston Scientific*<br>■ ESPERION*<br>■ Janssen*<br>■ NAMSA<br>■ Regeneron* | ■ Boston Scientific† | None |

*Significant relationship. †Spousal relationship.