Thrombosis & Haemostasis: Research

Open Access

Austin Publishing Group

Review Article

The Expanded Role of Apixaban in Cardiovascular Disease Management: A Literature Review

Halder R[1], Javed B[1], Ajmal M[1,2]*, Khakwani KZR[1], Lee KS[1,2] and Acharya T[1,2]

[1]Department of Cardiology, The University of Arizona, USA

[2]Department of Cardiology, Sarver Heart Center, USA

***Corresponding author:** Muhammad Ajmal, The University of Arizona, Sarver Heart Center, Tucson, Arizona, USA

Received: June 17, 2022; **Accepted:** July 20, 2022; **Published:** July 27, 2022

Abstract

Direct Oral Anticoagulants (DOACs) are widely used for stroke prevention in non-valvular atrial fibrillation, treatment of deep venous thrombosis and pulmonary embolism, and prophylaxis of Venous Thromboembolism (VTE) after hip and knee surgery. Apixaban, a Factor Xa inhibitor, is one of the most efficacious DOACs with some of the lowest bleeding rates. It has therefore been widely adopted into clinical practice. In the recent years, its usefulness has been tested outside traditional clinical paradigms in coronary artery disease, VTE in malignancy, and deep venous thrombosis prophylaxis in acute medical illnesses. Other off label uses include treatment of left ventricular thrombus and transient post procedural use in transcatheter aortic valve replacement and left atrial appendage occlusion device placement. This review systematically evaluates the clinical evidence and knowledge gaps in expanded clinical use of apixaban.

Key Points

1. This article highlights the role of apixaban in various cardiovascular diseases.

2. The article will serve as a guide for all the health care providers to comprehensively review the data pertaining to the apixaban.

3. Table 1 summarizes the indications, dosages, and approval of apixaban in various indications.

Introduction

Vitamin K Antagonists (VKA) have been used for anticoagulation in humans since 1954. However, due to various limitations like drug-drug interactions, drug-food interactions, narrow therapeutic window, and need for a regular blood test to monitor therapeutic effect, Direct Oral Anticoagulants (DOAC) have emerged as a potentially preferred alternative [1]. Apixaban, one of the most frequently prescribed DOACs, is a direct Factor Xa inhibitor that has been studied in various thromboembolic and atherothrombotic conditions. Factor Xa plays a key role in intrinsic and extrinsic coagulation pathways by downstream activation of thrombin [2]. Apixaban is a small molecule that reversibly inhibits both free and clot-bound Factor Xa [2]. It is administered orally, absorbed rapidly, has a 12-hour half-life (therefore dosed twice a day), and is excreted via biliary, intestinal, and renal pathways [3].

Till recently, its use was limited to stroke prevention in Non-Valvular Atrial Fibrillation (NVAF) and treatment of deep venous thrombosis or venous embolism, but more evidence is emerging for a variety of conditions like coronary artery disease as well as for thromboprophylaxis. The purpose of this review is to provide a comprehensive overview of the various indications of apixaban use.

Literature Search Criteria

A review of literature was carried out from the PubMed database utilizing search terms, "oral anticoagulation," "apixaban," "new oral anticoagulants," "randomized control trial," "non-valvular atrial fibrillation,""venous thromboembolism," "pulmonary embolism," "deep venous thrombosis," "venous thromboembolism prophylaxis," "coronary artery disease," "venous thromboembolism associated with cancer," "obesity," "Post Transcatheter Aortic Valve Replacement (TAVR)," "Left ventricular thrombus," "Heart Failure with Reduced Ejection Fraction," "Left Atrial Appendage Occlusion (LAAO)," "Antiphospholipid Syndrome (APS)," "Kidney disease," "Liver disease," "Safety," "Reversal," and a combination of the above terms. The articles were then manually examined to exclude duplicate entries. Search was limited from November 2020 to March 2021 All the retrieved articles were in English language. Observational studies, personal opinions, editorials, correspondences, and perspective articles were excluded. Full text versions of the included articles were downloaded and evaluated by the authors to compile a narrative review of apixaban in cardiovascular disease management. Relevant details of the pharmacokinetic properties of the drugs were added to complete the drug profile independent of the above-mentioned literature search.

Stroke Prevention in Non-Valvular Atrial Fibrillation

Atrial fibrillation is one of the most common clinically manifested arrhythmias causing significant morbidity and mortality via systemic arterial thromboembolism, particularly stroke [3]. Traditionally, warfarin has been used for anticoagulation to prevent strokes in atrial fibrillation based on an elevated CHA2DS2-VASc score [4,5] while others receive aspirin.

The AVERROES (Apixaban versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are

Citation: Halder R, Javed B, Ajmal M, Khakwani KZR, Lee KS and Acharya T. The Expanded Role of Apixaban in Cardiovascular Disease Management: A Literature Review. Thromb Haemost Res. 2022; 6(2): 1078.

Table 1: Indications, Dosage and Approval of Apixaban (DVT-Deep venous thrombosis, PE-pulmonary embolism, LAAO-Left atrial appendage closure).

Indication	Dosage& Duration of Treatment	RCT evidence	Net benefit	Year of approval	Region
Non-valvular atrial fibrillation	5 mg twice daily - indefinitely 2.5 mg twice daily if two of following:age ≥ 80 years, body weight ≤60 kg, serum creatinine ≥ 1.5mg/dL – indefinitely	Yes	Yes	2013	USA and Europe
Venous thromboembolism treatment	10 mg twice daily for first seven days, then 5 mg twice daily indefinitely	Yes	Yes	2014	USA and Europe
Long-term reduction of venous thromboembolism risk	2.5 mg twice daily after six months of initial treatment for DVT or PE	Yes	Yes	2014	USA and Europe
Venous thromboembolism prophylaxis following hip/knee replacement surgery	2.5 mg twice daily for 35 days after hip replacement surgery 2.5 mg twice daily for 12 days after knee replacement surgery	Yes	Yes	2014	USA and Europe
Venous Thromboembolism Prophylaxis in Acute Medical Illness	2.5 mg twice daily for 30 days	Yes	No	-	-
Treatment of Venous Thromboembolism with Cancer	10 mg twice daily for first seven days, then 5 mg twice daily indefinitely	Yes	Yes	-	-
Acute coronary syndrome	5 mg twice daily indefinitely	Yes	No		
Acute coronary syndrome or PCI with co-existing atrial fibrillation	5 mg twice daily indefinitely	Yes	Yes	-	
Left ventricular thrombus	5 mg twice daily indefinitely	No	-	-	-
Post TAVR	5 mg twice daily indefinitely	No	-	-	-
Post LAAO Closure	5 mg twice daily indefinitely	No	-	-	-

Unsuitable for Vitamin K Antagonist Treatment) trial demonstrated that apixaban compared to aspirin reduced the risk of stroke or systemic embolism by 55% (HR 0.45; 95% CI 0.32-0.62) without increasing the risk of major bleeding [6]. The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial subsequently showed that apixaban was not only non-inferior but in fact superior to warfarin in preventing stroke or systemic embolism with less bleeding and reduced mortality [7]. Specifically, in patients with atrial fibrillation and at least one additional risk factor for stroke, 5 mg twice daily of apixaban significantly decreased the risk of stroke and systemic embolism by 21%, major bleeding by 31%, and death by 11%. The major stroke reduction effect was via hemorrhagic stroke prevention [7]. A dose adjustment of 2.5 mg twice daily was used in subjects with two out of the following three high-risk features: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg per deciliter. The results of this trial led the Food and Drug Administration (FDA) to approve apixaban for stroke prevention in non-valvular atrial fibrillation in December 2012 [5]. Due to increased risk of thromboembolic complications in patients with atrial fibrillation and mechanical valves with another DOAC, dabigatran [8,9], apixaban was never systematically tested in subjects with valvular atrial fibrillation (currently defined as the presence of mechanical heart valve or moderate-to-severe mitral stenosis).

In the current American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2019 focused update on 2014 guidelines, apixaban has been given a class I recommendation (level of evidence B) [10] for stroke prevention in non-valvular atrial fibrillation with a CHA2DS2-VASc score of ≥2 in men and ≥3 in women [6]. In the 2014 ACC/AHA/HRS document, both sexes had a class I recommendation for use in CHA2DS2-VASc score ≥ 2 [7,11].

In a meta-analysis of phase-3 trials of DOACs, apixaban and dabigatran were found to be superior to warfarin in stroke prevention while rivaroxaban and edoxaban were non-inferior [12]. Further, apixaban and edoxaban had statistically lower rates of major bleeding compared to warfarin. Rates of major bleed with dabigatran, rivaroxaban, and warfarin were statistically similar. Thus, among all DOACs, only apixaban hasconsistently greater efficacy as well as safety compared to warfarin.

Venous Thromboembolism Treatment

Venous Thromboembolic (VTE) disease encompasses Deep Venous Thrombosis (DVT) and pulmonary embolism [8]. VTE has traditionally been treated with parenteral systemic anticoagulation transitioned to VKA for 6-12 months [13].

The AMPLIFY trial compared the safety and efficacy of apixaban 10mg twice daily for seven days, followed by 5mg twice daily with subcutaneous enoxaparin dosed at 1mg/kg every 12 hours for five days followed by warfarin (goal INR 2-3) among patients with acute VTE. The primary efficacy outcome of this study was recurrent symptomatic VTE or VTE-related death, which occurred at 2.3% in the apixaban group and 2.7% in the conventional therapy group (RR 0.84 [95% CI 0.60–1.18], P 0.001 for noninferiority). Major bleeding occurred in 0.6% of the apixaban arm and 1.8% in the conventional therapy group (RR 0.31 [95% CI 0.17–0.55], P,0.001 for superiority). Thus, apixaban was shown to be non-inferior to standard medical therapy for VTE and superior for bleeding risk reduction [14].

The AMPLIFY-EXT study further evaluated the extended use of apixaban for prophylaxis following the initial treatment for VTE. This study compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with VTE who had completed 6–12 months of anticoagulation therapy. The primary efficacy outcome was the composite of symptomatic recurrent VTE or all-cause death, which

occurred in 8.8% of the placebo group but only 1.7% in the apixaban 2.5 mg (RR 0.19 [95% CI 0.11–0.33], P0.001) and 1.7% in the apixaban 5 mg groups (RR 0.20 [95% CI 0.11–0.34], P0.001). There was no difference in the efficacy of apixaban 2.5 mg versus 5 mg; the RR was 0.97 (95% CI 0.46–2.02). The rate of major bleeding was 0.5% in the placebo group, 0.2% in the 2.5 mg apixaban group (RR 0.49 [95% CI 0.09–2.64]), and 0.1% in the 5 mg apixaban group (RR 0.25 [95% CI 0.03–2.24]). This study established that extended anticoagulation with apixaban at either 2.5 mg or 5 mg twice daily dose reduced the risk of recurrent VTE without increasing major bleeding rate [15].

These results led to the approval of apixaban for VTE treatment by the FDA in 2012 [9]. Based on these data and the data on other DOACs, the American College of Chest Physicians, in their 10th version of guidelines, recommended to prefer treatment of acute DVT/PE with DOACs over VKAs [16,17].

A systematic review and meta-analysis comparing rivaroxaban with apixaban in patients with acute VTE found that while both had equivalent efficacy in preventing recurrent VTE, apixaban hada lower risk of major and minor bleeding events [18].

Postoperative Venous Thromboembolism Prophylaxis after Hip and Knee Surgery

Venous Thromboembolism (VTE) is a serious complication after major orthopedic surgeries like hip and knee arthroplasty, and anticoagulants are used to prevent it. Low Molecular Weight Heparin (LMWH) for ten days was used as a standard of care after hip and knee arthroplasty based on the seventh American College of Chest Physicians recommendations on antithrombotic therapy [10] Thus clinical trials were conducted to see if DOACs like apixaban could replace LMWH to prevent VTE associated morbidity and mortality after orthopedic surgery [19].

Apixaban was studied in two large Phase III clinical trials of patients undergoing total knee replacement - ADVANCE-1 and ADVANCE-2 [20,21]. In the ADVANCE-1 trial, apixaban 2.5mg daily was compared to enoxaparin 30mg subcutaneous twice daily. The primary efficacy outcome occurred in 9.0% of the patients in the apixaban arm and 8.8% of the enoxaparin arm (RR 1.02 [95% CI 0.78–1.32], P0.06) [20]. The ADVANCE-2 trial had a different comparator arm and randomized patients to receive apixaban 2.5 mg twice daily or subcutaneous enoxaparin 40 mg once daily. The primary outcome occurred in 15% of patients in apixaban and 24% in enoxaparin arms (RR 0.62 [95% CI 0.51–0.74], P0.0001) [21]. This study established the non inferiority of apixaban for VTE prophylaxis after total knee replacement. A meta-analysis of three randomized trials of apixaban therapy compared with enoxaparin confirmed that apixaban was associated with a lower major bleeding risk than enoxaparin in apost-op setting (OR 0.55 [95% CI 0.32–0.96], P0.034) [22].

The ADVANCE-3 trial confirmed lower rates of venous thromboembolism without increased bleeding with the use of apixaban 2.5mg daily when compared with enoxaparin 40mg twice daily subcutaneously among patients undergoing hip replacement. Efficacy outcomes (composite of asymptomatic or symptomatic DVT, nonfatal PE, or all-cause death) occurred in 1.5% in the apixaban arm versus 3.9% in the enoxaparin arm (RR 0.36 [95% CI 0.22–0.54], P0.001 for both non inferiority and superiority). Major and clinically relevant non-major bleeding occurred in 4.8% of the patients in the apixaban arm and 5.0% in the enoxaparin arm (absolute difference in risk, -0.2% [95% CI -1.4% to 1.0%], P=0.72) [23]. Results of ADVANCE-2 and ADVANCE-3 led to the FDA approval of apixaban to prevent DVT following hip and knee placement surgery in 2012 [16]. Based on this data of apixaban and evidence on other DOACs, the American College of Chest Physicians recommended postoperative VTE prophylaxis with DOACs over VKA sin the 10th version of guidelines.

In a systematic review and meta-analysis comparing prolonged thromboprophylaxis with factor Xa inhibitors compared to short-term LMWH twice daily in the post-operative setting, there is low to moderate evidence that apixaban is equally effective and safe. When compared to daily LMWH, apixaban appears to be a superior thromboprophylaxis option [24].

Venous Thromboembolism Prophylaxis in Acute Medical Illness

The EXCLAIM (Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization) trial had previously assessed the potential advantage of extended pharmacologic prophylaxis with enoxaparin beyond the hospitalization period among patients with acute illness. This study found that although the rates of VTE were lower with extended anticoagulation, there was a significant increase in major bleeding [25].

The ADOPT (Apixaban Dosing to Optimize Protection from Thrombosis) trial evaluated the role of apixaban to prevent VTE in acutely ill patients during hospitalization and in the extended period following discharge from the hospital. The primary efficacy outcome in this study was a 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis, as detected with the use of systematic bilateral compression ultrasonography on day 30. This outcome occurred 2.71% in the apixaban group and 3.06% in the enoxaparin group (RR 0.87; 95% CI 0.62 to 1.23; P0.44). Regarding the safety profile, by day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (RR 2.58; 95% CI 1.02 to 7.24; P0.04). Thus, this study concluded that an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin in acutely ill patients. Also, apixaban was associated with significantly more major bleeding events than was with enoxaparin [26]. Apixaban is therefore not recommended routinely for the treatment of acute medical illness due to significant major bleeding events – in these cases, low molecular weight heparin, low-dose unfractionated heparin is the is the approved pharmacotherapy of choice.

Coronary Artery Disease

Patients with established cardiovascular disease remain at high risk for recurrent cardiovascular events. While anticoagulation with VKA reduces the incidence of recurrent ischemic events after myocardial infarction, bleeding risk is also increased when added to aspirin or with aspirin and clopidogrel [27]. APPRAISE (Apixaban for Prevention of Acute Ischemic Events),a phase II dose finding trial,

found that among patients with acute coronary syndromes when used in conjunction with aspirin or aspirin and clopidogrel, 10 mg a day of apixaban resulted in fewer ischemic events without a significant increase in bleeding [28].

The subsequent phase III clinical trial, APPRAISE-2, tested the hypothesis that that addition of apixaban to antiplatelet therapy would reduce the risk of recurrent ischemic events [29], however, apixaban 5mg twice daily in high-risk patients after an acute coronary syndrome, led to more major bleeding events without a significant reduction in recurrent ischemic events. Compared to placebo, a greater number of intracranial and fatal bleeding events occurred with apixaban. Thus, apixaban is not recommended as an adjunct treatment with antiplatelet therapy in high-risk patients after acute coronary syndrome.

Apixaban was also tested in the AGUSTUS trial, which was a multicenter, randomized, open label, two by two factorial trial [29]. In this trial the apixaban was compared with warfarin, and aspirin with placebo in patients with atrial fibrillation who had a recent acute coronary syndrome or underwent percutaneous coronary intervention and were planning to be on P2Y12 inhibitor for 6 months. Patients were randomized in a 1:1 fashion to either apixaban 5 mg twice daily (n = 2,306) or Vitamin K Antagonist (VKA) with an Internationalized Ratio (INR) goal of 2-3 (n = 2,308), or aspirin 81 mg daily (n = 2,307) or matching placebo (n = 2,307). The primary safety outcome, International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant nonmajor bleeding for apixaban vs. VKA, was 10.5% vs. 14.7%, $p < 0.0001$ while the primary safety outcome, ISTH major or clinically relevant nonmajor bleeding for aspirin vs. placebo, was 16.1% *vs.* 9.0%, $p < 0.0001$.In the secondary efficacy outcomes, patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%, P=0.002) and a similar incidence of ischemic events. While the incidence of death or hospitalization and of ischemic events in the aspirin group was similar to that in the placebo group [29,30].With regard to oral anticoagulants, the addition of rivaroxaban is indicated for patients at high thrombotic risk and not at high bleeding risk.

Treatment of Venous Thromboembolism with Cancer

VTE is common in patients with cancer, and subcutaneous low molecular weight heparin is the standard therapy in these patients [11]. Oral apixaban was studied in the CARVAGGIO trial and was compared to a therapeutic dose of the LMWH dalteparin in patients with active cancer and VTE diagnosis. Oral apixaban was found to be non-inferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism (HR 0.63; 95% CI 0.37 - 1.07; P<0.001 for noninferiority) without any increase in major bleeding (HR 0.82; 95% CI 0.40 - 1.69; P0.60) [31]. Given equivalent efficacy and safety, cancer associated VTE with apixaban must be a shared decision between the patient and provider. For most patients with malignancy who do not have renal insufficiency, treatment with low-molecular weight heparin rather than unfractionated heparin is indicated.

Post Transcatheter Aortic Valve Replacement (TAVR)

In the current 2014 guidelines by ACC/AHA on antithrombotic regimen after transcatheter aortic valve replacement (TAVR), clopidogrel 75 mg daily for the first six months after TAVR has been given a class IIB recommendation, along with lifelong aspirin 75 mg daily [12]. Concern of subclinical bioprosthetic leaflet thrombosis and its subsequent resolution with VKA therapy has prompted investigators to study apixaban for this indication. Following TAVR [32], Hypo-Attenuating Leaflet Thickening (HALT) and Hypo-Attenuation Affecting Motion (HAM) were identified as common findings [33]. HALT progression was less likely among patients in both the TAVR and SAVR groups who were taking oral anticoagulation (OR 0.014; P=0.036) [34]. Apixaban is currently being studied in the ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trial which tests itssu periority to standard of care to reduce the risk of post-TAVR thromboembolic complications [35]. At the moment, apixaban and other DOACs are not routinely recommended in prosthetic heart valves.

Left Ventricular (LV) Thrombus

DOACs have been used off-label to treat LV thrombus but the evidence for this indication is very limited [13]. A three-center retrospective cohort study performed on 514 patients with LV thrombus showed that DOACs are associated with higher rates of stroke and systemic embolism than warfarin [36-38]. However, due to patient and prescriber preference for apixaban and other DOACS over VKA, their off-label use for this indication has increased. A prospective clinical trial evaluating equivalence is needed to definitively answer this question.

Heart Failure with Reduced Ejection Fraction

Heart failure is considered a hypercoagulable state, and patients with acute or chronic heart failure are at increased risk for thrombotic events, including coronary thrombosis, intraventricular thrombosis, and systemic embolism. Given that VKA is not standard of care in heart failure, apixaban has not been studied for this indication either. Future trials may target this population to evaluate potential benefit.

Left Atrial Appendage Occlusion (LAAO)

Device occlusion of the LAA can be performed in patients with non-valvular atrial fibrillation who cannot take anticoagulants due to bleeding complications or do not wish to be on anticoagulants. In the landmark clinical trials of LAAO, warfarin was used transiently postoperatively [39,40]. However, in the real world, there is an increased peri-procedural use of DOACs [41]. Observational studies show that the risk of bleeding is similar between DOACs and warfarin, but clinical trial evidence is lacking.

Antiphospholipid Syndrome (APS)

APS in association with persistent antiphospholipid antibodies of lupus anticoagulant, anticardiolipin antibodies, and/or anti-beta 2 glycoprotein antibodies can manifest with arterial and venous thrombosis [42-48]. Apixaban is currently being compared to standard-intensity warfarin in the ASTRO-APS (Apixaban for

Secondary Prevention of Thromboembolism Among Patients With Antiphospholipid Syndrome) randomized control trial which is active but not yet started recruiting [49-54]. The standard oral anticoagulant treatment for thrombotic antiphospholipid syndrome is lifelong anticoagulation with warfarin or other vitamin K antagonists [55-59].

Consideration in the Elderly

There are specific pharmacokinetic challenges in the elderly due to aging, body composition, and reduction in overall muscle mass and total body water [60]. Consequently, a dose reduction is recommended for apixaban to 2.5 mg twice daily in patients with two of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum Cr greater than or equal to 1.5 mg/dL. No dose adjustment is required for dabigatran or rivaroxaban. Since DOACs generally have reduced pharmacological and dietary interactions compared to vitamin K antagonists, they may be the preferred agent in the elderly. Frailty and the risk of falls increase with age and predisposes this population to Intracranial Hemorrhage (ICH). Compared with warfarin, DOACs have a lesser risk of ICH and are thus recommended over vitamin K antagonists in patients with a high fall risk.

Consideration in Kidney Disease

In the ARISTOTLE trial, patients with CrCl<25 ml per minute and severe renal insufficiency (serum creatinine level of <2.5mg per deciliter) were excluded [8]. However, the FDA has approved apixaban 5 mg twice daily in patients with end-stage renal disease. This dose is reduced to 2.5 mg twice daily if the patient is over the age of 80 or has a bodyweight less than 60 kg [44]. A recent study using Medicare fee-for-service 5% claims data from 2007 to 2013 analyzed treatment and outcomes in patients with atrial fibrillation and ESRD [15]. In general, there was lower use of oral anticoagulation in patients with AF and ESRD. The use of anticoagulation (VKA, apixaban, rivaroxaban, and dabigatran) was not associated with reduced stroke or death but increased the risk of hospitalization for bleeding or intracranial hemorrhage [44].

Consideration in Liver Disease

No clinical data is available for the use of apixaban in patients with severe hepatic impairment, and its use is prohibited in Child-Pugh class B/C or any hepatic impairment associated with coagulopathy [16].

Consideration in Obesity

No large randomized controlled trials have specifically investigated the efficacy and safety of DOACs in the obese population [17]. Due this lack of evidence, the International Society of Thrombosis and Hemostasis in their 2016guidelines recommended against the use of DOACs in morbidlyobese patients with weight > 120 kg or body mass index >40 kg/m2. If for some reason DOACs are used, drug-specific anti-factor levels, like anti-factor Xa for apixaban is recommended [48].

Safety

Premature discontinuation is discouraged because of a higher risk of thrombosis. Although there are no definite guidelines on the subject, apixaban should probably be stopped for about two half-lives before major surgery and bedside procedures like spinal puncture [18,19]. Apixaban should not be used with P-glycoprotein and Cytochrome P450 3A4 (CYP3A) inhibitors (e.g., ketoconazole, itraconazole, or ritonavir) or inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because of variability in efficacy of apixaban and risk of increased thrombosis or bleeding [20].

Reversal

The factor Xa reversal agent, andexanet alpha, is a modified recombinant inactive form of human factor Xa. Andexanet alpha was studied in ANNEXA-4 (Andexanet Alpha, A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors), a single group cohort study [21] and was found to significantly reduced factor Xa activity and produce excellent or good hemostatic efficacy at 12 hours in 82% of the patients with major acute bleeding from factor Xa inhibitor use. Andexanet alpha was approved by the FDA in May 2018 [22].

Interrupting or Stopping Use

There is limited data comparing the risks and benefits of apixaban continuation or cessation. However, it is recommended to discontinue apixaban 24-48 hours before high bleeding risk procedures in patients with CrCl>60mL/minute, 72 hours before procedure if moderate renal impairment (CrCl 30-59 mL/minute), and 96 hours before high-risk endoscopic procedures in severe renal impairment (CrCl 15-29 mL/minute) [52]. For patients with low bleeding risk procedures, including dental and cutaneous procedures, low-risk cardiac procedures (i.e. implantable devices and endovascular repairs), apixaban may be continued [53].

Pharmacokinetics

As discussed, apixaban is a potent, direct, oral, reversible, and highly selective inhibitor of factor Xa which does not require antithrombin III for antithrombotic activity. It is predominantly metabolized by CYP3A4 [54]. The maximum plasma concentration occurs 3-4 hours after oral administration primarily through absorption from the small intestine and decreasing progressively through the gastrointestinal tract [55]. For doses up to 10 mg, the drug's absolute bioavailability is about 50% due to incomplete absorption and first-pass metabolism in the gut and the liver [56]. Bioavailability does not differ significantly if administered with meals [57]. In contrast, Rivaroxaban bioavailability ranges from 80-100%, depending on the dose and food intake; rivaroxaban requires administration with food to achieve similar bioavailabilty between a dose of 10mg and doses exceeding 15mg [58]. Protein binding is similar for both drugs (apixaban 87% and rivaroxaban 93%). However, compared with rivaroxaban, apixaban has less inter-subject variability in exposure, lower anti-factor Xa activity, and a higher trough and smaller peak-to-trough fluctuations in plasma concentration. This suggests more constant anticoagulation compared with rivaroxaban [59].

Conclusion

There is robust clinical trial evidence for the use of apixaban for stroke prevention in non-valvular atrial fibrillation, treatment of deep venous thrombosis and pulmonary embolism and postoperative venous thromboembolism prophylaxis after hip and knee surgery. While there is a role for apixaban post-acute coronary syndrome or PCI in patients who also need anticoagulation for concomitant atrial

fibrillation, bleeding risk outweighs benefit without atrial fibrillation. It appears as effective as the standard of care in thromboembolism prophylaxis for cancer patients but may cause more bleeding with extended use in acutely ill patients. There is a lack of randomized trial evidence for its use in patients with left ventricular thrombus, post TAVR and post LAAO occlusion device implantation, however off label clinical use is frequently seen. Due to lack of supporting evidence, apixaban use in heart failure and antiphospholipid syndrome should be avoided.

References

1. Ageno W, Gallus A.S, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral Anticoagulation Therapy. Chest. 2012; 141: e44S-e88S.
2. Cabral KP, Ansell JE. The role of factor Xa inhibitors in venous thromboembolism treatment. Vascular Health and Risk Management. 2015; 11: 117.
3. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, et al. Apixaban Metabolism and Pharmacokinetics after Oral Administration to Humans. Drug Metabolism and Disposition. 2009; 37: 74-81.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22: 983-988.
5. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. The BMJ. 2011; 342: d124-d124.
6. Connolly SJ, Eikelboom J, Joyner C, Diener H, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011; 364: 806-817.
7. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine. 2011; 365: 981-992.
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf. Accessed November 16, 2020
9. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. The New England journal of medicine. 2013; 369: 1206-1214.
10. January CT, Wann LS, Calkins H, Field ME, Chen LY, Furie KL, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart rhythm. 2019; 16: e66-e93.
11. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014; 130: e199-267.
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014; 383: 955-962.
13. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149: 315-352.
14. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. The New England journal of medicine. 2013; 369: 799-808.
15. Giancarlo Agnelli, Harry R Buller, Alexander Cohen, Madelyn Curto, Alexander S Gallus. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368: 699–708.
16. WARNING: (A) Premature Discontinuation of Eliquis Increases the Risk of Thrombotic Events. 2012.
17. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149: 315-352.
18. Aryal MR, Gosain R, Donato A, Yu H, Katel A, Bhandari Y, et al. Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. Blood advances. 2019; 3: 2381-2387.
19. Liu J, Zhao J, Yan Y, Su J. Effectiveness and safety of rivaroxaban for the prevention of thrombosis following total hip or knee replacement. Medicine. 2019; 98: e14539.
20. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. The New England journal of medicine. 2009; 361: 594-604.
21. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. The Lancet. 2010; 375: 807-815.
22. Huang J, Cao Y, Liao C, Wu L, Gao F. Apixaban versus enoxaparin in patients with total knee arthroplasty. A meta-analysis of randomised trials. Thrombosis and haemostasis. 2011; 105: 245-253.
23. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. The New England journal of medicine. 2010; 363: 2487-2498.
24. Caldeira D, Rodrigues FB, Pinto FJ, Ferreira JJ, Costa J. Thromboprophylaxis With Apixaban in Patients Undergoing Major Orthopedic Surgery: Meta-Analysis and Trial-Sequential Analysis. Clinical Medicine Insights: Blood Disorders. 2017; 10: 1179545X1770466.
25. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. The New England journal of medicine. 2011; 365: 2167-2177.
26. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama M, Nicol P, et al. Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility. Annals of Internal Medicine. 2010; 153: 8.
27. Es RFV, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. The Lancet. 2002; 360: 109-113.
28. Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, et al. Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome: Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial. Circulation. 2009; 119: 2877-2885.
29. John H. Alexander, Renato D. Lopes, Stefan James, Rakhi Kilaru, Yaohua He, et al. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome: NEJM. 2011; 365: 699-708.
30. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. The New England journal of medicine. 2003; 349: 146-153.
31. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. The New England journal of medicine. 2020; 382: 1599-1607.
32. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129: 2440-2492.
33. Sondergaard L, Backer OD, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. European Heart Journal. 2017; 38: 2201-2207.
34. HALT, HAM Common After TAVR and SAVR? American College of

Cardiology. Accessed March 28, 2021.

35. Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis - Full Text View - ClinicalTrials.gov. Accessed December 29, 2020.

36. Fleddermann AM, Hayes CH, Magalski A, Main ML. Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus. The American journal of cardiology. 2019; 124: 367-372.

37. Robinson AA, Trankle CR, Eubanks G, Schumann C, Thompson P, Wallace RL, et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. JAMA cardiology. 2020; 5: 685.

38. Bösche LI, Afshari F, Schöne D, Ewers A, Mügge A, Gotzmann M. Initial Experience With Novel Oral Anticoagulants During the First 45 Days After Left Atrial Appendage Closure With the Watchman Device. Clinical Cardiology. 2015; 38: 720-724.

39. Ajmal M, Hutchinson MD, Lee K, Indik JH. Outcomes in patients implanted with a Watchman device in relation to choice of anticoagulation and indication for implant. Journal of Interventional Cardiac Electrophysiology. 2021: 1-8.

40. Cohen H, Efthymiou M, Isenberg DA. Use of direct oral anticoagulants in antiphospholipid syndrome. Journal of Thrombosis and Haemostasis. 2018; 16: 1028-1039.

41. Alexander JE, Investigators F. The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Alexander at Duke Clinical Research Institute, F. P. Polack and Others, S. F. Lumley and Others, & Group, A. (2011, November 10).

42. Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome: NEJM. Retrieved December 29, 2020, from

43. Pokorney SD, Black-Maier E, Hellkamp AS, Friedman DJ, Vemulapalli S, Granger CB, et al. Oral Anticoagulation and Cardiovascular Outcomes in Patients With Atrial Fibrillation and End-Stage Renal Disease. Journal of the American College of Cardiology. 2020; 75: 1299-1308.

44. Graff J, Harder S. Anticoagulant Therapy with the Oral Direct Factor Xa Inhibitors Rivaroxaban, Apixaban and Edoxaban and the Thrombin Inhibitor Dabigatran Etexilate in Patients with Hepatic Impairment. Clinical Pharmacokinetics. 2013; 52: 243-254.

45. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2016; 14: 1308-1313.

46. Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrology Dialysis Transplantation. 2019; 34: 265-277.

47. Gogarten W, Hoffmann K, Aken HV. [Recommendations for the administration of conventional and new antithrombotic agents from the perspective of anesthesiology]. Der Unfallchirurg. 2010; 113: 908-914.

48. Connolly SJ, Crowther M, Eikelboom JW, Gibson MC, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. The New England Journal of Medicine. 2019; 380: 1326-1335.

49. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Cott EMV, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. American Journal of Hematology. 2019; 94: 697-709.

50. Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointestinal endoscopy. 2016; 83: 3-16.

51. Sunkara T, Ofori E, Zarubin V, Caughey ME, Gaduputi V, Reddy M. Perioperative Management of Direct Oral Anticoagulants (DOACs): A Systemic Review. Health Services Insights. 2016; 9s1 :HSI.S40701.

52. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. British Journal of Clinical Pharmacology. 2013; 75: 476-487.

53. Byon W, Nepal S, Schuster AE, Shenker A, Frost CE. Regional Gastrointestinal Absorption of Apixaban in Healthy Subjects. The Journal of Clinical Pharmacology. 2018; 58: 965-971.

54. Wang L, Zhang D, Raghavan N, Yao M, Ma L, Frost CA, et al. In Vitro Assessment of Metabolic Drug-Drug Interaction Potential of Apixaban through Cytochrome P450 Phenotyping, Inhibition, and Induction Studies. Drug Metabolism and Disposition. 2010; 38: 448-458.

55. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review. Clinical Pharmacokinetics. 2019; 58: 1265-1279.

56. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical Pharmacokinetic and Pharmacodynamic Profile of Rivaroxaban. Clinical Pharmacokinetics. 2013; 53: 1-16.

57. Frost C, Song Y, Barrett YC, Wang J, Pursley J, Boyd RA, et al. A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. Clinical Pharmacology : Advances and Applications. 2014; 6: 179.

58. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism. Circulation. 2015; 132: 194-204.

59. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. Revista espanola de cardiologia. 2017; 70: 50.

60. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015; 17: 1467-1507.