Therapeutic Class Overview
Oral Anticoagulants

INTRODUCTION

- The oral anticoagulants include BEVYXXA® (betrixaban), ELIQUIS® (apixaban), PRADAXA® (dabigatran), SAVAYSA® (edoxaban), XARELTO® (rivaroxaban), and warfarin (COUMADIN®, JANTOVEN®).
- Warfarin has been the principal oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy. However, warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- Four target-specific oral anticoagulants (TSOACs), ELIQUIS, PRADAXA, SAVAYSA, and XARLETO, are indicated for the reduction of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), otherwise known as events caused by a venous thromboembolism (VTE). PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE. PRADAXA, XARELTO, and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing hip replacement surgery and XARELTO and ELIQUIS have further indications for knee replacement surgery. BEVYXXA is the only agent in class indicated for patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the US, affecting approximately 2.7 to 6.1 million people in 2010. AF has been associated with death either directly or cited as an underlying cause contributing to mortality. Stroke is the most concerning complication of AF. Before the widespread use of anticoagulants, and after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke (*Benjamin et al, 2017*). Approximately 5 to 8% of patients who require percutaneous coronary intervention (PCI) with stents have AF (*Gibson et al, 2016*).
- In patients with AF, oral anticoagulants are recommended for those who are at an intermediate or greater risk of stroke and selection should be based on individual patient characteristics (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).
- VTE encompasses both DVT and PE. The precise number of people affected is unknown, but it is estimated to affect ~900,000 US patients (*CDC, 2017*). Of those who suffer a DVT, approximately a third will have a recurrence within 10 years. Knee and hip replacement surgeries are associated with a high risk of VTE, which can lead to recurrent VTE events as well as post-thrombotic syndrome, and PE, which can be fatal. Without anticoagulant therapy, 40% to 50% of patients undergoing hip replacement surgery suffer VTE. This rises to 70% to 80% in hip fracture (*American Academy of Orthopaedic Surgeons [AAOS], 2011; Guyatt et al, 2012; Kearon et al, 2016*).
- Hospitalization is a risk factor for VTE with an estimated 22% of VTE occurrences following non-surgical hospital admissions (*Heit et al, 2002*). Additionally, an estimated 4.6 per 1000 admissions are complicated by symptomatic VTE, which can lead to a higher risk of morbidity and mortality (*Zakai et al, 2013*).
- Pharmacological anticoagulants available for the treatment of VTE (not due to orthopedic surgery) include parenteral anticoagulation (low molecular weight heparin [LMWH], fondaparinux, or intravenous [IV] or subcutaneous [SC] unfractionated heparin [UFH]) typically administered with warfarin, and the TSOACs (XARELTO, ELIQUIS, PRADAXA, or SAVAYSA) (*Guyatt et al, 2012; Kearon et al, 2016; Micromedex® 2.0, 2017*).
- Thromboprophylaxis is recommended to prevent VTE in patients undergoing total hip or knee replacement. Pharmacological anticoagulants available for the prophylaxis of VTE after orthopedic surgery include aspirin, LMWHs, warfarin, PRADAXA, and factor (F) Xa inhibitors (ARIXTRA® [fondaparinux], XARELTO, or ELIQUIS) (*AAOS, 2011; Guyatt et al, 2012*).
- The oral anticoagulants work through varied mechanisms of action. XARELTO, SAVAYSA, BEVYXXA, and ELIQUIS are selective FXa inhibitors, while PRADAXA is a direct thrombin inhibitor. Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors. Vitamin K, therefore, serves as a reversal agent for warfarin.

- In 2015, the first TSOAC reversal agent, PRAXBIND® (idarucizumab), was FDA-approved. PRAXBIND is indicated for the reversal of PRADAXA's anticoagulation effects as needed for emergency surgery, urgent procedures, and in life-threatening or uncontrolled bleeding (*PRAXBIND prescribing information, 2015*).
- There are no specific antidotes for BEVYXXA, ELIQUIS, SAVAYSA or XARELTO. ANDEXXA® (andexanet alfa) is an investigational agent that was submitted to the FDA for approval. Studies currently support use with ELIQUIS and XARELTO. In August 2016, the FDA issued a complete response letter (CRL) requesting additional information. In August 2017, Portola Pharmaceuticals announced that they re-submitted the biologics licensing application (BLA) addressing deficiencies noted in the CRL (*Portola Pharmaceuticals press release, 2017*).
- Another antidote, ciraparantag, is an intravenously administered small molecule which has demonstrated complete and sustained reversals of SAVAYSA and LOVENOX without rebound anticoagulation in Phase 2 trials and the reversal of PRADAXA, XARELTO, ELIQUIS, fondaparinux, and heparin ex vivo (*Perosphere press release, 2017*).

- Medispan class: Anticoagulants; Thrombin Inhibitors - Dabigatran; Coumarin Anticoagulants; Direct FXa Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
BEVYXXA (betrixaban)	-
ELIQUIS (apixaban)	-
PRADAXA (dabigatran)	-
SAVAYSA (edoxaban)	-
XARELTO (rivaroxaban)	-
COUMADIN, JANTOVEN (warfarin)	✔

(*Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	BEVYXXA (betrixaban)	ELIQUIS (apixaban)	PRADAXA (dabigatran)	SAVAYSA (edoxaban)	XARELTO (rivaroxaban)	COUMADIN JANTOVEN (warfarin)†
Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement						✔
Prophylaxis and treatment of venous thrombosis and its extension, PE						✔
Reduce the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI						✔
Reduce the risk of stroke and systemic embolism in patients with NVAF		✔	✔	✔ ‡	✔	
Prophylaxis of DVT, which may lead to PE, in patients undergoing knee (TKR) or hip (THR) replacement surgery		✔			✔	
Prophylaxis of DVT and PE in patients undergoing THR surgery			✔			
Treatment of DVT and PE		✔	✔ *	✔ *	✔	
Reduction in the risk of recurrence of DVT and PE following initial therapy		✔	✔		✔	
Prophylaxis of VTE in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE	✔ §					

*Prior to treatment, patients should have been treated with parenteral anticoagulant for 5 to 10 days.
†Limitation of use: Warfarin has no direct effect on an established thrombus, nor does it reverse ischemic tissue damage.
‡Not indicated in NVAF patients with creatinine clearance (CrCL) > 95 mL/min due to increased rates of ischemic stroke.
§Limitation of use: Use has not been established in patients with prosthetic heart valves.

(*Prescribing information: BEVYXXA, 2017; COUMADIN, 2016; ELIQUIS, 2016; JANTOVEN, 2011; PRADAXA, 2015; SAVAYSA, 2016; XARELTO, 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Warfarin has been the principal oral anticoagulant for more than 60 years and the evidence demonstrating the safety and efficacy in Food and Drug Administration (FDA)-approved indications is well established (*Aguilar, 2005; Cundiff et al, 2006; DiNisio et al, 2012; Hutten, 2006; Lopes et al, 2013; Middeldorp et al, 2014; Salazar et al, 2010; Saxena, 2004; van der Heijden et al, 2001*).
- There is no direct comparator evidence of the TSOACs; therefore, caution should be exercised when drawing conclusions based on indirect data.

Non-valvular Atrial Fibrillation:

- Four large randomized controlled trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48, and ROCKET AF) were the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively. Baseline populations varied for the PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials, with a mean proportion of 64%, 62%, 65%, and 55% time in therapeutic range (TTR) for warfarin patients and a mean baseline $CHADS_2$ score of 2.1, 2.1, 2.8, and 3.5, respectively (*Connolly et al, 2009; Connolly et al, 2011; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011*).
- The primary efficacy endpoint was stroke or systemic embolism, in which the following outcomes were reported:
  - PRADAXA was superior (relative risk [RR] for PRADAXA150 mg twice daily vs warfarin, 0.66 [95% confidence interval {CI}, 0.53 to 0.82], P < 0.001).
  - ELIQUIS was superior (Hazard ratio [HR] for ELIQUIS 5 mg twice daily vs warfarin, 0.79 [95% CI, 0.66 to 0.95], P = 0.01).
  - SAVAYSA was non-inferior (HR for SAVAYSA 60 mg once daily vs warfarin, 0.79 [97.5% CI, 0.63 to 0.99], P < 0.001; HR for SAVAYSA 30 mg once daily vs warfarin, 1.07 [97.5% CI, 0.87 to 1.31], P = 0.005).
  - XARELTO was non-inferior (HR for XARELTO 15 to 20 mg once daily vs warfarin, 0.88 [95% CI, 0.75 to 1.03], P < 0.001).
- In terms of safety, the following important outcomes were observed in trials:
  - All TSOACs had fewer intracranial hemorrhages (ICH) compared to warfarin.
  - For major bleeds, ELIQUIS and SAVAYSA were superior to warfarin (ELIQUIS HR, 0.69 [95% CI, 0.6 to 0.8], P < 0.001; SAVAYSA HR, 0.8 [95% CI, 0.71 to 0.91], P < 0.001) and PRADAXA and XARELTO were non-inferior to warfarin (PRADAXA RR, 0.93 [95% CI, 0.81 to1.07], P = 0.31; XARELTO HR, 1.04 [95% CI, 0.9 to1.2], P = 0.58).
  - For gastrointestinal (GI) bleeds, warfarin significantly out-performed PRADAXA, SAVAYSA, and XARELTO (PRADAXA RR, 1.5 [95% CI, 1.19 to 1.89], P < 0.001; SAVAYSA HR, 1.23 [95% CI, 1.02 to 1.5], P = 0.03; XARELTO HR, not reported [incidence, XARELTO 3.2% vs warfarin 2.2%], P < 0.001); however, ELIQUIS had a similar incidence of GI bleeds when compared to warfarin (ELIQUIS HR 0.89 [95% CI, 0.7 to 1.15], P = 0.37).
- In 2016, the Alere INRatio device, which was used in the ROCKET AF trial, was recalled due to the potential for falsely low INR results. An article from the British Medical Journal (BMJ) suggested that an independent assessment of trial data should be performed. Researchers from the FDA, Bayer, Johnson and Johnson, and the Duke Clinical Research Institute performed a post-hoc data analysis and concluded that the recalled devices did not have significant clinical effects on the primary efficacy and safety trial outcomes. The FDA and European Medicines Agency (EMA) concluded that any incorrect INR measures would have marginal effects on the study outcomes; therefore, they should not impact the safety or benefit-risk balance of XARELTO (*Cohen, 2016; EMA press release, 2016; FDA press release, 2016*)
- Extension trials and additional analyses were conducted for the thromboprophylaxis of NVAF and the following key results were demonstrated:
  - After 2.3 years of PRADAXA treatment, slightly higher rates of stroke and systemic embolism, in addition to increased rates of major bleeding were observed in the long-term trial, RELAY-ABLE, compared to the RE-LY trial, particularly in the FDA-approved 150 mg dose (*Connolly et al, 2013*).
  - One pre-specified secondary analysis of the ENGAGE AF-TIMI 48 trial demonstrated ischemic cerebrovascular event rates were similar with SAVAYSA 60 mg and warfarin, whereas SAVAYSA 30 mg was less effective than warfarin (*Giugliano et al, 2014*). Another pre-specified analysis found that patients with genetic variants of CYP2C9 and

VKORC1 derived a greater early safety benefit in bleeding rates with edoxaban over warfarin (*Mega et al, 2015*). An analysis of the ENGAGE-AF-TIMI 48 trial found that patients with valvular heart disease had an increased risk of death (P < 0.001), major adverse cardiovascular events (P < 0.001), and major bleeding (P = 0.02) than patients without valvular heart disease, but did not change the efficacy and safety result of the higher SAVAYSA dose vs warfarin (*De Caterina et al, 2017*).

- Data regarding GI adverse events and myocardial infarction with PRADAXA treatment have been conflicting. A subgroup analysis of GI adverse events found that PRADAXA demonstrated a statistically significant risk of non-bleeding upper GI effects, which also resulted in a statistically larger proportion of patients discontinuing PRADAXA due to these effects (*Bytzer et al, 2013*).
- A subgroup analysis demonstrated a nonsignificant increase in MI with PRADAXA compared to warfarin but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of PRADAXA were consistent in patients at higher and lower risk of myocardial ischemic events (*Hohnloser et al, 2012*). In contrast, a meta-analysis demonstrated that PRADAXA is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute VTE, ACS, short term prophylaxis of DVT) when compared against different controls (warfarin, enoxaparin, or placebo). It was not accompanied by an increase in mortality (*Uchino, 2012*).
- One observational cohort study of 134,000 Medicare patients was conducted by the FDA to compare PRADAXA to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within six months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. PRADAXA was found to be associated with a lower risk of ischemic stroke (HR, 0.8; 95% CI, 0.67 to 0.96), ICH (HR, 0.34; 95% CI, 0.26 to 0.46) and death (HR, 0.86; 95% CI, 0.77 to 0.96) vs warfarin. Risk for GI bleeding was higher for PRADAXA (HR, 1.28; 95% CI, 1.14 to 1.44) vs warfarin, and MI risk was similar (HR, 0.92; 95% CI, 0.78 to 1.08). Most results were similar to RE-LY; however, the MI risk was found to be similar between groups rather than an increased risk for PRADAXA as discovered in RE-LY. Also important to note, an increased risk of GI bleeds associated with PRADAXA was similar to the RE-LY study but differs from data found in the Mini Sentinel analysis which found less risk of GI bleeds with new users of PRADAXA vs warfarin (*FDA Drug Safety Communication, 2014*).

- In NVAF patients who require AF cardioversion, standard oral anticoagulant therapy generally consists of a warfarin-based regimen to prevent thrombosis. More recently, FXa inhibitors have been evaluated for this use. Caution should be exercised when interpreting results of these studies as both were underpowered to demonstrate statistically significant differences for efficacy and safety endpoints. Key results are as follows:
  - The X-VeRT trial randomized 1,504 patients with AF undergoing elective cardioversion to XARELTO dosed between 15 to 20 mg daily depending on renal function or a VKA in a 2:1 ratio. The primary endpoint (defined as a composite of stroke, transient ischemic attack, peripheral embolism, MI, and CV death) occurred in 0.5% of XARETO-treated patients vs 1% of VKA-treated patients. Additionally, the proportion of patients who had major bleeding were similar in the XARELTO and VKA treatment groups (0.6% vs 0.8%, respectively) (*Cappato et al, 2014*).
  - The ENSURE-AF trial randomized 2,199 NVAF patients undergoing cardioversion to SAVAYSA 30 to 60 mg daily vs an enoxaparin/warfarin regimen. The primary efficacy endpoint (defined as a composite of stroke, systemic embolic event, MI, or CV mortality) occurred in 0.5% of SAVAYSA-treated patients vs 1% of enoxaparin/warfarin-treated patients. Additionally, the proportion of patients who had a first major or clinically relevant non-major bleeding occurrence were similar (1% for each group) (*Goette et al, 2016*).

Triple anticoagulant therapy after cardiac procedures

- Some patients require triple anticoagulant therapy in cases of cardiac procedures, including PCI, which may be indicated in patients with AF with certain co-morbid diseases. There is limited evidence to guide appropriate treatment. Evidence has been controversial and often outcomes vary greatly according to the population studied requiring clinicians to balance the risk of thrombosis and ischemic stroke with that of potential bleeding. Studies have demonstrated that a $P2Y_{12}$ inhibitor plus aspirin are superior to warfarin in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent, but found oral anticoagulation was superior to dual antiplatelet therapy (DAPT) in reducing the risk of ischemic stroke in patients with AF (*Connolly et al, 2006; Cutlip et al, 1999; Gibson et al, 2016; Leon et al, 1998*).
  - Prior trials examining the use of oral anticoagulants vs DAPT post-procedurally has yielded mixed results. The ACTIVE-W trial found DAPT was inferior to warfarin for the prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking oral anticoagulation therapy; however, in the STARS trial, DAPT was superior to an oral anticoagulant for the prevention of thrombosis related to coronary stent insertion (*Connolly et al,*

2006; Cutlip et al, 1999). Most evidence with triple therapy has included warfarin and consists of small open-label (OL) RCTs or observational studies (*Dewilde et al, 2013; Fiedler et al, 2015*).
  - Recent American Heart Association (AHA) guidance recommends an assessment of CHA2DS2-VASc risk score to estimate the thromboembolic risk and the HASBLED risk score to estimate the hemorrhagic risk. The AHA recommends including the patient in a shared decision regarding the selection of DAPT vs triple therapy as well as the duration of therapy post-procedurally. Although the AHA acknowledges that both European and Canadian guidelines suggest TSOACs over warfarin for triple therapy, this has been based on lower quality observational data and post-hoc analyses (*Raval et al, 2017*). Current AHA guidance acknowledges that in spite of limited data, certain patients for whom it is difficult to reach and maintain therapeutic INR levels with warfarin may warrant the use of a TSOAC with DAPT (but not in combination with prasugrel or ticagrelor) after PCI (*Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017*).
- Studies are currently underway examining the benefits and risks of triple anticoagulant therapy. These studies, including the recently published PIONEER-AF-PCI trial and the ongoing RE-DUAL PCI, RT-AF, SAFE-A, and AUGUSTUS studies, will provide further insights into the use of a TSOAC with DAPT in patients undergoing PCI (*Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017*). A number of studies have been conducted with three of the TSOACs which included triple therapy anticoagulant regimens for the treatment of secondary ACS prevention; however, this indication has not been FDA-approved and the percentage of patients who had concomitant AF has not been well documented:
  - ELIQUIS and PRADAXA have been studied in patients after an ACS via the APPRAISE trials and REDEEM trials, respectively. Trial outcomes resulted in minimal to no clinical benefit; however, an increased risk of harm was observed as bleeding events (*Alexander et al, 2009; Cornel et al, 2015; Ogawa et al, 2013; Oldgren et al, 2011*).
  - XARELTO has been studied at doses of 2.5 mg or 5 mg twice daily vs placebo in 15,526 patients with recent ACS and followed for approximately two years via the DB, PC, ATLAS trial. ACS patients were also administered DAPT therapy with a low-dose aspirin or thienopyridine (either clopidogrel or ticlopidine). XARELTO 2.5 mg twice daily dosing not only significantly reduced the primary endpoint (defined as the composite of death from CV causes, MI, or stroke; P = 0.02), but unlike the 5 mg dosing, the 2.5 mg dose also reduced the rate of death from CV or any cause (P = 0.002 for both). This benefit, however, was tempered by an increased risk of non-coronary artery bypass grafting (CABG) thrombolysis in myocardial infarction (TIMI) major bleeding (P < 0.001) and ICH (P = 0.04) vs placebo (*Mega et al, 2012*).
  - The recently conducted PIONEER-AF-PCI trial was a large, OL, randomized safety trial (N = 2,124) conducted in patients with NVAF undergoing PCI with stent placement and compared triple therapy strategies with XARELTO and warfarin. Patients were randomized to: (1) XARELTO 15 mg once daily plus clopidogrel 75 mg daily for 12 months, or (2) XARELTO 2.5 mg twice daily plus DAPT with a prespecified duration of 1, 6 or 12 months, or (3) warfarin plus DAPT with a prespecified duration of 1, 6 or 12 months. Patients administered XARELTO-based regimens had a lower risk of the primary safety endpoint of clinically significant bleeding (composite of major or minor TIMI bleeding or bleeding requiring medical attention) compared to warfarin (17.4% and 26.7%, respectively; P < 0.001). Clinically significant bleeding was driven by bleeding requiring medical attention. For the secondary efficacy endpoints, patients experienced no difference in major adverse CV events (defined as a composite of death from CV causes, MI, or stroke) or stent thrombosis compared to warfarin plus DAPT; however, caution should be exercised as the study was not powered for this outcome and clinical efficacy remains uncertain (*Gibson et al, 2015; Gibson et al, 2016*).

VTE treatment

- Six large, randomized controlled trials (RE-COVER, RE-COVER II, AMPLIFY, Hokusai-VTE, EINSTEIN-DVT and EINSTEIN-PE) evaluated the efficacy and safety of PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively, for the treatment of acute VTE (although PRADAXA and SAVAYSA trials had 5 to 10 days treatment with a parenteral anticoagulant prior to initiating treatment). Baseline populations for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials varied greatly including the following characteristics (*Schulman et al, 2009; Schulman et al, 2009; Agnelli et al [a], 2013; Büller et al, 2013; Bauersachs et al, 2010; Büller et al, 2012; Prins et al, 2013*):
  - Patients aged ≥ 75 years ~10%, 14%, 13.5%, and 13 to 17%, respectively
  - Prior VTE ~22%, 16%, 18%, and 19 to 20%, respectively
  - Unprovoked VTE ~ 35%, 89.8%, 65.7%, and 62 to 64.5%, respectively
  - Cancer at baseline ~4.3%, 2.7%, 9.3%, and 5.2%, respectively
  - Duration of treatment: 6 months, 6 months, 3 to 12 months, and measures at 3, 6, and 12 months, respectively
  - TTR ~ 60%, 61%, 64%, and 58 to 63%, respectively

- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - For RE-COVER, recurrent VTE and related deaths occurred in 2.4% in the PRADAXA arm and 2.1% in the warfarin arm (P < 0.001 for non-inferiority). Major bleeding was similar (1.6% PRADAXA vs 1.9% warfarin), but more PRADAXA patients discontinued treatment due to adverse events (9%) compared to warfarin (6.8%; P < 0.05) (*Schulman et al, 2009*).
  - In RE-COVER II, symptomatic VTE or VTE- related deaths occurred in 2.3% of PRADAXA patients vs 2.2% of warfarin patients (P < 0.001 for non-inferiority). Major bleeding was similar; however, warfarin had significantly more overall bleeds in 22.1% of patients compared to 15.6% PRADAXA patients (P < 0.05) (*Schulman et al, 2014*).
  - In AMPLIFY, non-inferiority was met for the primary outcome of recurrent symptomatic VTE or death related to VTE in 2.3% ELIQUIS patients vs 2.7% conventional therapy patients (RR, 0.84; 95% CI, 0.6 to 1.18). Significantly more major bleeding was observed with conventional therapy (1.8%) compared to patients treated with ELIQUIS (0.6%) (*Agnelli et al [a], 2013*).
  - For Hokusai-VTE, SAVAYSA was non-inferior to warfarin for the prevention of recurrent VTE after treatment with parenteral anticoagulants (in 3.2% SAVAYSA vs 3.5% warfarin after 12 months follow-up; HR, 0.89; 95% CI, 0.7 to 1.13; P < 0.001 for non-inferiority). Significantly lower rates of major or clinically relevant non-major bleeding were observed in 8.5% of SAYVASA patients compared to 10.3% of warfarin patients (P = 0.004), but major bleeding was similar (P = 0.35) (*Büller et al, 2013*).
  - The results from EINSTEIN-DVT demonstrated XARELTO to be non-inferior to standard therapy (2.1% for XARELTO vs 3% for enoxaparin/VKA; P < 0.001 for non-inferiority) for symptomatic recurrent VTE. Identical rates (8.1%) of major or non-major clinically relevant bleeding were shown. Net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding favored XARELTO (reported in 2.9% XARELTO vs 4.2% enoxaparin/VKA patients; P = 0.03) (*Bauersachs et al, 2010*).
  - In EINSTEIN-PE, XARELTO was shown to be non-inferior to enoxaparin/VKA (2.1% XARELTO vs 1.8% enoxaparin/VKA; HR, 1.12; 95% CI, 0.75 to 1.68) for symptomatic recurrent VTE. The principal safety outcome, clinically relevant bleeding, occurred in 10.3% of XARELTO patients and 11.4% of standard therapy patients (HR, 0.9; 95% CI, 0.76 to 1.07; P = 0.23). Major bleeding was observed in 1.1% XARELTO patients and 2.2% in the standard-therapy group (HR, 0.49; 95% CI, 0.31 to 0.79; P = 0.003). Net clinical benefit occurred in 3.4% of XARELTO patients and 4% of standard therapy patients (HR, 0.85; 95% CI, 0.63 to 1.14; P = 0.28) (*Büller et al, 2012*).

Reduction in Recurrent VTE

- Four large randomized controlled trials (RE-MEDY, RE-SONATE, AMPLIFY-EXT, and EINSTEIN-EXT) were evaluated for the reduction in recurrent VTE and the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, and XARELTO vs placebo, respectively (however, PRADAXA is the only agent compared to warfarin as observed in the RE-MEDY trial). Each trial was an extension of the acute VTE trials mentioned previously (*Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013*). The EINSTEIN CHOICE trial also evaluated the rate of recurrent VTE with long-term TSOAC treatment (*Weitz et al 2017*).
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - The RE-MEDY (comparing PRADAXA to warfarin) and RE-SONATE (comparing PRADAXA to placebo) trials had similar efficacy results with recurrent VTE reported in 1.8% PRADAXA vs 1.3% warfarin (P = 0.01 for non-inferiority) in the RE-MEDY trial and 0.4% PRADAXA vs 5.6% placebo (P < 0.001) in the RE-SONATE trial. However, RE-MEDY displayed lower major bleeding in the PRADAXA group (0.9% PRADAXA vs 1.8% warfarin; HR, 0.52; 95%, 0.27 to 1.02) compared to that of the RE-COVER trials (*Schulman et al, 2013*).
  - In AMPLIFY-EXT, extended treatment with ELIQUIS demonstrated superiority vs placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause (8.8% placebo vs 1.7% for each ELIQUIS 2.5 and 5 mg groups). Across the trial, the rates of major bleeding were low and comparable (placebo 0.5% vs 0.2% and 0.1% for ELIQUIS 2.5 and 5 mg, respectively) (*Agnelli et al [b], 2013*).
  - In the EINSTEIN-EXT, XARELTO was superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; P < 0.001). Rates of major bleeding were similar (0.7% vs 0%; P = 0.11). The outcome of net clinical benefit was significantly in favor of XARELTO, with symptomatic recurrent VTE plus major bleeding reported in 2% of XARELTO patients vs 7.1% of placebo patients (P < 0.001) (*Bauersachs et al, 2010*).
  - Recently, the EINSTEIN CHOICE trial (N = 3,365) evaluated the rates of recurrent VTE with a long duration of treatment with XARELTO 10 mg (N = 1,127), 20 mg (N = 1,107), or aspirin 100 mg (N = 1,131) once daily after 6 to 12 months of therapy. Patients in the XARELTO 10 and 20 mg groups had a significantly lower rate of recurrence of

VTE compared to aspirin 100 mg (1.2 vs 1.5 vs 4.4%; P < 0.001 for both XARELTO groups). The rates of major bleeding were similar between groups (0.4 vs 0.5 vs 0.3%, respectively). Of note, patients within the study were younger than a real world population; therefore, results may not be generalizable (*Weitz et al 2017*).

- Current guidelines recommend LMWH in patients who have recurrent VTE, including those currently stable on VKA or TSOAC therapy (*Kearon et al, 2016*).

VTE prophylaxis for total knee (TKR) and/or hip (THR) replacement surgery

- Nine large randomized, double blinded (DB) trials (RE-NOVATE and RE-NOVATE II [hip], RECORD 1 and 2 [hip], RECORD 3 and 4 [knee], ADVANCE 1 and 2 [knee], and ADVANCE 3 [hip]) were the basis for clinical efficacy and safety for PRADAXA, XARELTO, and ELIQUIS vs enoxaparin, respectively in VTE prophylaxis for TKR or THR surgeries. Duration of treatment, dose strength, and frequency varied for each group among trials.
- When evaluating anticoagulation therapies for patients undergoing THR or TKR endpoints use of the surrogate measure, asymptomatic DVT, detected by mandatory venography. The American College of Chest Physicians (ACCP) guidelines find this outcome unsatisfactory due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding. The guidelines provide suggestions to estimate reductions in symptomatic thrombosis; however, this is contingent on available evidence. Many studies rely on asymptomatic DVT events to determine differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates (*Guyatt et al, 2012*).
- Data from the THR trials found XARELTO and ELIQUIS to be superior to enoxaparin 40 mg once daily and PRADAXA to be non-inferior to enoxaparin 40 mg once daily when prescribed for orthopedic prophylaxis (*Eriksson et al, 2008; Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011; Kakkar et al, 2008; Lassen et al, 2010 [a]; Lassen et al, 2010 [b]*).
  - RE-NOVATE and RE-NOVATE II: The RE-NOVATE trial compared 150 and 220 mg of dabigatran to enoxaparin 40 mg per day and the RE-NOVATE II trial compared 220 mg of dabigatran to enoxaparin 40 mg per day in over 5,500 patients. In both trials, dabigatran was as effective as enoxaparin in reducing the risk of VTE and mortality after THR surgery (P for non-inferiority < 0.001). The incidence of major bleeding did not differ significantly among groups (enoxaparin 0.9% to 1.6% vs dabigatran 1.3% to 2%) (*Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011*).
  - ADVANCE-3: Apixaban 2.5 mg twice daily was superior to enoxaparin in approximately 5,400 patients in reducing the risk of VTE and mortality after THR surgery (P < 0.001). The incidence of adjudicated major bleeding events were similar between groups (enoxaparin 0.8% vs apixaban 0.7%) (*Lassen et al, 2010 [b]*).
  - RECORD 1: Rivaroxaban 10 mg once daily was superior to enoxaparin in approximately 5,600 patients for the combined endpoint of any DVT, nonfatal PE, or all-cause mortality up to day 42 for rivaroxaban and ranged from 1.1% to 2% compared to 3.7% to 9.3% for enoxaparin. Major VTE was decreased 0.2% to 0.6% with rivaroxaban compared with 2% to 5.1% with enoxaparin. The incidence of major bleeding was similar between groups (enoxaparin 0.1% vs rivaroxaban 0.3%; P = 0.18) (*Eriksson et al, 2008; Kakkar et al, 2008*).
- Studies in patients undergoing a TKR have conflicting results with evidence demonstrating superiority of XARELTO and ELIQUIS when compared to enoxaparin 40 mg dose. However, TKR studies evaluating the US enoxaparin recommended dose of 30 mg twice daily have demonstrated ELIQUIS to be inferior to enoxaparin for total VTE (RR, 1.02; 95% CI, 0.78 to 1.32; P for non-inferiority = 0.06) through the ADVANCE-1 trial (*Lassen et al, 2009*), and XARELTO has demonstrated superiority to enoxaparin for the primary efficacy endpoint (*Turpie et al, 2009*).
- It is important to note that guidelines favor LMWH over ARIXTRA, ELIQUIS, PRADAXA, XARELTO, or UFH (*AAOS, 2011; Guyatt et al, 2012*).

General VTE prophylaxis for the medically ill:

- Currently, BEVYXXA is the only oral anticoagulant specifically FDA-approved as prophylaxis in patients with restricted mobility from acute illness and other risk factors. The APEX trial was a randomized, DB trial which compared the safety and efficacy of an extended duration of BEVYXXA to a short duration of enoxaparin in patients who were hospitalized due to an acute illness and had risk factors for VTE. A total of 7,513 patients were randomized to BEVYXXA 160 mg orally on day 1, followed by 80 mg once daily for 35 to 42 days (and a subcutaneous placebo injection for 6 to 14 days) or to enoxaparin 40 mg administered subcutaneously once daily for 6 to 14 days (and an oral placebo tablet for 35 to 42 days). Patients with renal insufficiency received 50% of the dose for each medication. In the first cohort analyzed, patients with an elevated D-dimer level, the difference between BEVYXXA and enoxaparin on the primary composite of

asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42 did not reach statistical significance (6.9 vs 8.5%, respectively; RR, 0.81; 95% CI, 0.65 to 1; P = 0.054). In patients with an elevated D-dimer level or an age ≥ 75 years, the composite endpoint was reached in 5.6 vs 7.1%, respectively (RR, 0.8; 95% CI, 0.66 to 0.98; P = 0.03), and in the overall population, it was reached in 5.3 vs 7%, respectively (RR, 0.76; 95% CI, 0.63 to 0.92; P = 0.006). However, because the first test did not reach statistical significance, these subsequent outcomes were considered exploratory. In the overall population, there was no significant difference in the incidence of major bleeding through day 7 after discontinuation of therapy (0.7 vs 0.6%, respectively) (*Cohen et al, 2016*).
    - Additionally, BEVYXXA compared with enoxaparin significantly reduced the incidence of all cause strokes (0.54 vs. 0.97%, respectively; P = 0.032), ischemic strokes (0.48 vs 0.91%, respectively; P = 0.026), and a composite of all cause stroke or transient ischemic attack (0.65 vs 1.1%, respectively; P = 0.034) through 77 days of follow up (*Gibson et al, 2017*).
- For patients who are medically ill and at risk for a DVT or PE, two studies (ADOPT and MAGELLAN) have been conducted for ELIQUIS and XARELTO, respectively. Both TSOACs were compared to enoxaparin 40 mg daily for approximately 10 days to ELIQUIS 2.5 mg twice daily for 30 days and XARELTO 10 mg once daily for 35 days, respectively. The following efficacy and safety outcomes were reported in each trial:
    - ADOPT: ELIQUIS was demonstrated to be similar to enoxaparin for the primary endpoint of composite of total VTE and VTE-related death at 30 days (RR, 0.87; 95% CI, 0.62 to 1.23; P = 0.44) and at 90 days (RR, 1.06; 95% CI, 0.69 to 1.63; P = not reported). Enoxaparin treatment was associated with significantly less risk of bleeding compared to ELIQUIS (*Goldhaber et al, 2011*).
        - MAGELLAN: XARELTO was demonstrated to be as effective as enoxaparin for the primary endpoint of asymptomatic proximal or symptomatic VTE at day 10 (RR, 0.97; 95% CI, 0.71 to 1.31; P = 0.003 for non-inferiority) and superior to enoxaparin at day 35 (RR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02 for superiority). Enoxaparin treatment was associated with significantly less risk of bleeding compared to XARELTO (*Cohen et al, 2013*).
        - The clinical relevance of asymptomatic VTE is unknown in the MAGELLAN trial. The ADOPT trial included a number of endpoints, including the composite of VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT, and it is not clear if any of the individual measures were significantly different.

Safety in renal insufficiency:

- One meta-analysis of ten randomized controlled trials examined patients with mild to moderate renal insufficiency and AF, acute DVT/PE, or extended treatment of VTE who were administered recommended doses of TSOACs (e.g., ELIQUIS, PRADAXA, or XARELTO). The analysis of key outcomes demonstrated that TSOACs were non-inferior and had improved bleeding compared to conventional anticoagulant treatment with LMWH, VKA, LMWH followed by VKA, or aspirin therapy (*Sardar et al, 2014*).

CLINICAL GUIDELINES

- In terms of current reputable guidelines, the following has been recommended:
    - For the prevention of stroke and systemic embolism in patients with NVAF, guidelines generally recommend oral anticoagulation in patients with NVAF at intermediate to high risk of stroke, or in certain patients with ≥ 1 moderate risk factors for stroke or thrombosis. TSOACs are considered to be a reasonable option in patients with native aortic valve disease, tricuspid valve disease, or mitral regurgitation, and in AF with a CHA_2DS_2-VASc score ≥ 2. Warfarin is generally recommended over the TSOACs, particularly for prosthetic or bioprosthetic valve thrombosis. Expert consensus guidelines stipulate that continuous uninterrupted VKA therapy has demonstrated lower bleeding risks vs interrupted treatment with heparin bridging for certain procedures such as pacemaker implants or implantable cardioverter defibrillators (ICD) in most NVAF patients. Reputable societies encourage decisions to be made based on patient characteristics and a risk/benefit analysis (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).
    - All TSOACs have demonstrated non-inferiority to conventional therapy for acute VTE. The ACCP guidelines recommend the TSOACs over warfarin for the first 3 months of therapy for non-cancer associated VTE. Warfarin is recommended over LMWH for long-term VTE therapy; however LMWH is preferred in patients with cancer (*Guyatt et al, 2012; Kearon et al, 2016*).

- For patients with recurrent VTE and currently administered anticoagulants, the ACCP guidelines recommend patients be switched to LMWH, at least temporarily, in lieu of warfarin and TSOACs. If a recurrent VTE occurs while a patient is taking long-term LMWH, then a dose increase of 1/4 or 1/3 is recommended (*Guyatt et al, 2012; Kearon et al, 2016*).
- For VTE prophylaxis in patients undergoing TKR or THR surgery, the AAOS does not recommend a specific medication (*AAOS, 2011*). The ACCP does favor LMWH over ARIXTRA, ELIQUIS, XARELTO, or UFH (*Guyatt et al, 2012*). If a TSOAC is prescribed, the treatment duration of ELIQUIS and XARELTO is a minimum of 10 to 14 days for a TKR (prescribing information recommends 12 days) and 35 days for a THR which is in agreement with the prescribing information.

SAFETY SUMMARY

- Contraindications:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
  - BEVYXXA, COUMADIN, ELIQUIS, JANTOVEN, PRADAXA and XARELTO also have contraindications in patients with a severe hypersensitivity to any component of the products.
  - PRADAXA has an additional contraindication in patients with mechanical prosthetic heart valves; additionally, the indication for BEVYXXA has a limitation of use in patients with prosthetic heart valves as this population has not been studied.
  - COUMADIN and JANTOVEN are contraindicated in patients with hemorrhagic tendencies or blood dyscrasias, recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces, threatened abortion, eclampsia, preeclampsia, unsupervised patients with conditions associated with potential high level of non-compliance, spinal puncture, other diagnostic or therapeutic procedures with the potential for uncontrollable bleeding, major regional or lumbar block anesthesia, malignant hypertension, or bleeding tendencies associated with active ulceration, overt bleeding of the GI, genitourinary, or respiratory tract, CNS hemorrhage, cerebral aneurysms, dissecting aorta, bacterial endocarditis, pericarditis, or pericardial effusions.
- A boxed warning exists for:
  - PRADAXA, XARELTO, SAVAYSA, and ELIQUIS with regards to the increased risk of thrombotic events when prematurely discontinuing therapy without adequate continuous anticoagulation. BEVYXXA, or treatment with the aforementioned agents, increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis in patients receiving neuraxial anesthesia or undergoing spinal puncture. The optimal timing between the administration of PRADAXA, SAVAYSA, or ELIQUIS and neuraxial procedures is not known.
  - SAVAYSA should not be used in NVAF patients with CrCL > 95 mL/min. In trials, these patients had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin.
  - COUMADIN and JANTOVEN may cause major or fatal bleeding. Drugs, dietary changes, and other factors affect INR levels achieved with COUMADIN or JANTOVEN therapy. Regular monitoring of INR in all patients is recommended.
- Warnings/Precautions:
  - Warnings and precautions for all agents within the oral anticoagulant class include an increased risk of serious or potentially fatal bleeding (including hemorrhage). Patients should be evaluated for signs and symptoms of blood loss or thrombotic events when treated with oral anticoagulants.
  - Additional warnings and precautions for the TSOACs (ELIQUIS, PRADAXA, SAVAYSA, and XARELTO) include a risk of thrombotic events (including stroke) after premature discontinuation, use is not recommended in patients with heart valves (ie, prosthetic, bioprosthetic, mechanical valves, or moderate to severe mitral stenosis), and an increased risk of long-term or permanent paralysis from an epidural or spinal hematoma when neuraxial anesthesia or spinal/epidural puncture is employed in patients treated with an antithrombotic agent.
  - ELIQUIS and XARELTO have a warning and precaution that use is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present with hemodynamic instability or receive thrombolysis or pulmonary embolectomy.
  - COUMADIN, JANTOVEN, and XARELTO has a warning and precaution in pregnant women due to the potential for obstetric hemorrhage. XARELTO may also cause emergent delivery. COUMADIN and JANTOVEN are contraindicated during pregnancy; however, the benefits may outweigh the risks in pregnant patients with mechanical heart valves at high risk of thromboembolism.
  - BEVYXXA and XARELTO have a warning and precaution of use in renal impairment. XARELTO has a warning and precaution of use in hepatic impairment; additionally, BEVYXXA is not recommended for use in these patients.

- An additional warning and precaution for SAVAYSA is reduced efficacy in NVAF patients with CrCL > 95 mL/min.
- COUMADIN and JANTOVEN have a warning and precaution that fatal and serious calciphylaxis or calcium uremic arteriolopathy has been reported with use in patients with and without end stage renal disease. When calciphylaxis is diagnosed, warfarin should be discontinued and an alternate anticoagulant considered. Additional warnings and precautions include the potential for tissue necrosis or gangrene, systemic atheroemboli, cholesterol microemboli, possible limb ischemia, necrosis, and gangrene in patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Should any of these issues occur, COUMADIN or JANTOVEN should be discontinued. Should HIT or HITTS occur, treatment with COUMADIN or JANTOVEN may be considered after the platelet count has normalized.

- Adverse events:
  - The most common adverse reactions reported with these agents include bleeding (all agents), anemia (SAVAYSA), rash (SAVAYSA), abnormal liver function tests (SAVAYSA), and gastritis-like symptoms (PRADAXA).
- Drug interactions:
  - BEVYXXA and PRADAXA have a warning and precaution of concomitant use with P-gp inducers or inhibitors, and XARELTO has a warning and precaution of combined use with dual P-gp and strong CYP3A4 inhibitors or inducers. Generally use with these products should be avoided. Although not a warning and precaution, interactions between strong P-gp inhibitors or inducers, CYP3A4 inhibitors or inducers, and oral anticoagulants either in combination or when co-administered alone are noted within the ELIQUIS and SAVAYSA labeling.
  - Concomitant use with other drugs (ie, aspirin, platelet inhibitors, antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin reuptake inhibitors [SSRIs], and serotonin norepinephrine reuptake inhibitors [SNRIs]) that impair hemostasis increase the risk of bleeding.
  - Numerous drug and dietary interactions exist for warfarin.
- Additional safety considerations:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
    - Two oral anticoagulants have reversal agents available for urgent situations. These include warfarin (COUMADIN and JANTOVEN) and dabigatran (PRADAXA). Vitamin K functions as a reversal agent for warfarin, and idarucizumab (PRAXBIND) is a specific reversal agent for PRADAXA.
    - A specific reversal agent for ELIQUIS, SAVAYSA, and XARELTO is not available. Hemodialysis does not significantly contribute to clearance. The use of prothrombin complex concentrates (PCC), or other procoagulant reversal agents such as activated prothrombin complex concentrate (APCC) or recombinant FVIIa may be considered but has not been evaluated in studies.
      - Andexanet alfa is a reversal agent under clinical development. In August 2016, a CRL was issued by the FDA questioning manufacturing and clinical data. In August 2017, Portola Pharmaceuticals re-submitted the BLA addressing deficiencies noted in the CRL (*Portola Pharmaceuticals press release, 2017*).

DOSING AND ADMINISTRATION

- Table 3 outlines general dosing recommendations. Please refer to prescribing information for additional details regarding certain drug interactions, various special populations, converting to other anticoagulants, and guidance as it relates to surgical procedures.

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
BEVYXXA (betrixaban)	Capsule: 40 mg, 80 mg	Reduction in the risk of DVT and PE in hospitalized patients with acute medical illness with restricted mobility and other VTE risk factors: 160 mg as a single dose, followed by 80 mg once daily for 35 to 42 days; CrCL 15 to 29 mL/min or taking concomitant P-gp inhibitors: 80 mg as a single dose, followed by 40 mg once daily for 35 to 42 days	--	Take with food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ELIQUIS (apixaban)	Tablet: 2.5 mg, 5 mg	Reduce the risk of stroke in NVAF: 5 mg twice daily In NVAF patients with at least 2 of the following characteristics: (1) age ≥ 80 years, (2) Body weight ≤ 60 kg, or (3) serum creatinine ≥ 1.5mg/dL, the recommended dose is 2.5 mg twice daily. Prophylaxis of DVT following hip or knee replacement surgery: Knee: 2.5 mg twice daily for 12 days; Hip: 2.5 mg twice daily for 35 days. Note: First dose should be taken 12 to 24 hrs after surgery. Treatment of DVT and PE: 10 mg twice daily for 7 days, followed by 5 mg twice daily. Reduction in the risk of DVT and PE recurrence: 2.5 mg twice daily after at least 6 months of treatment for DVT or PE.	--	For patients unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tabs may be crushed and are stable in water, D5W, apple juice or applesauce. May deliver through a nasogastric tube after mixed in 60 mL of D5W or water.
PRADAXA (dabigatran)	Capsule: 75 mg, 110 mg, 150 mg	Reduce the risk of stroke in NVAF: CrCL > 30 mL/min: 150 mg twice daily; CrCL 15 to 30 mL/min: 75 mg twice daily; CrCL 30 to 50 mL/min with concomitant use of P-gp inhibitors (only dronedarone or ketoconazole): 75 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 30 mL/min. Treatment of DVT and PE/Reduction in the risk of DVT and PE recurrence:* CrCL > 30 mL/min: 150 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min. Prophylaxis of VTE following hip replacement surgery: CrCL > 30 mL/min: 110 mg on the first day, then 220 mg once daily for 28 to 35 days; Note: The initial dose should be taken 1 to 4 hrs after surgery. Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min.	--	Take with or without food.
SAVAYSA (edoxaban)	Capsule: 15 mg, 30 mg, 60 mg	Reduce the risk of stroke in NVAF: CrCL 95 to 51 mL/min: 60 mg once daily; for CrCL 15 to 50 mL/min: 30 mg once daily; Do not use for CrCL > 95 mL/min Treatment of DVT and PE: 60 mg once daily following 5 to 10 days of initial parenteral	--	Take with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		anticoagulant; CrCL 15 to 50 mL/min, weight ≤ 60 kg, or taking concomitant P-gp inhibitors: 30 mg once daily		
XARELTO (rivaroxaban)	Tablet: 10 mg, 15 mg, 20 mg Starter pack (tablet): 15 and 20 mg	Prophylaxis of DVT following hip or knee replacement surgery: Knee: 10 mg once daily for 12 days Hip: 10 mg once daily for 35 days Note: The initial dose should be taken 6 to 10 hrs after surgery. Reduce the risk of stroke in NVAF: CrCL > 50 mL/min: 20 mg once daily with the evening meal CrCL 15 to 50 mL/min: 15 mg once daily with the evening meal Treatment of DVT and PE: 15 mg twice daily with food, for first 21 days. Then after 21 days, 20 mg once daily with food for remaining treatment Reduction in the risk of recurrence of DVT and of PE: 20 mg once daily with food	--	The 10 mg, 15 mg and 20 mg tablets may be crushed and are stable in water or applesauce for up to 4 hours.
COUMADIN; JANTOVEN (warfarin)	Tablet: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg	Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 for most bioprosthetic and mechanical heart valves and an INR of 2.5 to 3.5 for tilting disk valves, bileaflet mechanical valves in the mitral position, or caged ball or caged disk valves Prophylaxis and treatment of venous thrombosis and its extension, PE: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 and treat for a minimum of 3 months and reassess the risk-benefit ratio of long-term treatment. Reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; for high risk patients with MI, maintain an INR of 2 to 3 (moderate intensity) plus low-dose aspirin ≤ 100 mg/day for at least 3 months after MI	An INR > 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding Dosing may be modified in patients with certain identified genotypes.	

CONCLUSION

- Four TSOACs, PRADAXA, XARLETO, SAVAYSA, and ELIQUIS, are all indicated for the reduction of stroke and systemic embolism in NVAF and for the treatment of DVT and PE, otherwise known as events caused by a VTE. PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE; and DVT and PE prophylaxis in patients undergoing THR. XARELTO and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing TKR surgery. Warfarin has various indications, including prophylaxis and/or treatment of PE; prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement prophylaxis and/or treatment of venous thrombosis and its extension; and to reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI. BEVYXXA is the only agent in class indicated for patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- Warfarin has long-term efficacy and safety data and is generically available. Trial evidence and recommendations from current clinical guidelines support the use of warfarin for all FDA-approved indications.
- Therapy with warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- The major advancement with the TSOACs is that they do not require routine laboratory monitoring; however, this may make it difficult for physicians to objectively assess adherence to therapy. In addition, their propensity for drug and dietary interactions is less than warfarin. There is uncertainty regarding how to manage bleeding or perioperative management in patients treated with TSOACs. There are no FDA-approved assays or calibration reagents to measure the effect of the TSOACs. However, partial thromboplastin time (PTT) and thrombin time (TT) can be useful for measuring the effects of PRADAXA (*Raval et al, 2017*).
- PRADAXA is the first TSOAC with an available antidote, idarucizumab (*PRAXBIND prescribing information, 2015*). There are no specific antidotes for BEVYXXA, ELIQUIS, SAVAYSA, or XARELTO; however, antidotes, ciraparantag and andexanet alfa, are in the pipeline (*Perosphere press release, 2017; Portola Pharmaceuticals press release, 2017*).
- Warfarin, BEVYXXA, SAVAYSA, and XARELTO are approved for once-daily dosing, while ELIQUIS is administered twice-daily. Based on the indication, PRADAXA may be administered once or twice-daily. BEVYXXA, ELIQUIS, PRADAXA, SAVAYSA, and XARELTO require a dose adjustment in patients with renal impairment and are only available as branded products.
- No head-to-head studies have been conducted comparing the TSOACs. Also, there is a lack of long-term efficacy and safety data and limited real-world experience with the TSOACs.
- In terms of current available evidence, the following has been demonstrated:
  - For those TSOACs FDA-approved for the prevention of stroke and systemic embolism in patients with NVAF, all TSOACs have been found to be superior or non-inferior to warfarin within pivotal trials; however, clinical differences have not been clearly defined (*Connolly et al, 2009; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011*).
  - ELIQUIS, PRADAXA, SAVAYSA, and XARELTO have demonstrated non-inferiority to conventional therapy for acute VTE. XARELTO (EINSTEIN-PE only) and ELIQUIS have also demonstrated significant reductions in major bleeds; however, PRADAXA and SAVAYSA have similar rates of major bleeding compared to that observed with conventional therapy. Due to the design of the trials, SAVAYSA and PRADAXA also require 5 to 10 days of parenteral anticoagulation prior to initiating treatment (*Agnelli et al [a], 2013; Bauersachs et al, 2010; Büller et al, 2013; Büller et al, 2012; Prins et al, 2013; Schulman et al, 2009; Schulman et al, 2014*).
  - For the reduction of risk recurrence of VTE as demonstrated in extended VTE trials, PRADAXA, ELIQUIS, and XARELTO have demonstrated superiority to placebo for recurrent VTE; however, bleeding rates were comparable. PRADAXA has demonstrated non-inferiority to warfarin with less risk of major or clinically relevant bleeding and had lower major bleeding rates than those rates observed in the RE-COVER trials (*Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013*).
  - For VTE prophylaxis in patients undergoing TKR or THR surgery, XARELTO has demonstrated superiority to enoxaparin doses in both THR and TKR studies. ELIQUIS was found to be superior for THR and when compared to enoxaparin 40 mg once daily for TKR; however, ELIQUIS was found to be inferior to the US enoxaparin recommended dose of 30 mg twice daily (*Eriksson et al, 2008; Kakkar et al, 2008; Lassen et al, 2009; Lassen et al, 2010 [b]; Turpie et al, 2009*). The FDA has approved PRADAXA for VTE prophylaxis associated with THR surgery

after non-inferiority was demonstrated compared to enoxaparin 40 mg once daily and bleeding rates were similar (*Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011*).

- In hospitalized patients with restricted mobility from acute illness and other VTE risk factors, the use of oral anticoagulants has demonstrated a likelihood to reduce VTE when administered prophylactically. Studies have been conducted with BEVYXXA, ELIQUIS, and XARELTO; however, only BEVYXXA is specifically FDA-approved for this indication. ELIQUIS and XARELTO have demonstrated non-inferiority or were similar to enoxaparin, but were also associated with an increased bleeding risk. BEVYXXA was associated with numerically fewer events of asymptomatic or symptomatic proximal DVT, non-fatal PE, or VTE-related death compared to enoxaparin, but no increased incidence of major bleeding (*Cohen et al, 2013; Cohen et al, 2016; Gibson et al, 2017; Goldhaber et al, 2011*).
- Reputable societies encourage decisions to be made based on indication, patient characteristics, and a risk/benefit analysis (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kearon et al, 2016; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).

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