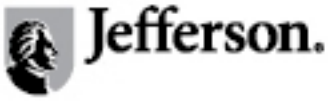

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Practical Management of Anticoagulation in Patients with Atrial Fibrillation

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Abbreviations

AC = Anticoagulation clinic
ACC = American College of Cardiology
ACS = Acute coronary syndrome
AF = Atrial fibrillation
DOAC = Direct-acting oral anticoagulant
DAPT = Dual antiplatelet therapy
FDA = Food and Drug Administration
FFP = Fresh Frozen Plasma
ICH = intracranial hemorrhage
IV = intravenous
INR = International normalized ratio
OACT = Oral anticoagulant therapy
PCC = Prothrombin Complex Concentrate
TTR = Time in therapeutic range
VKA = Vitamin K antagonist

INTRODUCTION

In September 2013, following a series of pivotal trials and drug approvals, the American College of Cardiology (ACC) convened a roundtable discussion at Heart House to address clinical issues regarding oral anticoagulant alternatives to warfarin in patients with nonvalvular atrial fibrillation (AF). The meeting included representatives of specialty societies, the U.S. Food and Drug Administration (FDA), industry, and patient advocates (**Appendix 1**). Discussions covered 4 general topics:

1) Initiation and interruption of anticoagulant therapy
2) Quality, cost and team-based management of anticoagulation
3) Management of bleeding and emergency care
4) Complex disease states and special populations

Discussion was supplemented with focused literature reviews of the English language literature in Pub Med to November, 2014 that pertained to the roundtable themes.

Data from the ACC PINNACLE Registry showed large variations in percentage of appropriate anticoagulation for AF even before the introduction of direct acting oral anticoagulants (DOACs) (1). Management of anticoagulation crosses the bounds of specialty and type of practice (**Central Illustration**). This review attempts to provide practical consensus recommendations as well as to point out gaps in knowledge and areas of future inquiry.

ASSESSING BENEFITS AND RISKS OF ORAL ANTICOAGULANTS

Oral anticoagulant therapy (OACT) reduces stroke risk in patients with non-valvular AF. Patients with valvular AF and those with prosthetic mechanical heart valves or significant (moderate to severe) mitral stenosis were excluded from clinical trials, and therefore this document will not suggest changes in their management. Patients with non-valvular AF

(paroxysmal, persistent, or permanent) with or without symptoms are all considered for OAC based on their individual risk profile.

The 2014 AF guidelines recommend the use of CHA_2DS_2-VASc scoring system (**Table 1**) (2) instead of $CHADS_2$ (3), because it increases the number of patients who meet criteria for anticoagulation therapy while more accurately identifying truly low risk patients. Many patients, (women, those aged 65-75, and patients with vascular disease) are redistributed from the low- to higher-risk categories (3).

Several bleeding risk scores are available including HAS-BLED and ATRIA (4, 5), which may identify patients at higher risk of bleeding; however, more information is needed on their clinical utility (2). Tools, such as the AnticoagEvaluator and the Stroke Prevention in Atrial Fibrillation Risk Tool, are available at the point of care to estimate risk of stroke and benefits of anticoagulation therapy in patients with AF (6, 7).

CLINICAL TRIALS COMPARING DOACS WITH VITAMIN K ANTAGONISTS

There are 2 classes of DOACs: factor Xa (FXa) inhibitors such as rivaroxaban, apixaban and edoxaban, and direct thrombin inhibitors such as dabigatran. **Table 2** highlights selected trials comparing safety and efficacy of DOACs to adjusted dose warfarin with target INR of 2-3. These trials have limitations, including noninferiority study designs and relatively short treatment follow-up. The median time in therapeutic range (TTR) for warfarin patients was ≤ 69% in each of the trials; the results may have been different if the patients had achieved a greater percentage of TTR. Limited guidance is provided concerning the potential advantage of using DOACs in patients on warfarin with TTR > 75%. When data from the trials are combined, DOACs appear to reduce stroke, intracranial hemorrhage (ICH), and overall mortality compared

to warfarin, with similar major bleeding risks. On the other hand, gastrointestinal bleeding appears increased with rivaroxaban, edoxaban 60 mg, and dabigatran compared to warfarin (8).

THE RIGHT DRUG FOR THE RIGHT PATIENT

Appropriate drug selection depends on approved indications, patient characteristics, concomitant medications, clinician and patient preference, and cost. Therapy with well-managed warfarin and with high TTR is appropriate for certain patients. Several reports quantify the relationship between TTR and major clinical outcomes in patients with AF (9, 10). Patients with TTR < 58% despite adequate warfarin dosing adjustment may benefit from a DOAC (11). Clinical trials have also shown lower risks of intracranial hemorrhage (ICH) with DOACs when compared to warfarin.

Individual response to warfarin varies with age, gender, body mass index, concomitant meds, certain foods, and genotype. Warfarin has a relatively narrow therapeutic index. Overdosing can result in bleeding; under dosing can result in thrombosis. Patients treated with warfarin should have an INR determined at least weekly during initiation of therapy, and regular ongoing monitoring when INR is stable and within range. Genetics influence VKA response; however, genetic testing to predict VKA response has not been widely adopted nor has it been shown to be of value in randomized trials (12, 13). Home monitoring of VKA therapy is reasonable in selected patients (14) including those who have difficult access to lab services. Many insurance plans, including Medicare, cover the cost of a device and once-weekly use of test strips. Several nationwide VKA home management services accept commercial and Medicare health insurance (15).

The DOACs' mechanism of action, dosing information, drug interactions, and recommended monitoring schedules are listed in **Table 3**. Although DOACs are more expensive than warfarin,

advantages for some patients include a lack of dietary limitations, fewer drug interactions and elimination of INR testing.

Patients taking OACs require baseline and periodic lab monitoring (16). DOAC dosing is sensitive to changes in renal function. A summary of dosing changes relative to renal function can be found in **Table 3.** Although many laboratories report renal function as the estimated glomerular filtration rate (eGFR), renal function should be estimated using the Cockcroft-Gault equation, [(140-age)x(weight in kg)x(0.85 if female)/(72)x(creatinine in mg/dL)] to determine the appropriate DOAC dose.

Patients with severe renal impairment were excluded from the large phase III trials evaluating DOACs, and therefore warfarin remains the treatment of choice for AF patients with severe renal impairment or end-stage renal disease (2). However, the FDA has approved apixaban in patients with end-stage renal disease on hemodialysis based on pharmacokinetic modeling data.

DRUG INTERACTIONS

Drug interactions should be considered when prescribing any oral anticoagulant therapy (OACT) (**Tables 3, 4**). All patients should be instructed to alert the clinician prescribing the OACT any time changes in other medications are made (**Table 5**). Warfarin has many food and drug interactions (17) although some are not well documented. Non-prescription medications, e.g. acetaminophen, fish oil, herbal supplements and grapefruit juice, can potentiate the effect of VKAs (18-21).

DOACs are also subject to drug interactions. Rivaroxaban and apixaban interact with drugs that are strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and are impacted by the efflux transporter P-glycoprotein (22) . Rifampin, a P-glycoprotein inducer, should not be used with edoxaban or dabigatran. Medications that inhibit the P-glycoprotein system increase

dabigatran and edoxaban plasma concentrations. Concomitant use of quinidine, dronedarone, or verapamil with edoxaban significantly increase edoxaban exposure (23). Although the dose of edoxaban was reduced by 50% in patients on concomitant verapamil, quinidine, or dronedarone in ENGAGE AF-TIMI 48, the FDA does not recommend dose reduction in patients who are taking concomitant P-gp inhibitors (24). Patients on antiretroviral therapy, cyclosporine, azole antifungals, and macrolides were excluded from ENGAGE AF-TIMI 48 and their use in patients on DOACs should be avoided as they increase edoxaban concentrations.

INTERRUPTION OF DRUG THERAPY

Short-term interruption of OACT is safe for most low risk invasive procedures. Management of OACT should be individualized for patients at higher thromboembolic risk who are undergoing high-risk procedures. Procedures that pose a high risk of bleeding include intracranial, intraspinal, retroperitoneal or intrathoracic surgery. Intraocular procedures and neuraxial anesthesia may present risks to patients with even minor bleeding. Bridging with a parenteral agent, e.g. unfractionated heparin or low molecular weight heparin, is common but the data on prevention of embolic events are limited and the rate of bleeding is significantly increased (25). The decision to bridge must balance the risk of an embolic event against the risk of bleeding (26).

TRANSITIONING BETWEEN ANTICOAGULANTS

The INR monitoring is needed when transitioning patients from VKA to a DOAC, to avoid over-anticoagulation. INR targets when switching from warfarin to a DOAC are summarized in **Table 4.** If switching from a DOAC to VKA, bridging with a short-acting parenteral agent or a lower dose of the DOAC may be needed. INR should be at least twice weekly and VKA dose adjusted using a reliable algorithm until the INR reaches 2.0 to avoid excess bleeding or thrombotic

events (27). When transitioning from parenteral agents to DOACs, the DOACs can be initiated up to 2 hours before the next dose of the parenteral agent or when stopping the intravenous (IV) infusion. For those patients transitioning from FXa inhibitors to parenteral agents, the parenteral agents can be started at the intended time for the next dose of FXa inhibitor. When converting from dabigatran to a parenteral agent, the starting time is dependent on the patient's creatinine clearance (**Table 5**).

LONG-TERM MANAGEMENT OF OACT

National guidelines and regulatory agencies endorse coordinated-care anticoagulation management models to maximize patient outcomes (14, 28-31). Despite data showing that coordinating care through anticoagulation clinics (ACs) improves patient outcomes and reduces costs when compared to usual medical care (14, 28, 29), only 30-40% of patients on VKAs are managed in an AC (32).

The scope of AC services should include management of DOACs (32). Therapy with both DOACs and VKAs require continual patient education (**Table 6**), evaluation for drug interactions, and periodic laboratory monitoring (**Table 3**), all of which could be coordinated through institutional protocols or through ACs that facilitate initiation, compliance, transition between agents, and interruption for procedures.

MANAGEMENT OF BLEEDING AND EMERGENCY CARE

Even with the best coordinated care, bleeding complications will occur. Clinical trials comparing VKA with DOACs for stroke prevention in AF have shown an annual rate of major bleeding ranging from 2.1% to 3.6% of patients. Fatal bleeding occurs in up to 0.5% (33-36). Major bleeding is associated with higher mortality. In an analysis of 5 phase III clinical trials, 30-day mortality after a major bleeding episode was 13% with warfarin and 9% with dabigatran (37).

Minor bleeding may predict major bleeding (5, 38) and lead to discontinuation of effective anticoagulation therapy, underscoring the importance of both preventing and effectively managing bleeding episodes. With VKA therapy, regular monitoring and appropriate dose adjustment will improve anticoagulation quality and reduce bleeding. For DOACs, adjustment of dose based on renal function is crucial. With both VKA and DOACs, avoidance of concomitant aspirin and other antiplatelet agents, including long acting NSAIDs, whenever possible, is important.

BLEEDING DEFINITIONS

Bleeding severity in outpatient trials of anticoagulation was defined by the International Society on Thrombosis and Haemostasis (39) and has been revised (40). For this review those definitions have been modified to enhance their clinical relevance (**Figure 1**).

GENERAL ASSESSMENT OF THE BLEEDING PATIENT RECEIVING OACT

Management of the bleeding patient on an anticoagulant is outlined in **Figure 2**. Basic assessment includes determination of the site, onset, and volume of bleeding, and whether bleeding is ongoing. The time of last ingestion of the anticoagulant is especially important with DOACs. Concomitant medications should be reviewed (**Table 3**). An assessment of comorbid conditions and evidence of cardiac decompensation should be done. Laboratory assessment includes a CBC with platelet count, PT and aPTT, serum electrolytes and renal and hepatic function.

LABORATORY MONITORING OF ANTICOAGULANTION

VKA TREATED PATIENTS. The prothrombin time (PT)/INR is essential to the assessment of the VKA-treated patient with bleeding. Invasive procedures to define and correct the bleeding

source are often delayed until the INR is reduced. The type and amount of reversal agent is often based on the degree of PT prolongation, although there are few data correlating clinical outcomes with the initial INR level and few data correlating clinical improvement with the use of reversal agents.

DOAC TREATED PATIENTS. Figure 3 summarizes the potential use of coagulation assays in the assessment of the bleeding patient taking a DOAC (41). A prolonged aPTT indicates an anticoagulant effect of dabigatran and a prolonged PT an anticoagulant effect of the FXa inhibitors. However, elevated plasma levels of dabigatran and FXa inhibitors may occur with normal aPTT or PT values, making them less useful in the assessment of the bleeding patient. Different PT and aPTT reagents vary widely in their sensitivity to the DOACs.

Furthermore, there may be some danger in relying on conventional parameters to define reversal therapy in a bleeding patient receiving a DOAC. For example, an aPTT of > 2.5 times control suggests a supratherapeutic dabigatran concentration (42). A reversal agent may take several hours after ordering to reach the patient. Since the half-life of dabigatran is relatively short, by the time a reversal agent is administered, the reversal drug dose may be excessive, resulting in clotting. This highlights one of the difficulties in the design of clinical trials to assess reversal agents (43).

The dilute thrombin time, a functional test of the effect of thrombin on fibrin formation, provides a reasonable estimate of dabigatran concentration across a wide range of drug levels (42), and is commercially available (Hemoclot). Ecarin-based assays, including the ecarin clotting time (ECT) and chromogenic ecarin assays, correlate well with dabigatran concentration, but are not widely available.

The anticoagulant effect of FXa inhibitors can be assessed by anti-FXa levels. Data linking anti-FXa levels with bleeding and thrombosis related to FXa inhibitors are unavailable. Calibration of anti-factor Xa assays with specific FXa inhibitors is recommended.

AGENTS TO REVERSE ANTICOAGULATION

The introduction of DOACs has made therapy to reverse anticoagulation more complex. Newer agents (such as Prothrombin Complex Concentrate or PCC) are expensive and not always readily available. Many institutions have developed protocols for management of the patient treated with OACT who experiences major bleeding. Consultation with a hematologist is recommended.

VITAMIN K. VKAs reduce the synthesis of functional vitamin K-dependent coagulation factors, providing a rationale for vitamin K therapy as a reversal agent. Intravenous (IV) vitamin K does not begin to reduce INR for 6 hours, often taking longer than 24 hours for complete reversal (44). IV vitamin K may result in allergic reactions (particularly when given as a bolus) and IV infusions should generally be limited to patients with major bleeding. Subcutaneous and intramuscular administration is not recommended. Oral vitamin K is used for minor bleeding with an elevated INR. Although effective at lowering the INR, there are few data demonstrating improvement in outcomes with vitamin K. High doses of vitamin K will prolong the time to achieve a therapeutic INR when warfarin is restarted. Vitamin K does not reverse the anticoagulant effect of DOACs.

FRESH FROZEN PLASMA. Fresh frozen plasma (FFP) and blood transfusion provide volume, a potential advantage in a volume-depleted patient, but a potential disadvantage in patients with heart failure or renal dysfunction. FFP is readily available, although there are delays associated with thawing frozen plasma. For a patient with a high INR who is actively bleeding, it may be necessary to administer > 1500 mL of FFP to meaningfully increase

coagulation factors. Even with reduction in INR, there are few data showing improvement in outcomes with FFP. FFP in clinically feasible quantities does not reverse the anticoagulant effect of DOACs.

PROTHROMBIN COMPLEX CONCENTRATE. For patients with an elevated INR receiving VKA, a 10-30 minute infusion of prothrombin complex concentrate (PCC) improves INR values within minutes and lasts 12-24 hours. The half- lives of infused factors are similar to endogenous factors. Vitamin K is generally recommended for use with PCC to sustain the reversal effect.

The impact of PCC appears to be different with different DOACs. PCC did not normalize the aPTT, ecarin clotting time, and thrombin time in healthy volunteers who had received dabigatran, but immediately reversed a prolonged PT and an abnormal thrombin potential in rivaroxaban-treated healthy volunteers (45). Studies show that reversal of an anticoagulation effect can occur within 15 minutes, but may differ between direct thrombin inhibitors and FXa inhibitors. Recent studies show that PCC reverses anticoagulant activity in healthy volunteers given either dabigatran or rivaroxaban within 2 hours (46). The composition of PCC varies with the manufacturer. Four-factor PCC contains factors II, VII, IX, and X. Three-factor PCC contains little or no factor VII. In healthy volunteers who received rivaroxaban, 3-factor PCC restored thrombin generation better than 4-factor PCC, but4-factor PCC produced larger reductions in mean prothrombin time within 30 minutes. These discrepancies may be related to differences in factor concentration in these agents (47).

Data linking improved clinical outcomes with the use of PCC in DOAC-treated patients are lacking. In addition there is concern about myocardial infarction and arterial thromboembolism with the more potent agents (48, 49) that must be balanced against potential benefits. Some

forms of PCC contain heparin, a concern in patients with heparin- induced thrombocytopenia. The dose of PCC is 20-50 units/kg and the wholesale cost is about $1.25/unit.

OTHER REVERSAL AGENTS. Recombinant factor VIIa has been effective for reversal of the anticoagulant effect of VKA (50-52). Impact on laboratory parameters occurs within minutes and lasts 2-6 hr, but impact on bleeding consequences remains to be determined (53), and there is concern about the risk of thrombosis (48).

Three additional reversal agents are currently being evaluated. Idarucizumab, a specific antibody to dabigatran (anti-Dabi Fab), has been reported to restore systemic blood coagulation in animal studies (43) and in healthy volunteers. The REVERSE-AD trial studying the use of this agent in uncontrolled bleeding is underway. Andexanet alfa, a modified FXa molecule that binds to FXa inhibitor allowing the patient's intrinsic FXa to participate in coagulation, has been reported to provide rapid and near-complete reversal of factor X inhibitors in healthy volunteers. Aripazine, a small synthetic molecule with broad activity against heparin products and factor X agents is undergoing testing in healthy subjects (54).

MANAGEMENT OF MAJOR BLEEDING

Standard measures in the management of major bleeding in a patient taking an oral anticoagulant include fluid and blood resuscitation, identification and treatment of the bleeding source, and avoidance of administration of additional antithrombotics or antiplatelet drugs. Prompt reversal of the antithrombotic effects is desirable.

VKAs. Reversal of anticoagulation should be considered in a patient receiving VKAs who has major bleeding and an INR $\geq$ 1.5. Vitamin K 5-10 mg should be administered by slow IV infusion (14).

In 40 patients with a mean INR of 9.4, low dose 3-factor PCC (25 units/kg) and high dose 3-factor PCC (50 units/kg) lowered the INR by 50% and 43% respectively (55). Adding plasma further reduced the INR by 89% and 88%. In another randomized study, 4-factor PCC was compared with fresh frozen plasma (FFP) in 219 nonsurgical patients with warfarin associated bleeding (mean INR 3.7). Within 1 hr of the start of infusion, more than two-thirds of the 4-factor PCC group had an INR < 1.3 compared with none in the FFP group (56).

The use of PCC is recommended as first line therapy in patients on VKAs with life threatening major bleeding (14). Doses can be repeated in 6 hr. Delays in the administration of PCC have been reported (57) perhaps reflecting lack of familiarity with new therapies or the lack of ready availability of these products.

DOACs. Gastric lavage could be considered for patients who experience major bleeding, if DOACs ingestion has been recent. Administration of activated charcoal may be helpful if the DOAC has been ingested within 2-6 hours (58).

Data on patients treated with DOACs who have major bleeding are limited. Given the poor prognosis of major bleeding, especially CNS bleeding, in patients treated with DOACs, , some recommend PCC, activated PCC, or as a last choice activated factor VIIa to treat severe or life-threatening bleeding (59). However, there is no clinical evidence to support this recommendation.

Because dabigatran is approximately 35% plasma bound, dialysis is a consideration in the event of major bleeding, particularly in the setting of renal insufficiency. Rivaroxaban, apixaban and edoxaban are highly protein bound and hemodialysis is likely to be ineffective.

A high mortality rate associated with ICH occurs regardless of the type of anticoagulant. Measures to reverse the anticoagulant effect of VKAs have been shown to improve INR values

but not clinical outcomes. Agents to reverse the anticoagulant effect of DOACs are in development but there is concern that once ICH has occurred, even timely reversal of the anticoagulant effect may not improve clinical outcomes.

MANAGEMENT OF CLINICALLY RELEVANT NON-MAJOR BLEEDING

VKAs. The use of reversal agents in patients with clinically relevant non-major bleeding depends on the age of the patient, the amount of bleeding, whether bleeding is ongoing, the INR, the severity of anemia, and co-morbid conditions of the patient. Oral vitamin K could be considered in this situation (14) but the risks of a prolonged period of time with subtherapeutic INR values must be weighed against the benefits. Determining and treating the cause of bleeding is important, so that anticoagulation can be safely resumed.

DOACs. Given the short half- life of DOACs, the potential thrombotic risk of non-specific reversal agents, and the lack of evidence to support their use, reversal agents are not recommended for patients with clinically relevant non-major bleeding (59).

MANAGEMENT OF MINOR BLEEDING OR ELEVATED INR VALUES

VKAs. In a patient with minor bleeding, decisions on warfarin dosing should be made dependent upon the INR.

If the INR is > 10, management includes the following steps: 1) stop VKA therapy, 2) administer 2.5-5 mg of oral vitamin K (13), 3) monitor the INR every 12-14 hours, and 4) restart VKA therapy as INR approaches therapeutic range.

If the patient is at high risk for bleeding based on advanced age, recent bleeding, anemia, heart failure, malignancy, renal dysfunction and other variables (60), oral vitamin K can be considered in the non-bleeding patient with an INR > 10. In a non-bleeding patient with an INR > 4.5 and < 10, VKA should be held for 1 or 2 doses. Data on bleeding risk are conflicting in this situation

(61, 62). Vitamin K is generally not recommended unless there are patient specific reasons that make bleeding more likely as previously outlined.

DOACS. DOACs have short half-lives, and for patients with minor bleeding, omitting several doses of the anticoagulant may be the only therapy required beyond local measures (e.g., applying pressure). The duration of DOAC hiatus depends on the amount of bleeding and the thromboembolic risk.

MANAGEMENT AFTER BLEEDING

Patients recovering from major bleeding are frequently anemic, but are at risk for future bleeding (5). Resumption of anticoagulant therapy in such patients is problematic and yet, these patients may also be at high risk of thromboembolic events (63). In 1 study of 442 patients with a gastrointestinal bleed associated with warfarin, 260 (58.8%) restarted warfarin, sometimes as early as 4 days later (64). Those patients who did not resume warfarin had a higher risk of death and thromboembolic events. Similar findings were noted in patients after warfarin-associated CNS bleeding. Of 284 patients, 91 (32%) were re-started on warfarin prior to hospital discharge. Compared with those not started on warfarin, patients re-started on warfarin had lower mortality and had no increase in bleeding (65). After major bleeding, the location and severity of bleeding and whether the source of bleeding was effectively treated affects the decision of when and if anticoagulation should be re-started.

VKA-TREATED PATIENTS. If bleeding occurred in a VKA-treated patient with a high INR who is at high risk for stroke, a reasonable course of action after resolution of the bleeding episode might be to restart warfarin with careful follow-up of INR values. If a drug interaction with warfarin can be identified and avoided, VKAs can be restarted with more confidence. Alternatively, if the bleeding was not gastrointestinal or the TTR was low, it may be appropriate

to substitute a DOAC for warfarin therapy. Recent guidelines suggest the use of antiplatelet agents in this situation, although at a class IIb level (66).

If bleeding occurs in a VKA treated patient with an INR of 2-3, the clinician should avoid the temptation to lower the INR goal, due to increased risk of thromboembolic events with an INR below 2 (67). In patients with bleeding and a normal INR, knowledge of the TTR (68) may be helpful.

DOAC-TREATED PATIENTS. Minor bleeding in a DOAC-treated patient presents a unique challenge. Reducing the dose of the DOAC also may reduce stroke prevention benefits. Changing to an alternative DOAC in cases of minor bleeding may be an option. If minor gastrointestinal bleeding occurs in a patient on dabigatran or rivaroxaban, the patient should switch to apixaban, or edoxaban 30 mg since gastrointestinal bleeding is more common with dabigatran (33) and perhaps with rivaroxaban (34) than the other 2 agents. Other patients might benefit from a switch from a DOAC to a VKA.

No clinical trials currently address the question of administration of either warfarin or a DOAC following major bleeding. However, if a patient at high risk for stroke has a major bleeding episode associated with VKA and a normal INR, alternative therapies might be considered. Clinical trials of direct thrombin inhibitors and FXa inhibitors in stroke prevention in AF have consistently shown a > 50% reduction in CNS bleeding with the newer agents compared with warfarin, although the mechanism is uncertain.

CONCOMITANT COMPLEX DISEASE STATES THAT OCCUR IN AF PATIENTS ON OACT

Patients with AF requiring OACT frequently have comorbid conditions that increase risks of bleeding, impact the risk benefit ratio of anticoagulation, or require additional therapy such as

antiplatelet agents. The evolution of therapy in such patients is on going. This is especially true with the use of DOACs plus anti-platelet therapy (either single or dual).

Combining antiplatelet agents with anticoagulants increases the risk of bleeding. In the RE-LY trial (20) the risk of major bleeding increased from 2.8%/year to 4.8%/year when antiplatelet agents were added to warfarin. The risk of major bleeding was 2.6%/year with dabigatran 150 mg bid but increased to 4.4%/year with the addition of antiplatelet agents. A similar analysis from the ARISTOTLE trial noted increased bleeding when aspirin was used in conjunction with either warfarin or apixaban, although the absolute bleeding risk was higher with the combination of aspirin and warfarin compared with aspirin and apixaban (69).

Two ongoing trials may inform the question. The Randomized Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy Strategy with Warfarin in patients with non-valvular AF that have undergone PCI with stents (RE-DUAL PCI) will evaluate clinically relevant bleeding and thromboembolic events in patients treated with dabigatran plus a P2Y12 inhibitor compared with the current standard of warfarin plus dual antiplatelet therapy (DAPT). An 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 (PIONEER-AF PCI) will compare clinically significant bleeding in 3 arms of therapy: (1) rivaroxaban 15 mg daily plus a P2Y12 inhibitor, (2) rivaroxaban 2.5 mg bid plus a P2Y12 inhibitor and aspirin 75-100 mg daily, or (3) a VKA adjusted to an INR of 2-3, plus a P2Y12 inhibitor and aspirin 75-100 mg daily.

RECENT CORONARY STENT AND NEW ONSET AF

AF occurs in 5 to 10% of myocardial infarction patients and is associated with higher mortality compared to patients without AF (70). If stroke risk is low based on CHA_2DS_2-VASc score then

such patients could be treated with DAPT without the addition of anticoagulation. Observational data from the Danish registry (18) suggest that anticoagulants plus clopidogrel appear to be safer than triple therapy, although the efficacy of this combination has not been evaluated in randomized trials. Data from an open-label randomized trial in PCI patients (71) reported less bleeding and no increase in ischemic complications in patients treated with clopidogrel plus VKA compared with triple therapy. However, larger blinded studies are needed to confirm these findings. In patients who require triple therapy, the use of bare metal stents should be encouraged, and the duration of triple therapy kept as short as possible.

ELECTIVE STENTING IN PATIENTS WITH ESTABLISHED AF ON ANTICOAGULANTS

In patients with established AF on coumadin requiring elective stenting, concomitant glycoprotein IIb/IIIa inhibitors should generally be avoided. Radial access and bare metal stenting are preferred, as the former reduces access site bleeding and the latter minimizes the duration of triple therapy. As the duration of DAPT shortens with newer generation drug-eluting stents, this approach is changing and clinical trials are ongoing. Previously such patients may have been transitioned to warfarin, but these studies may affect this approach. If triple therapy (including VKA) is used low-dose aspirin plus clopidogrel is recommended in lieu of ticagrelor or prasugrel, since bleeding risks with VKA in conjunction with ticagrelor or prasugrel are higher than with clopidogrel. A lower target INR for warfarin (2.0-2.5) should be considered (72). A recent European Consensus paper (73) suggests a 3-phase approach in patients with AF and elective stenting. Patients at high stroke and high bleeding risk (CHA_2DS_2-VASc ≥ 2 and HAS-BLED ≥ 3) should receive 4 weeks of triple therapy, up to 12 months of clopidogrel or aspirin plus an anticoagulant, and lifetime anticoagulation with or without an antiplatelet drug. Patients

at lower stroke and bleeding risk (CHA_2DS_2-VASc of 1 and HAS-BLED 0-2) should receive 4 weeks to 6 months of triple therapy, up to 12 months of clopidogrel or aspirin plus an anticoagulant, and lifetime anticoagulation.

ACUTE CORONARY SYNDROMES IN PATIENTS WITH ESTABLISHED AF ON ANTICOAGULANTS

Low dose rivaroxaban (2.5 mg bid) for acute coronary syndromes (ACS) is approved in Europe as adjunctive therapy. This dose may not be optimal for the prevention of stroke in patients with AF, and rivaroxaban is not approved for this indication in the United States. Temporary discontinuation of DOAC should be considered in patients who are on DOACs at the time of an ACS, and if either ticagrelor or prasugrel is administered, since bleeding risks with these agents plus DOACs are unknown. Low dose is preferable to full dose aspirin. Bivalirudin may be a preferable acute anticoagulant, due to bleeding risk in the face of residual DOAC effect. Parenteral anticoagulation with heparin can be undertaken after DOAC effect has dissipated (16). Bare metal stenting and radial approach is preferable (59). Recent ACC/AHA ACS Guidelines state that anticoagulation may be interrupted at the time of procedure and that it "may be reasonable" to consider clopidogrel and anticoagulants in lieu of triple therapy (2). The European Consensus paper (74) suggested a similar 3 phase approach in ACS, with the patients at highest risk of both stroke and bleeding receiving 4 weeks of triple therapy followed by up to 12 months of a single antiplatelet plus anticoagulation, and patients at low risk receiving 6 months of triple therapy followed by up to 12 months of a single antiplatelet drug plus anticoagulation.

PATIENTS WITH ESTABLISHED AF ON ANTICOAGULANTS WITH MEDICALLY MANAGED CORONARY DISEASE

Although patients with medically managed coronary artery disease following ACS may benefit from dual antiplatelet therapy, (74) treatment must be individualized in patients who are concomitantly on anticoagulants. The Warfarin-Aspirin Reinfarction II (WARIS II) Trial demonstrated a reduction in subsequent MI rates with warfarin and aspirin compared to warfarin alone (75), although it should be noted that this was not an AF trial. Data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) (76) also support the use of warfarin instead of antiplatelet therapy in stable CAD, by showing that the MI rate in AF patients assigned to warfarin was similar to those assigned to aspirin plus clopidogrel. In patients with stable CAD with AF and an ACS > 1 year previously, care should be individualized; single antiplatelet therapy or no antiplatelet therapy with anticoagulation may be preferred options (2).

PATIENTS WHO DEVELOP AF > 1 MONTH AFTER BARE METAL STENT OR > 6 MONTHS AFTER DRUG ELUTING STENT

Data are conflicting about whether patients with stable CAD should be treated with a DOAC or warfarin alone, assuming this is warranted based on CHA_2DS_2-VASc score. In the RE-LY trial (31), there was a trend towards increased myocardial infarction, and meta-analysis suggested an association with direct thrombin inhibitors and myocardial infarction (77). However, ischemic events were not increased in RE-LY (78) and a "real world" Danish study of dabigatran use did not suggest an increased frequency of myocardial infarction (79). Similarly a survey of 134,414 Medicare patients (37,587 patient-years) treated with dabigatran or warfarin for non valuvlar AF showed no increase in MI with dabigatran (80). **Figures 4a and 4b** summarize recommendations for OACT with various coronary artery disease conditions.

PATIENTS WITH CEREBRAL VASCULAR DISEASE AND ATRIAL AF

PATIENTS NOT PREVIOUSLY ON ANTICOAGULANTS. Patients presenting with acute ischemic stroke or transient ischemic cerebral attack of presumed cardio-embolic origin should receive anticoagulation therapy. The timing and initiation of therapy depends upon the size of the stroke and the perceived risk of hemorrhagic transformation (66). In such patients, all DOACs may be preferable to warfarin because of the universally reduced risk of ICH. Although this is true in the convalescent phase of presumed thromboembolic stroke (after > 1 month) it has not been studied in the acute phase of such strokes. New AHA/ASA Guidelines recommend individualized therapy with VKA (Class 1, level of evidence A), apixaban (Class 1, level of evidence A, dabigatran (Class 1, level of evidence B) or rivaroxaban (Class IIa, level of evidence B) (81). The European Society of Cardiology AF Guidelines suggest the use of DOAC over VKA in most patients with non-valvular AF based on net clinical benefit (Class IIa recommendation) (82). Because of the rapid onset of action, bridging therapy with low molecular weight heparin is not required. For patients unable to take anticoagulants, aspirin is an alternative option and the addition of clopidogrel might be reasonable. Two clinical trials of DOACs compared to aspirin in patients with embolic strokes of undetermined source (RE-SPECT- ESUS [dabigatran] and NAVIGATE- ESUS) are currently recruiting patients) (83, 84). Previous studies have demonstrated a high prevalence of AF detected by prolonged monitoring in patients presenting with cryptogenic TIA or stroke (66, 85). Anticoagulation strategies in this subset of patients have not been rigorously tested for risk and benefit.

PATIENTS PREVIOUSLY MAINTAINED ON OACT PRESENTING WITH ACUTE ISCHEMIC STROKE

In patients previously maintained on DOACs, the balance of risks versus benefits of thrombolytic therapy for acute ischemic stroke is unclear. If there is uncertainty about the time since last

administration of the DOAC or if blood studies, e.g. PTT for dabigatran, or PT for FXa inhibitors indicate residual drug effect, thrombolysis should generally not be offered. In patients treated with warfarin, the risk of ICH with use of recombinant tissue plasminogen activator appears to be low when the INR is ≤1.7 (86).

PATIENTS IN CONVALSCENT PHASE OF ISCHEMIC STROKE TREATED WITH VKAS

In theory, patients presenting with an ischemic stroke and a therapeutic INR represent a drug failure of VKA and may be candidates for DOACs. Patients with stroke ≥ 2 weeks prior to presentation appear to have the same relative benefits of DOAC versus warfarin (87, 88). If early initiation of a DOAC is contemplated in a patient previously on warfarin it would seem prudent to allow the effect of warfarin to dissipate prior to initiating therapy.

PATIENTS WITH HEMORRHAGIC STROKE ON OACT

Hemorrhagic stroke is a complication of anticoagulant therapy. VKAs account for 12-14% of patients with ICH (89). Anticoagulants should be immediately discontinued and efforts to reverse anticoagulation undertaken as previously described. Although patients who develop hemorrhagic stroke on warfarin could theoretically be candidates for a DOAC in the convalescent phase, this hypothesis is untested, as most DOAC studies exclude patients with prior ICH. Package labeling for both VKAs and DOACs state that ICH is a contraindication for anticoagulation unless the cause of the hemorrhage has been identified and corrected. According to the stroke guidelines patients at high risk for recurrent hemorrhage may be considered candidates for antiplatelet therapy in lieu of anticoagulation. (Class IIB, level of evidence B) (66).

PATIENTS WITH SIGNIFICANT CAROTID STENOSIS AND AF

Patients with carotid stenosis are often prescribed antiplatelet therapy for stroke prevention. At this time, it is unknown whether the addition of antiplatelet therapy improves outcomes compared to anticoagulation alone in patients with AF and carotid disease. Carotid endarterectomy for which single agent antiplatelet therapy is usually prescribed may be preferred over carotid artery stenting that requires DAPT (59, 90). More data are needed, and this topic is not addressed in the new stroke guidelines.

PATIENTS WITH PERIPHERAL ARTERY DISEASE AND AF

There are no data on the combination of DAPT and anticoagulation in patients with AF and peripheral artery disease managed with percutaneous intervention (90). Patients with medically managed peripheral artery disease are generally prescribed antiplatelet therapy. The addition of anticoagulation increases bleeding risk, as demonstrated in the WAVE Trial (89), in which patients with peripheral artery disease were assigned to warfarin plus an anti-platelet agent compared to an anti-platelet agent alone. Combined therapy was not associated with an improvement in the combined endpoints of MI, stroke, or cardiovascular death or MI, stroke, cardiovascular death or severe ischemia (coronary or peripheral arterial). The risk of life-threatening bleeding, however, occurred in 4.0% of the combined group and 1.2% of the anti-platelet group. Therefore, risk benefit ratio needs to be estimated in deciding whether these patients should receive concomitant antiplatelet therapy and anticoagulation. Single antiplatelet therapy makes good clinical sense under these circumstances, since the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (91) of aspirin alone compared with clopidogrel plus aspirin in patients at high risk for cardiovascular events demonstrated that the addition of clopidogrel did not reduce the rate of the primary endpoint of MI, stroke, or cardiovascular death, but that bleeding increased with DAPT.

THE USE OF DOACS IN PATIENTS WITH MECHANICAL HEART VALVES AND IN THE SETTING OF CARDIAC SURGERY

The RE-ALIGN study tested high-dose dabigatran as an alternative to warfarin in patients with mechanical heart valves. This study was stopped early due to excessive bleeding and higher thromboembolic events in patients treated with dabigatran. The rapid onset of action of dabigatran in the postoperative cardiac surgery setting appears to pose a risk of serious bleeding, -particularly pericardial bleeding requiring reoperation. Until further results are available, the use of all the DOACs should be avoided for patients with mechanical prosthetic valves outside of a clinical trial. The FDA prescribing information for the DOACs are even more restrictive, stating that they should be avoided in all prosthetic valves, although DOACs were used in patients with bioprosthetic valves in several AF clinical trials. The data from RE-ALIGN with high-dose dabigatran raised concern for the use of these drugs in the immediate cardiac postoperative surgical setting (92).

DOACS AT THE TIME OF CARDIOVERSION

Patients who have AF or atrial flutter lasting > 48 hours are required to have therapeutic INR (2-3) for 3-4 weeks prior to cardioversion regardless of method (pharmacological or electrical) or CHA_2DS_2-VASc score (2, 93-95). Alternatively, for patients who have not been on 3-4 weeks of continuous therapeutic VKAs, transesophageal echocardiography is reasonable prior to cardioversion (2, 96). With VKAs, awaiting therapeutic INRs weekly up to the time of cardioversion has led to delays in cardioversion (97).

Three major randomized clinical trials have evaluated subsets of patients who underwent cardioversion (RELY, ROCKET AF, ARISTOTLE). A prospective study involving the use of rivaroxaban has also been published (98). In all studies the risk of stroke was low in the weeks

following cardioversion and was comparable to that with VKA. Of note is the fact that transesophageal echocardiography did not reduce the rate of thromboembolic events (99). Based on these data, for patients with AF or atrial flutter of unknown duration, or duration ≥ 48 hr anticoagulation with DOACs is required for ≥ 3 weeks prior to cardioversion and should be continued for ≥ 4 weeks post cardioversion (2).

THE ROLE OF DOACS IN AF ABLATION

Current recommendations for the prevention of stroke at the time of AF ablation are for continuous VKA (warfarin) anticoagulation with a low level therapeutic range (2.0-2.5). Because it is difficult to maintain an INR within this narrow range, DOACs may assume a more important role. Single and multicenter studies have examined the efficacy and safety of DOACs compared with uninterrupted warfarin in patients undergoing AF ablation (100-105). In general, centers and operators are either transitioning patients to warfarin for the periprocedural period or stopping the DOAC 1-2 days prior to procedure without bridging (106).

A prospective matched multicenter observational study of 290 patients compared therapeutic warfarin (2-3.5) to dabigatran 150 mg bid for 3 weeks prior to ablation (with dabigatran held morning of procedure and resumed 3 hours post). A significant increase in composite bleeding and thromboembolic complications was noted with dabigatran (101). Several studies in which dabigatran was held at least 24 hours prior to procedure and restarted 4-22 hr later did not show any significant bleeding or thromboembolic complications compared to warfarin. These data suggest dabigatran should be interrupted ≥ 24 hours prior to the procedure in order to prevent significant bleeding (102-104).

A multicenter, prospective study evaluated the safety and efficacy of rivaroxaban in comparison with uninterrupted warfarin therapy during AF ablation. Rivaroxaban was held 16 hours prior to

ablation and resumed 6 hours after hemostasis was obtained. There was no difference in major or minor bleeding complications. One TIA occurred in each group and no periprocedural stroke or mortality occurred in either group. The authors concluded rivaroxaban, with the dose held on the day of procedure, appears to be equally safe and effective when compared to uninterrupted warfarin (101).

CONCLUSIONS

Roundtable discussion of 4 major topics related to the integration of DOACs into clinical practice resulted in consensus in many areas, but questions and challenges in others. A poll of the participants was unanimous in the opinion that the stakeholder groups need to continue dialogue about the integration of these drugs into practice. **Table 5** includes a list of unanswered questions is listed below.

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FIGURE LEGENDS

Central Illustration. Complex Interactions Surrounding the Anticoagulation Patient

New drugs, such as the direct acting oral anticoagulants (DOACs) are tested for safety and efficacy in clinical trials involving specific patient populations with rigorous inclusion and exclusion criteria. Labels with prescribing instructions are written based on those trial data and data from a limited number of supporting trials using specific patient samples to test a limited number of drug interactions and a few select special patient populations. Once approved for use, these drugs are introduced into a much more complex system of care. Patients taking DOACs move between hospital care and outpatient care, and interact with many health care workers in a complex system. Patients taking DOACs have multiple co-morbidities, and take DOACs for long periods of time. Coordination of care is of the utmost importance to provide safe and effective management of oral anticoagulation in the modern healthcare environment.

Figure 1. Definitions of Bleeding

Figure 2. Acute Management of Bleeding in a Patient Receiving Oral Anticoagulation

All patients receive a basic level of care (green box) with additional care provided depending upon the degree of bleeding (yellow and red boxes.

apTT = activated partial thromboplastin time; CBC = complete blood count; CYP3A4 = Cytochrome P450 3A4; DOACs = direct oral anticoagulants; FFP = fresh frozen plasma; NSAIDs = nonsteroidal anti-inflammatory drugs; P-gp = P-glycoprotein; PT = prothombin time

Figure 3. Laboratory testing for anticoagulant activity.

Red bars correspond to the approxiate range of detectability (i.e. sensitivity) and vertical hatching to the approximate range over which drug plasma levels may be quantified (i.e. linearity) of each assay to below, within, and above typical on-therapy plasma concentrations of DOACs (41).

Figure 4a. Patients on Anticoagulants for AF Requiring Coronary Artery Stenting

ACS = acute coronary syndrome; AF = atrial fibrilliation; ASA = aspirin; BMS = bare metal stent; INR = international normalized ratio; VKA = vitamin K antagonist

Figure 4b. Patients on DAPT for Coronary Artery Stent who Develop AF

ACS = acute coronary syndrome; AF = atrial fibrilliation; DAPT = dual antiplatelet therapy; DOAC = direct-acting oral anticoagulant; VKA = vitamin K antagonist

Figure 5. Unanswered Questions

Table 1. The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2–VASc

Risk Factor	Score
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years old	2
Diabetes mellitus	1
Stroke or transient ischemic attack or thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (i.e., female gender)	1
Maximum total points	**9**

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Table 2. Summary of Selected DOACs Clinical Trials

	RE-LY (33) N = 18,113 (3 arms)*	ROCKET-AF (34) N = 14,264	ARISTOTLE (35) N = 18,201	ENGAGE AF-TIMI 48 (36) N = 21,105 (3arms)†
Drug, dose	Dabigatran 150 mg BID	Rivaroxaban 20 mg/daily	Apixaban 5 mg BID	Edoxaban 60/30 daily
Adjusted dose?	No	Yes, at randomization only: 15 mg daily if CrCl 30-49 mL/min	Yes, at randomization only: 2.5 mg BID if two of: age ≥ 80 y, weight < 60 kg, SCr ≥ 1.5 mg/dL	Yes, at randomization and during study: Both doses halved if any 1 of the following: CrCl 30-50 mL/min, weight ≤ 60 kg, use of verapamil, quinidine, or dronedarone
Design	Randomized open-label	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy	Randomized double-blind, double-dummy
Mean age, y	71.5	73	70	72
Prior stroke/ transient ischemic	20%	55%	19%	28%

attack/systemic embolism				
Mean $CHADS_2$	2.2	3.5	2.1	2.8
Warfarin-naïve	50.4%	37.6%	43%	41%
Comparator Warfarin INR 2-3	67% TTR (median)	58% TTR (median)	66% TTR (median)	68% (median)
Comparator Warfarin INR 2-3	64% TTR (mean)	55% TTR (mean)	62% TTR (mean)	65% (mean)
Outcome (RR ±95% CI)				
Stroke/Systemic embolism	0.66 (0.53-0.82)	0.88 (0.75-1.03)	0.79 (0.66-0.95)	0.88 (0.75-1.03)
Ischemic stroke	0.76 (0.60-0.98)	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.00 (0.83-1.19)
Hemorrhagic stroke	0.26 (0.14-0.49)	0.59 (0.37-0.93)	0.51 (0.35-0.75)	0.54 (0.38-0.77)
Major bleeding	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.80 (0.71-0.91)
Intracranial hemorrhage	0.40 (0.27-0.60)	0.67 (0.47-0.93)	0.42 (0.30-0.58)	0.47 (0.34 -0.63)
Gastrointestinal bleeding	1.50 (1.19–1.89)	1.39 (1.19–1.61)	0.89 (0.70–1.15)	1.23 (1.02–1.50)
Cardiovascular mortality	0.85 (0.72-0.99)	0.89 (0.73-1.10)	0.89 (0.76-1.04)	0.86 (0.77-0.97)
All-cause mortality	0.88 (0.77-1.00)	0.85 (0.70-1.02)	0.89 (0.80-0.998)	0.92 (0.83-1.01)

*Results are shown for dabigatran 150 mg BID.

†Results are shown for edoxaban 60 mg daily

Estimate Creatinine Clearance (CrCL) using Cockcroft-Gault formula:
(140-age)x(weight in kg)x(0.85 if female)/(72)x(creatinine in mg/dL)

Table 3. FDA Approved Direct Acting Oral Anticoagulants for Non-Valvular Arial Fibrillation*

	Dabigatran (Pradaxa®) (108)	**Rivaroxaban (Xarelto®) (109)**	**Apixaban (Eliquis®) (110)**	**Edoxaban (Savaysa®) (24)**
Mechanism of Action	Direct Thrombin Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor

Dosing for Non-Valvular AF†	150 mg twice daily	20 mg daily with evening meal	5 mg twice daily	If CrCL‡ > 50 mL/min to ≤ 95 mL/min: 60 mg daily
Dosing considerations for Non-Valvular AF with renal adjustments	**If CrCL‡ is 15-30 mL/min:** 75 mg twice daily **If CrCL is < 15 mL/min: Avoid use**	If CrCL‡ **is 15-50 mL/min:** 15 mg daily with evening meal	**If the patient has at least 2 of the following:** - Age ≥ 80 years old - Weight ≤ 60 kg - SCr ≥ 1.5 mg/dL: 2.5 mg twice daily	If CrCL‡ > 95 mL/min: do not use; may have an increased risk of ischemic stroke as compared to warfarin If CrCL‡ 15-50 mL/min: 30 mg daily
Dosing considerations for Non-Valvular AF with hepatic adjustments	Administration in patients with moderate hepatic impairment (Child-Pugh B) showed no evidence of change in exposure or pharmacodynamics	Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic impairment associated with coagulopathy	Mild hepatic impairment: No dose adjustment needed Moderate hepatic impairment: No dosing recommendation available Severe hepatic impairment: Avoid use	Avoid use in patients with Child-Pugh B and C hepatic impairment
Drug Interactions	Avoid concomitant use with P-gp inducers (e.g., rifampin). P-gp inhibitors and impaired renal function can lead to increased exposure to dabigatran: avoid concomitant use with severe renal impairment (<	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, ritonavir, erythromycin) or reduce apixaban dose Avoid concomitant use	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, ritonavir, erythromycin) or reduce apixaban dose Avoid concomitant use	Avoid concomitant use with P-gp inducers (e.g., rifampin)

	30mL/min); for moderate renal impairment reduce dose to 75mg twice daily when used concomitantly with dronedarone or systemic ketoconazole	with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, phenytoin, carbamazepine) Avoid concomitant use with other anticoagulants	with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, phenytoin, carbamazepine) Concomitant use with antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID increases bleeding risk	
Major Adverse Effects	Dyspepsia, bleeding	Bleeding	Bleeding	Bleeding
Monitoring§	Baseline laboratory assessment: Hemoglobin/hematocrit, liver function, renal function, PT/INR At every visit: Adherence, signs/symptoms of bleeding or thromboembolism, side effects, concomitant medications (including over-the-counter) Annual laboratory assessment: Hemoglobin/hematocrit, renal function, liver function If CrCl 30-60 mL/min, > 75 years old, or fragile: renal function q 6 months If CrCl 15-30 mL/min: renal function q 3 months If condition changes that might impact anticoagulation therapy: check renal and/or liver function			

*Other indications for these agents are not included in this table. Refer to the prescribing information for complete information

† May need to adjust dose or avoid based on concomitant medications.

‡ Estimate Creatinine Clearance (CrCL) using Cockcroft-Gault formula: (140-age)x(weight in kg)x(0.85 if female)/(72)x(creatinine in mg/dL)

§ Adapted from (16)

AF=atrial fibrillation; CrCL= Creatinine Clearance; CYP3A4=Cytochrome P450 3A4; INR=International Normalized Ratio; NSAID=Nonsteroidal anti-inflammatory drug; P-gp=P-glycoprotein; PT=Prothrombin Time.

Table 4. Selected Drug Interactions with Direct Acting Oral Anticoagulants*

	Mechanism of Drug Interaction	Dabigatran (Pradaxa®) (108)	Rivaroxaban (Xarelto®) (109)	Apixaban (Eliquis®) (110)	Edoxaban (Savaysa®) (24)
Carbamazepine	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Clarithromycin	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	No adjustment needed	Reduce dose from 5mg twice daily to 2.5mg twice daily If on 2.5mg twice daily, discontinue apixaban	No specific recommendations
Dronedarone	P-gp inhibitor	With CrCL 30-50 mL/min, reduce dose to 75mg twice daily	No specific recommendations	No specific recommendations	No adjustment needed
Itraconazole	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	Avoid use	Reduce dose from 5mg twice daily to 2.5mg twice daily If on 2.5mg twice daily, discontinue apixaban	No specific recommendations
Ketoconazole	Strong inhibition of CYP3A4 and P-gp	With CrCL 30-50 mL/min, reduce dose to 75mg	Avoid use	Reduce dose from 5mg twice daily to 2.5mg twice daily If on 2.5mg	No specific recommendations

		twice daily		twice daily, discontinue apixaban	
Phenytoin	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Rifampin	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	Avoid use
Ritonavir	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	Avoid use	Reduce dose from 5mg twice daily to 2.5mg twice daily If on 2.5mg twice daily, discontinue apixaban	No specific recommendations
St. John's wort	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations

* This is not a comprehensive list of all drug interactions. Please refer to individual medication manufacturer prescribing information for complete information
Estimate Creatinine Clearance (CrCL) using Cockcroft-Gault formula:
(140-age)x(weight in kg)x(0.85 if female)/(72)x(creatinine in mg/dL)

CYP3A4 = Cytochrome P450 3A4; P-gp = P-glycoprotein; CrCL = Creatinine Clearance

Table 5. Transitioning between Anticoagulants and Interruption of Therapy*

Conversion	Apixaban (Eliquis®) (110)	Rivaroxaban (Xarelto®) (109)	Dabigatran (Pradaxa®) (108)	Edoxaban (Savaysa®) (24)
From Warfarin to DOAC	Stop warfarin and start apixaban when INR < 2	Stop warfarin and start rivaroxaban when INR < 3(109)	Stop warfarin, start dabigatran when INR < 2	Stop warfarin and start edoxaban when INR ≤ 2.5
From DOAC to Warfarin‡	Stop apixaban and start warfarin and parenteral anticoagulant when next dose of apixaban would be due; discontinue parenteral agent when INR in therapeutic range	Stop rivaroxaban and start warfarin and parenteral anticoagulant when next dose of rivaroxaban would be due; discontinue parenteral agent when INR in therapeutic range	If CrCL ≥ 50mL/min, start warfarin 3 days before stopping dabigatran If CrCL 30-50 mL/min, start warfarin 2 days before stopping dabigatran If CrCL 15-30 mL/min, start warfarin 1 day before stopping dabigatran If CrCl < 15 mL/min, no available recommendation	Oral option: Reduce edoxaban dose by 50% and start warfarin; check INR at least weekly and just prior to edoxaban dose. When INR ≥ 2, discontinue edoxaban. Parenteral option: Stop edoxaban; start parenteral anticoagulant and warfarin at time the next dose of edoxaban would be due. When INR ≥ 2, discontinue edoxaban.
From Parenteral Agent to DOAC	Discontinue parenteral agent; start apixaban at the time the next dose of parenteral agent would be due	LMWH: Discontinue LMWH; start rivaroxaban 0-2 hours before next scheduled evening dose of LMWH and omit administration of LMWH Unfractionated	LMWH: Discontinue LMWH; start dabigatran 0-2 hours before the time the next dose of LMWH would be due. Unfractionated heparin intravenous infusion: Initiate	LMWH: Discontinue LMWH; start edoxaban at the time the next dose of LMWH would be due. Unfractionated heparin intravenous infusion: Initiate

		heparin intravenous infusion: Initiate rivaroxaban when discontinuing heparin infusion	dabigatran when discontinuing heparin infusion	edoxaban 4 hours after discontinuing heparin infusion
From DOAC to Parenteral Anticoagulant	Discontinue apixaban; start parenteral agent at the time the next dose of apixaban would be due	Discontinue rivaroxaban; start parenteral agent at the time the next dose of rivaroxaban would be due	If CrCL ≥ 30 mL/min; discontinue dabigatran; start parenteral agent 12 hours after last dabigatran dose If CrCL < 30 mL/min; discontinue dabigatran; start parenteral agent 24 hours after last dabigatran dose	Discontinue edoxaban; start parenteral agent at the time the next dose of edoxaban would be due
From DOAC to DOAC	Discontinue apixaban; start DOAC at the time the next dose of apixaban would be due	Discontinue rivaroxaban; start DOAC at the time the next dose of rivaroxaban would be due	No information available; consider patient specific characteristics (eg., renal function, risk of bleeding or stroke)	Discontinue edoxaban; start DOAC at the time the next dose of edoxaban would be due
Temporary Interruption of DOAC for Surgery and Other Invasive Procedures	**Moderate – High Risk Bleeding:** Discontinue at least 48 hours prior to surgery or invasive procedure **Low Risk Bleeding**: Discontinue at least 24 hours prior to surgery or invasive procedure	Discontinue at least 24 hours prior to surgery or invasive procedure	If **CrCl ≥ 50 mL/min:** Discontinue at least 1-2 days prior to surgery or invasive procedure **If CrCL < 50 mL/min:** Discontinue at least 3-5 days prior to surgery or invasive procedure	Discontinue at least 24 hours prior to surgery or invasive procedure

* Refer to the prescribing information for complete information

‡ DOACs can impact INR so INR monitoring during conversion from DOAC to warfarin is not clinically useful

DOAC=Direct Acting Oral Anticoagulants; CrCL=Creatinine Clearance; INR=International Normalized Ratio

Estimate Creatinine Clearance (CrCL) using Cockcroft-Gault formula:
(140-age)x(weight in kg)x(0.85 if female)/(72)x(creatinine in mg/dL)

Table 6. Education Topics for Oral Anticoagulants

VKA and DOACS	
Anticoagulation basics	Reason for anticoagulation
	How medication reduces AF complications
	Generic, trade names
	Onset, duration of action
	Duration of therapy
	Reversibility
	Storage
Adherence	When to take doses
	What to do if a dose is missed
	Do not run out of this medication; consequence of non-adherence
	Consequence of taking too much
Risk and benefits	Common signs and symptoms of clot; what to do if they occur
	Common signs and symptoms of bleeding; what to do if they occur
	Need for birth control in women of childbearing age
Preventative care	Precautionary measures to minimize risk of trauma or bleeding
	Potential drug interactions; which providers to notify when medication
	Regimen changes
Alcohol	Avoid/limit alcohol intake
Aspirin	Avoid unless clearly indicated
NSAIDs	Avoid or minimize use
Self-care	Common adverse effects, allergic reactions
Accessing healthcare	Which providers to notify of anticoagulant use
	Which providers to notify when dental, surgical, invasive procedures are scheduled
	Carrying identification (medication bracelet or necklace, wallet card)
General laboratory monitoring	Frequency, what will be checked
Dabigatran Only	
Adherence	Swallow whole, do not break, crush, or open capsule. Take with full glass of water.
Storage	Keep in original container; do not put in pillbox (do not discard desiccant)
Self-care	May increase GI upset; discuss with clinician if bothersome.
Rivaroxaban Only	

Adherence	Take with food (evening meal)
VKA Only	
Diet	Influence of dietary vitamin K, need for consistency
INR monitoring	Meaning, significance, target
	Frequency

AF = atrial fibrillation; DOACs = direct-acting oral anticoagulants (apixaban, dabigatran, rivaroxaban); GI = gastrointestinal; INR = international normalized ratio; NSAIDs = Non-steroidal anti-inflammatory agents. VKA = Vitamin K Antagonist.

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