Anticoagulants
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	DVT prophylaxis				DVT Treatment
		Hip Replacement	Knee Replacement	Hip Fracture Surgery	Abdominal Surgery	
Injectable						
dalteparin (Fragmin®)[1]	Pfizer	X	-	-	X	-
enoxaparin (Lovenox®)[2]	generic, Sanofi-Aventis	X	X	-	X	X (without PE in outpatient setting, with or without PE in inpatient setting)
fondaparinux (Arixtra®)[3]	generic, Mylan	X	X	X	X	X
Oral						
apixaban (Eliquis®)[4]	Bristol-Myers Squibb	X	X	-	-	X
dabigatran (Pradaxa®)[5,6]	generic, Boehringer Ingelheim	X (oral capsule only)	-	-	-	X*
edoxaban (Savaysa®)[7]	Daiichi Sankyo	-	-	-	-	X*
rivaroxaban (Xarelto®)[8]	Janssen	X	X	-	-	X†
warfarin‡	generic§	-	-	-	-	X

* Dabigatran capsules and edoxaban are indicated for the treatment of deep vein thrombosis (DVT)/pulmonary embolism (PE) in adults treated with a parenteral anticoagulant for 5 to 10 days (adults). Dabigatran oral capsules are also approved for the treatment of venous thromboembolism (VTE) in pediatric patients ≥ 8 years old who have been treated with a parenteral anticoagulant for ≥ 5 days. Dabigatran oral pellets are approved for the treatment of VTE in pediatric patients 3 months to < 12 years old who have been treated with a parenteral anticoagulant for ≥ 5 days.

† Rivaroxaban is also approved for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to < 18 years after ≥ 5 days of initial parenteral anticoagulant treatment.

‡ Warfarin, although not approved by the United States (US) Food and Drug Administration (FDA) for these purposes, has also been used off-label for DVT prophylaxis following select surgeries (e.g., hip, knee, abdominal).[9]

Other Indications

dalteparin (Fragmin)

- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI) when concurrently administered with aspirin
- Deep vein thrombosis (DVT) prophylaxis for immobile medical patients who are at risk for thromboembolic complications

- Extended treatment of symptomatic venous thromboembolism (VTE) (proximal DVT and/or pulmonary embolism [PE]), to reduce the recurrence of VTE in patients with cancer
- Treatment of symptomatic VTE to reduce the recurrence of VTE in pediatric patients 1 month of age and older

enoxaparin (Lovenox)

- For the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction in conjunction with aspirin
- DVT prophylaxis to prevent thromboembolic complications in medical patients with severely restricted mobility during acute illness
- Treatment of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with subsequent percutaneous coronary intervention (PCI)

fondaparinux (Arixtra)

- Treatment of acute PE when initial therapy is administered in the hospital and with warfarin

apixaban (Eliquis)

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)
- For the treatment of PE
- To reduce the risk of recurrent DVT and PE following initial therapy

dabigatran (Pradaxa)

- To reduce the risk of stroke and systemic embolism in adult patients with NVAF (oral capsule only)
- To reduce the risk of recurrence of DVT and PE following initial therapy (pellet only: pediatric patients 3 months to < 12 years of age; oral capsule: pediatric patients ≥ 8 years of age and adults)

edoxaban (Savaysa)

- To reduce the risk of stroke and systemic embolism in patients with NVAF

rivaroxaban (Xarelto)

- To reduce the risk of stroke and systemic embolism in patients with NVAF
- For the treatment of PE
- For the reduction in the risk of recurrence of DVT and of PE for patients at continued risk for recurrent DVT and/or PE following initial 6-months treatment for DVT and/or PE
- To reduce the risk of major cardiovascular (CV) events (CV death, MI, and stroke) in patients with coronary artery disease (CAD) when used in combination with aspirin
- To reduce the risk of major thrombotic vascular events (MI, stroke, acute limb ischemia, major amputation of a vascular etiology) in patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD, when used in combination with aspirin

- For the prophylaxis of VTE and VTE-related death during hospitalization and post-hospital discharge in adult patients admitted 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 and not at high risk of bleeding
- For thromboprophylaxis in pediatric patients ≥ 2 years old with congenital heart disease after the Fontan procedure

warfarin

- Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement
- Reduce the risk of death, recurrent myocardial infarction, and thromboembolic events, such as stroke or systemic embolization, after myocardial infarction
- Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism (PE)

The focus of this review will be on the outpatient use of the injectable anticoagulants, which include the low molecular weight heparins (LMWHs) and fondaparinux, and the novel oral anticoagulants apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin.

OVERVIEW

Venous Thromboembolism (VTE)

Venous thromboembolism (VTE) is a significant public health problem in the United States (US). The disease manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major consequence of various surgical procedures and medical conditions. DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the extremities, most commonly the legs. Embolization of a thrombus results in PE if it lodges in the pulmonary artery or 1 of its branches and blocks pulmonary blood flow.[10,11]

The exact number of patients impacted by DVT and PE is unknown; however, it is estimated these conditions affect up to 900,000 people in the US every year.[12] An estimated 10% to 30% of patients with DVT or PE are estimated to die within 1 month of diagnosis.

Clinical risk factors for VTE include immobility or paralysis; trauma or surgery involving the lower extremities, pelvis, hips, or abdomen; malignancy; a history of VTE; obesity; any state leading to increased estrogen levels, including pregnancy and hormone replacement therapy; indwelling central venous catheters; cardiac dysfunction; inflammatory bowel disease; nephrotic syndrome; and acquired (e.g., cancer) or inherited hypercoagulability disorders. Generally, the risk of VTE increases with the number of risk factors present, major traumas, and age.[13,14] Due to the risk of morbidity and fatal PE associated with DVT, prophylaxis has become the standard of care for patients at high risk for thrombosis.

Based on presence of the risk factors outlined above, the 9th American College of Chest Physicians (CHEST) Evidence-Based Clinical Practice Guidelines published in 2012, with updates in 2016 and 2021 recommend various regimens of parenteral and/or oral anticoagulants with or without mechanical devices, such as graduated compression stockings and/or intermittent pneumatic compression devices.[15,16,17] In patients undergoing orthopedic surgery (total hip replacement or knee replacement), DVT prophylaxis with LMWH, unfractionated heparin (UFH), fondaparinux, vitamin K antagonist ([VKA]; e.g., warfarin), or aspirin, and also the newer agents apixaban (Eliquis), dabigatran (Pradaxa), and rivaroxaban (Xarelto) (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C) is recommended postoperatively for at least 10 to 14 days. LMWH is recommended over the other alternative agents (Grade 2B-2C). Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux [Arixtra], rivaroxaban [Xarelto], and VKA), possible decreased efficacy (UFH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban [Eliquis], dabigatran [Pradaxa], and rivaroxaban [Xarelto]). In patients undergoing hip fracture surgery, CHEST recommends the use of 1 of the following for antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux (Arixtra), low-dose UFH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C).

Initial treatment options for VTE consist of either intravenous (IV) or subcutaneous (SC) UFH, SC LMWH, or fondaparinux (Arixtra) for at least 5 days and until the international normalized ratio (INR) is in therapeutic range for at least 24 hours if the patient is being transitioned to warfarin. VKA therapy should overlap parenteral anticoagulant therapy and should be initiated on the first treatment day. LMWH or fondaparinux (Arixtra) is suggested over UFH for the treatment of acute DVT of the leg, acute PE, or acute upper extremity DVT (UEDVT) of the axillary or more proximal veins (Grades 2B and 2C). Rivaroxaban (Xarelto) and apixaban (Eliquis) are also indicated for the treatment of DVT in adults without the requirement for initial treatment with a parenteral anticoagulant. In patients with DVT of the leg, or PE and no cancer, CHEST recommends dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), or edoxaban (Savaysa) over VKA therapy for treatment phase (3 month) anticoagulant therapy (strong recommendation, moderate-certainty evidence). For patients with cancer, CHEST recommends an oral factor Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for both the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence). In patients with DVT of the leg who are treated with VKA, a therapeutic INR range of 2 to 3 (target INR of 2.5) for all treatment durations (Grade 1B) is recommended. For patients with VTE secondary to a nonsurgical, transient (reversible) risk factor, CHEST recommends anticoagulation therapy for 3 months over a shorter period (Grade 1B for proximal DVT or PE, Grade 2C for distal DVT) or an extended period (Grade 1B). For patients with a first episode of unprovoked DVT or PE, anticoagulation is recommended for 3 months over extended therapy if there is a high bleeding risk (Grade 1B) or low-moderate bleeding risk (Grade 2B). In patients with DVT of the leg who receive extended therapy (no scheduled stop date), the guidelines suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C).

The 2012 CHEST Antithrombotic Therapy and Prevention of Thrombosis (9th Edition) recommends anticoagulant thromboprophylaxis with a LMWH, low-dose UFH, or fondaparinux (Arixtra) as injectable options for the prevention of thrombosis for acutely ill hospitalized medical patients at increased risk of thrombosis.[18] Rivaroxaban was not indicated for use in these patients until October 2019.

The American Society of Clinical Oncology (ASCO) 2019 update to their evidence-based clinical practice guideline on prophylaxis and treatment of VTE in cancer patients states that cancer patients are significantly more likely to develop VTE than people without cancer.[19] Additionally, cancer patients exhibit increased rates of VTE recurrence and more bleeding complications during VTE treatment. Both prophylaxis and treatment regimens are generally more aggressive in cancer patients than in other populations. For example, most patients hospitalized for any condition who also have an active malignancy should receive anticoagulation therapy as prophylaxis unless there is active bleeding or another contraindication. In the outpatient setting, routine thromboprophylaxis is not recommended for cancer patients. However, the use of apixaban, rivaroxaban or LMWH as prophylaxis may be indicated for certain high-risk patients, including those with a Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen; the Khorana score, used to identify patients with cancer at elevated risk for this complication, ranges from 0 to 6 with higher scores indicating a higher risk of venous thromboembolism. Patients with multiple myeloma receiving thalidomide or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered prophylaxis with either aspirin or LMWH dependent on risk assessment. Cancer patients undergoing major surgery should have anticoagulation continued for at least 7 to 10 days postoperatively and possible extended prophylaxis with a LMWH for up to 4 weeks for select high risk patients undergoing pelvic or abdominal surgery. Initial anticoagulation for treatment of VTE in patients with cancer may include LMWH, UFH, fondaparinux or rivaroxaban. Per the ASCO guidelines, for patients initiating VTE treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days unless the patient has severe renal impairment. There is strong evidence to support a recommendation for long-term anticoagulation with a LMWH, edoxaban or rivaroxaban for at least 6 months rather than a VKA.

The American Society of Hematology (ASH) has also issued clinical practice guidelines on the management of VTE.[20,21,22,23,24,25] Recommendations included prophylaxis for medical patients, VTE diagnosis, treatment of VTE and DVT, management of anticoagulation therapy, heparin-induced thrombocytopenia (HIT), VTE in cancer patients, VTE in pregnancy, VTE in surgical patients, and pediatric VTE treatment. For the initial management of DVT and/or PE, ASH suggests the use of direct oral anticoagulants (DOACs) over VKAs, except in select populations (creatinine clearance [CrCl] < 30 mL/min, moderate to severe liver disease, antiphospholipid syndrome) but does not suggest one DOAC over another. Subsequently, the duration of primary treatment is dependent on risk factors and if the DVT or PE was considered provoked or unprovoked. A shorter course of primary therapy (3 to 6 months) is preferred over a longer course (6 to 12 months) in patients with a provoked (transient or chronic risk factor) or unprovoked incident. Indefinite therapy as secondary prevention following the primary therapy is suggested in patients with chronic risk factors who had a provoked DVT or PE. This is also suggested for patients not at high risk of bleeding who had an unprovoked DVT or PE. Anticoagulants are suggested over aspirin for secondary prevention using continuation with standard dose (or lower dose) DOACs (dosing suggested) or a VKA (target INR of 2 to 3 recommended). For recurrence, during VKA therapy, a LMWH is suggested over DOAC therapy. When anticoagulants are used for VTE prophylaxis, the guidelines prefer LMWH over UFH or DOACs. They also note that managing anticoagulation therapy is complex; therefore, to optimize management of anticoagulation therapy, ASH suggests patients should receive care from specialized anticoagulation management service centers versus primary care physicians whenever possible. Additionally, for patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures, ASH recommends against periprocedural bridging with LMWH or UHF. In patients with acute HIT, suggested treatment options include argatroban, bivalirudin, danaparoid, fondaparinux, or a DOAC. Several recommendations and suggestions are described in depth in the guidelines for patients with cancer. Notably, they suggest parenteral thromboprophylaxis over no prophylaxis only in high-risk ambulatory patients receiving systemic cancer therapy; however, no thromboprophylaxis is recommended over VKA therapy. DOAC therapy (apixaban or rivaroxaban) is suggested over no prophylaxis for patients with a high risk of thrombosis. Thromboprophylaxis is not suggested in cancer patients with a central venous catheter.

Additional guidance is provided, including recommendations for initial treatment, those undergoing surgery, short-term treatment, and long-term treatment.

For pregnant patients, the 2016 CHEST guidelines prefer LMWH for the prevention and treatment of VTE, as there is a potential for other agents to cross the placenta.[26] The 2012 CHEST guidelines provide more detailed recommendations, in which they advise for women receiving anticoagulation for the treatment of VTE who become pregnant, use of LMWH over VKA during the first trimester (Grade 1A), in the second and third trimesters (Grade 1B), and during late pregnancy when delivery is near (Grade 1A).[27] For women requiring long-term VKA who are attempting pregnancy and are candidates for LMWH substitution, CHEST recommends performing frequent pregnancy tests and substituting LMWH for VKA once the patient is pregnant, instead of switching to LMWH while attempting to become pregnant (Grade 2C). For pregnant women, these guidelines recommend against oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., apixaban and rivaroxaban) inhibitors (Grade 1C). Although the efficacy of LMWH and UFH for this indication has not been verified by randomized, controlled trials, extrapolation of data from non-pregnant patients, along with the relative safety in this patient population, support the recommendation. Because of the lack of data, the CHEST guidelines make no distinction among enoxaparin (Lovenox) or dalteparin (Fragmin) for this use. More randomized, well-controlled trials are needed to evaluate use of LMWH as prophylaxis in pregnancy and the early post-natal period, according to a systematic review.[28] There are only limited data available regarding the safety of fondaparinux (Arixtra) during pregnancy; therefore, the 2012 CHEST guidelines recommend against its general use during pregnancy.[29]

The 2012 CHEST antithrombotic therapy in neonates and children guidelines recommend anticoagulant therapy with either UFH or LMWH in children with DVT (Grade 1B). Initial treatment with UFH or LMWH should be for at least 5 days (Grade 1B).[30] If warfarin will be subsequently prescribed, oral warfarin should be initiated as early as day 1 and discontinue LMWH or UFH on day 6 or later than day 6 if the INR has not exceeded 2 (Grade 1B). For ongoing therapy, the guidelines recommend LMWH or UFH. Warfarin or, alternatively, LMWH are recommended for children with idiopathic thromboembolism as in children with secondary thrombosis (in whom the risk factor has resolved) for at least 6 to 12 months and at least 3 months, respectively (Grade 2C). In children with recurrent idiopathic VTE, CHEST recommends indefinite treatment with VKA (Grade 1A).

Although evidence is strong that patients who have received the Fontan procedure require some form of thromboprophylaxis for prevention of thromboembolism, it is unclear which agent is preferred.[31] Some data suggest anticoagulation with warfarin, especially early following the surgery, is better than antiplatelet therapy with aspirin for prevention of thromboembolism. However, other data suggests antiplatelet therapy alone (aspirin) may provide protection adequate to oral anticoagulants (warfarin).[32,33] Although the risk is greatest during the first year following the Fontan procedure, it continues throughout the patient's lifetime.[34] Data are limited on the use of novel oral anticoagulants in these patients.[35] However, rivaroxaban (Xarelto) has received FDA approval for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.[36]

Atrial Fibrillation (AF)

Atrial fibrillation (AF) is a common arrhythmia ranging in prevalence from 2% in patients under 65 years of age to 9% for those 65 or older.[37] The prevalence is higher in men than in women and increases with age. More than a third of patients with AF are 80 years of age or older.[38,39] Patients with AF can have a reduction in cardiac output resulting in pooling of blood in the heart, atrial thrombus formation, and potential systemic embolization.[40] Ischemic stroke is the most frequent clinical manifestation of AF associated embolization. AF increases the risk of stroke 5-fold.[41] In patients with AF, CHEST recommends measuring thromboembolism risk using the CHA_2DS_2-VASc score, which considered risk factors such as gender, age, history of stroke, transient ischemic attack (TIA), or thromboembolism, as well as history of congestive heart failure (CHF), hypertension, diabetes mellitus, or vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque). The score ranges from 0 to 9, with higher numbers indicating more risk. The 2018 CHEST guidelines suggest no antithrombotic therapy in patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk for stroke (CHA2DS2VASc = 0 in males or = 1 in females)(Strong recommendation).[42] Patients with AF, including those with paroxysmal AF, without valvular heart disease who have 1 non-sex CHA2DS2VASc stroke risk factor are suggested to receive oral anticoagulation while patients considered at high risk of stroke (e.g., CHA2DS2VASc ≥ 2 in males or ≥ 3 in females) are recommended to receive oral anticoagulation. Where oral anticoagulation is recommended or suggested, CHEST suggests using a novel oral anticoagulant (NOAC) rather than adjusted-dose vitamin K antagonist therapy.

The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines for the management of AF recommend the use of antithrombotic therapy be based on shared decision-making, discussions of the risks of stroke and bleeding, and patient preference (Class 1; Level C).[43] The guidelines further recommend the choice of antithrombotic therapy be based on the risk of thromboembolism as measured by the CHA_2DS_2-VASc score (Class 1; Level B). According to these guidelines, oral anticoagulants are recommended in nonvalvular atrial fibrillation (NVAF) patients who have either had a prior stroke, TIA, or have a CHA_2DS_2-VASc score > 2. Options for these patients include warfarin (INR 2 to 3) (Level of Evidence: A), dabigatran (Pradaxa), rivaroxaban (Xarelto), or apixaban (Eliquis) (all level of evidence B). In NVAF patients who have a CHA_2DS_2-VASc score of 1, no treatment or aspirin may be considered (Class 2; Level B) and in NVAF patients with a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Class 2; Level A). Edoxaban (Savaysa) was not available at the time these guidelines were released; however, it is FDA approved to reduce the risk of stroke and systemic embolism in patients with NVAF. In 2019, the AHA/ACC/HRS released a focused update of their 2014 Guideline on the Management of Patients with Atrial Fibrillation based on new relevant clinical trial data.[44] All NOACs are now preferred over warfarin in NOAC-eligible patients with AF; however, patients with moderate-to-severe mitral stenosis or a mechanical heart valve are considered exceptions to this recommendation. In NOAC-eligible patients, NOACs were shown to be at least noninferior to warfarin in preventing stroke and systemic embolism and have a lower risk of bleeding. Apixaban is preferred in patients with end-stage renal disease or on dialysis while the other NOACs are not recommended in this population due to lack of evidence. Edoxaban is now included in the guidelines as an option for stroke prevention. The anticoagulant reversal agents idarucizumab (Praxbind®) and andexanet alfa (Andexxa®) are recommended in the event of life-threatening bleeding or an urgent procedure.

There is consensus throughout the published guidelines that all AF patients with mechanical heart valves should be treated with warfarin. Dabigatran (Pradaxa) is contraindicated in patients with mechanical heart valves due to an increased risk of bleeding.[45,46] Patients with AF and end-stage renal disease (ESRD) (CrCl < 15 mL/min) or those receiving hemodialysis should be treated with warfarin (Class IIa; Level B). Dabigatran (Pradaxa) and rivaroxaban (Xarelto) should not be used in patients with end-stage CKD or receiving hemodialysis due to lack of evidence regarding the balance between risks and benefits (Class III; Level C). Dosage recommendations are available for the use of dabigatran (Pradaxa), apixaban (Eliquis), and rivaroxaban (Xarelto) in patients with moderate to severe CKD and a CHA_2DS_2-VASc score > 2; however, safety and efficacy have not been established (Class IIb; Level C). Bridging therapy with UFH or LMWH for patients who require interruption of oral anticoagulant therapy should be contemplated. Considerations include the oral anticoagulant being interrupted, whether the patient has a mechanical heart valve, and the duration of time a patient will not be anticoagulated. These decisions should balance the risks of stroke and bleeding (Class I; Level C).

In 2020, the AHA/ACC updated their earlier guidelines on anticoagulation for AF in patients with valvular heart disease (VHD).[47] In patients with AF and native VHD (except for mitral stenosis) or with a bioprosthetic valve placed > 3 months prior, a NOAC is an effective alternative to a VKA and should be given based on CHA_2DS_2-VASc score (I, A). In those with rheumatic mitral stenosis, long-term anticoagulation with an oral VKA is recommended (I, C). VKA therapy is also recommended for new onset AF ≤ 3 months after surgical or transcatheter bioprosthetic valve replacement (Class IIa, B). NOACs are not recommended in patients with mechanical heart valves with AF who require long-term VKA therapy (III, B). Anticoagulation is needed in all patients with a mechanical valve, but newer anticoagulants have not been found to be safe or effective in these patients. The group recommends the use of VKA in these patients (I, A). In patients with a mechanical bileaflet or current-generation single tilting disc AVR and no risk factors for thromboembolism, the guidelines still recommend VKA to achieve an INR of 2.5 (I, B). VKA is recommended in patients with a mechanical heart valve and additional risk factors for thromboembolic events with a goal INR of 3 (I, B). VKA is also recommended to achieve an INR of 3 in patients with a mechanical mitral valve replacement (I, B). VKA with an INR target of 2.5 for 3 to 6 months after surgical bioprosthetic mitral or aortic valve replacements (MVR, AVR) in patients at low bleeding risk is reasonable (IIa, B-NR) according to guidelines. A lower target INR of 1.5 to 2 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors (IIb, B). VKA to achieve an INR of 2.5 is reasonable after transcatheter aortic valve replacement (TAVR) for ≥ 3 months in patients at low risk of bleeding. Oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prosthesis.

According to the Centers for Disease Control and Prevention (CDC), 1 in 6 deaths in 2020 from CV disease was attributed to stroke.[48] The 2014 American Academy of Neurology (AAN) guidelines, last reaffirmed in 2020, for the prevention of stroke in NVAF conclude dabigatran (Pradaxa) 150 mg twice daily is likely more effective than warfarin with a decreased risk for intracranial hemorrhage.[49] The guidelines also conclude rivaroxaban (Xarelto) is probably as effective as warfarin in preventing stroke or systemic embolism with a lesser frequency of intracranial hemorrhage and fatal bleeding. The AAN guidelines state apixaban (Eliquis) 5 mg twice daily has been shown to result in a reduced mortality compared to warfarin due to a decreased risk of bleeding, including intracranial bleeding, rather than its effect on reduction of cerebral or systemic embolism compared to warfarin. These guidelines also provide comparisons between the effectiveness and safety of oral anticoagulants to antiplatelet agents, such as aspirin and clopidogrel. Edoxaban (Savaysa) was not available at the time the 2014 AAN guidelines were published; it is, therefore, not included in the AAN review. Unresolved issues surrounding the use of the new anticoagulants in the setting of NVAF include the lack of data comparing these drugs to 1 another (all were compared only to warfarin) and the short duration of follow-up given the long-term real-world indication. In addition, drug activity cannot be assessed in routine clinical practice which may lead to under- or over-treatment of patients, questionable safety of treatment for an acute ischemic stroke with a thrombolytic agent in patients receiving apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto), or edoxaban (Savaysa), and the lack of an antidote in the setting of acute hemorrhage. However, some of these issues are being addressed. In October 2015, the FDA approved idarucizumab (Praxbind), a humanized monoclonal antibody fragment, to reverse anticoagulation for emergency or urgent procedures and life-threatening or uncontrolled bleeding in adult patients treated with dabigatran (Pradaxa).[50]

The 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with NVAF on long-term oral anticoagulation therapy provides some key recommendations for interruption of therapy due to a procedure.[51] In general, the decision to interrupt therapy should be based on type of oral anticoagulant, patient's bleeding risk, and procedure bleeding risk. Assessment of patient's bleeding risk should be done based on the HAS-BLED score, history of bleeding in prior 3 months, platelet abnormalities, INR, and history of procedural bleeding. Warfarin must not be interrupted in patients with a low risk of bleeding and no patient-specific factors that are likely to increase bleeding risk. In cases where warfarin does need to be interrupted, therapy must be stopped 3 to 4 days prior to procedure for an INR of 1.5 to 1.9; 5 days before for an INR of 2 to 3; ≥ 5 days for INR > 3; and INR must be rechecked 24 hours prior to procedure. For interruption of oral direct acting agents, the number of doses to skip should be based on creatinine clearance and bleeding risk of the procedure.

Coronary Artery Disease (CAD) and Peripheral Artery Disease (PAD)

Approximately 14 million Americans have CAD, and 8.5 million over the age of 40 years have PAD.[52,53] Prevention and treatment of atherosclerosis focus on modifiable risk factors. Therapy includes lifestyle changes and the medical treatment of hypertension, hyperlipidemia, and diabetes mellitus.[54] Antiplatelet medications (e.g., aspirin, clopidogrel, prasugrel, ticagrelor, vorapaxar) are indicated for reduction of thrombotic CV events in patients with established CAD or PAD.[55,56] In October 2018, rivaroxaban (Xarelto) became the first oral anticoagulant approved for use in combination with low-dose aspirin to reduce the risk of major CV or thrombotic events in patients with chronic CAD or PAD, respectively.

In patients with AF on an oral anticoagulant who need PCI, the 2020 ACC Expert Consensus Decision Pathway on anticoagulant and antiplatelet therapy in patients with AF or VTE who are undergoing PCI or with atherosclerotic CV disease recommends restarting oral anticoagulation with a DOAC (preferred) if previously on a DOAC or VKA.[57] A VKA may be considered in patients who were previously on a VKA. Both groups should also receive an antiplatelet. Additional guidance is provided for periprocedural management (duration dependent on the oral anticoagulant needed). For patients already on an antiplatelet agent with a new diagnosis of AF, when an oral anticoagulant is initiated, a DOAC is preferred. The pathway also provides guidance on anticoagulant therapy with antiplatelet therapy in patients with prior VTE who have undergone PCI. In general, the anticoagulant duration should be based on the VTE indication. Likewise, if the patient was already on antiplatelet therapy and has VTE, the pathway provides guidance for antiplatelet therapy when initiating the anticoagulant. In this case, DOACs are preferred for cancer-associated thrombosis (LMWH as an alternative) and for non-cancer-associated thrombosis (VKA with or without LMWH bridge therapy as an alternative).

Other Considerations

In 2020, the ACC updated their Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.[58] For major bleeding, anticoagulants should be interrupted, and measures should be initiated to control the bleeding. If the bleed is life-threatening or if other measures did not control the bleeding, a reversal or hemostatic agent (e.g., prothrombin complex concentrate [PCC], plasma, vitamin K, idarucizumab, andexanet alfa) is recommended. If the bleed is not a major bleed and does not require hospitalization, surgical or procedural intervention, or transfusion, the oral anticoagulant can be continued. If it does require hospitalization, surgical or procedural intervention, or transfusion, the oral anticoagulant should be stopped and measures to control bleeding should be implemented. Regarding agent-specific reversal recommendations, for a VKA, ACC recommends four-factor PCC, with a dose based on bleed location or INR. Plasma is an alternative in these patients. For dabigatran, idarucizumab is recommended in adults, for apixaban or rivaroxaban, andexanet alfa is recommended, and for betrixaban (no longer available) or edoxaban, non-FDA-approved used of high-dose andexanet alfa is recommended. For the non-VKA treatments, if the specific agent recommended is unavailable, the group recommends PCC or activated PCC, although activated charcoal within 2 to 4 hours of accidental ingestion may be considered. Once the patient is stable and there is a continued indication for an oral anticoagulant, delaying restarting the oral anticoagulant is suggested in patients who had a bleed at a critical site, who are at high-risk of rebleeding or death or disability due to rebleeding, where the source of the bleed could not be identified, when surgical or invasive procedures are planned, or when the patient chooses not to restart the oral anticoagulant. If the aforementioned factors do not apply, ACC suggests restarting the anticoagulation. The group suggests discontinuing anticoagulation in patients with NVAF with a CHA_2DS_2-VASc score < 2 in males and < 3 in females, recovered acute stress cardiomyopathy, or bioprosthetic valve placement (without AF) > 3 months prior, as well as those who had a temporary indication for oral anticoagulation (e.g., post-surgical prophylaxis, anterior MI without left ventricular thrombus, post-left atrial appendage [LAA] closure device placement) or their first provoked VTE > 3 months prior. Additional information on specific dosing for reversal and management agents, transfusion recommendations, laboratory recommendations, timing of reinitiation, bleed location, and pharmacokinetic parameter considerations are detailed in the pathway.

PHARMACOLOGY[59,60,61,62,63,64,65,66,67]

Unfractionated heparin and LMWH (dalteparin [Fragmin], enoxaparin [Lovenox]) are classified as indirect thrombin inhibitors because these agents exert anticoagulant action, in part, by binding to and potentiating the activity of antithrombin III (ATIII), a naturally occurring thrombin inhibitor. UFH exerts its anticoagulant effect by enhancing the capacity of ATIII to inactivate thrombin. LMWH also produces anticoagulant action through ATIII; however, LMWH primarily inhibits clotting factor Xa rather than thrombin. Therefore, LMWH has less effects on partial thromboplastin time (PTT), virtually eliminating the need for laboratory monitoring. LMWH exhibits more consistent bioavailability, resulting in less interpatient dose-response variation and permitting standardized dosing. Another advantage of LMWH is the ease of subcutaneous (SC) route of administration. In addition, the incidence of thrombocytopenia appears to be lower with LMWH than with UFH.[68]

Fondaparinux (Arixtra) is a selective factor Xa inhibitor which binds to antithrombin III (ATIII). By inhibiting factor Xa, thrombin generation and thrombus formation are inhibited without direct effects on thrombin. Also, fondaparinux does not bind significantly to platelet factor 4, a factor involved in immune-related HIT.

Dabigatran etexilate (Pradaxa) is an oral prodrug of dabigatran. Dabigatran and its active metabolites (acyl glucuronides) are competitive, direct thrombin inhibitors of both free and clot-bound thrombin. Dabigatran reversibly inhibits the active site of thrombin and prevents thrombin-induced platelet aggregation and the development of a thrombus by preventing the thrombin-mediated conversion of fibrinogen to fibrin during the coagulation cascade.[69] INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring. The activated partial thromboplastin time (aPTT) test provides an approximation of dabigatran's anticoagulant effect.

Apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto) are oral direct factor Xa inhibitors. These agents reversibly block the active site of factor Xa in a selective manner and do not require a cofactor, such as ATIII, for activity.[70] The anticoagulant effect of apixaban, edoxaban, and rivaroxaban cannot be monitored with standard laboratory testing (e.g., INR, aPPT).

Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S. Warfarin interferes with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase complex 1 (VKORC1) enzyme complex, which reduces the regeneration of vitamin K1 epoxide. The degree of depression is dependent on the warfarin dose, and, to some extent, by the patient's VKORC1 genotype. The anticoagulant effects of warfarin are stereoselective; the S-isomer of warfarin is 3 to 5 times more potent than the R-isomer, but generally has a more rapid clearance. Therapeutic doses of warfarin decrease the total amount of active vitamin K dependent clotting factors made by the liver by 30% to 50%. An anticoagulation effect generally occurs within 24 hours after administering warfarin. However, peak anticoagulant effects may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. Warfarin does not directly affect established thrombus and does not reverse ischemic tissue damage. It prevents further extension of the formed clot and prevents secondary thromboembolic complications.

PHARMACOKINETICS[71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86]

Drug	Bioavailability (%)	Half-life (hr)	Average Molecular Weight (daltons)	Anti-Xa: Anti-IIa Activity	Peak Anti-Xa Activity (hrs)
Injectable					
dalteparin (Fragmin)	87	3-5*	5,000	2-4: 1	4
enoxaparin (Lovenox)	~ 100	4.5-7	4,500	2.7-3.7: 1	3-5
fondaparinux (Arixtra)	100	17-21	1,728	Anti-Xa only	3

Data presented for pharmacokinetics are for SC administration of all products. Delayed elimination of all the products may occur with severe liver or kidney insufficiency. hr = hours

* In pediatric patients, the mean elimination half-life of dalteparin increased with age and ranged from 2.25 hours (3 weeks to < 8 weeks of age) to 6.28 hours (≥ 12 years to < 20 years of age).

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Metabolism	Excretion (%)
Oral				
apixaban (Eliquis)	50	12	CYP 3A4 major CYP1A2, CYP2C8, CYP2C9, CYP2C19 minor O-demethylation and hydroxylation	Urine: 27 Feces: 50
dabigatran (Pradaxa)	3-7	12-17	Esterase-catalyzed hydrolysis	Urine
edoxaban (Savaysa)	62	10-14	Hydrolysis, conjugation, and oxidation by CYP3A4	Urine: 50
rivaroxaban (Xarelto)	80-100 (10 mg) 66 (20 mg)*	5-13†	Oxidative degeneration catalyzed by CYP3A4/5 & CYP2J2	Urine: 36 Feces: 7
warfarin	100; with peak concentration generally reached within first 4 hours	20-60 (mean 40)	Hepatic-primarily via CYP2C9	Urine: 92, primarily as metabolites

* The absolute bioavailability of rivaroxaban is dose-dependent. The estimated bioavailability for 10 mg dose is 80% to 100%, and it is not affected by food. The absolute bioavailability for the 20 mg dose is approximately 66% in a fasting state and increases when administered with food. Both the 15 mg and 20 mg doses should be administered with food.

† For pediatric patients treated for VTE, the half-life decreased with decreasing age, with mean half-life values of 4.2 hours for adolescents, 3 hours for children 2 to 12 years old, 1.9 hours in children 0.5 to < 2 years old, and 1.6 hours in children < 0.5 years old.

CONTRAINDICATIONS/WARNINGS[87,88,89,90,91,92,93,94,95]

Parenteral

All injectable agents in the class carry a boxed warning regarding the risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is performed in patients who are anticoagulated or scheduled to be anticoagulated with LMWHs, heparinoids, or fondaparinux (Arixtra) for prevention of thromboembolic complications. Epidural or spinal hematomas can result in long-term or permanent paralysis. Patients at highest risk are those with indwelling epidural catheters for administration of analgesia and patients concurrently on nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants. Increased risk is also seen in traumatic or repeated epidural, spinal puncture, spinal deformity, or spinal surgery. Frequent monitoring for signs and symptoms of neurologic impairment should be performed. The benefit and risks of LMWH or fondaparinux therapy should be considered before neuraxial intervention.

Fondaparinux and LMWH are contraindicated in patients with active major bleeding. Fondaparinux is contraindicated in patients with a positive *in vitro* anti-platelet antibody associated thrombocytopenia. Dalteparin is contraindicated in patients with a history of heparin-induced thrombocytopenia (HIT) or history of HIT with thrombosis. Enoxaparin is contraindicated in patients with a history of HIT within the past 100 days or in the presence of circulating antibodies. In clinical trials of patients with acute symptomatic VTE, platelet count < 100,000/mm^3 occurred in 12.6% of adults with cancer and 37% of pediatric patients with or without cancer. Thrombocytopenia of any degree should be monitored closely for all parenteral anticoagulants. If the platelet count falls below 100,000 cells/mm^3, discontinuation or interruption of therapy should be considered. LMWH should be used with extreme caution in patients with HIT.

LMWHs are contraindicated in patients with hypersensitivity to any LMWH, UFH, or pork products. In addition, hypersensitivity to benzyl alcohol is considered a contraindication for the multi-dose formulation of enoxaparin and dalteparin as both contain benzyl alcohol as a preservative. LMWHs cannot be used interchangeably (unit for unit) with heparin or other LMWHs as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

Dalteparin (Fragmin) is contraindicated in unstable angina, non-Q-wave MI, or acute VTE in patients undergoing regional anesthesia. In addition, dalteparin is contraindicated for prolonged VTE prophylaxis. Placement or removal of an epidural catheter is best performed when dalteparin's anticoagulant effects are low. Placement or removal of a catheter should be delayed for ≥ 12 hours after administration of 2,500 IU once daily, ≥ 15 hours after the administration of 5,000 IU daily, and ≥ 24 hours after administration of higher doses. A specific recommendation for timing of a subsequent dalteparin dose cannot be made. Prescribers should consider delaying the next dose for ≥ 4 hours based on a risk to benefit. Additionally, patients with a severe renal impairment (CrCl < 30 mL/min) may have prolonged elimination of dalteparin; consider doubling the timing of catheter removal, at least 24 hours for lowers doses (2,500 or 5,000 IU) and at least 48 hours for higher doses (200 IU/kg daily; 120 IU/kg twice daily). Dalteparin should be used with caution in patients with an increased risk of hemorrhage; bleeding can occur at any site during dalteparin therapy. In addition, dalteparin prefilled syringes may contain natural rubber latex in the needle shield that may cause allergic reactions in those allergic to latex.

Enoxaparin (Lovenox) labeling includes recommendations for epidural catheter placement or removal if the procedure is required. The placement or removal of a catheter should be delayed for at least 12 hours after administration of low doses (30 mg once or twice daily or 40 mg once daily) of enoxaparin and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of enoxaparin. These delays are not a guarantee that neuraxial hematoma will be avoided. Patients receiving the 0.75 mg/kg or 1 mg/kg twice daily dose should not receive the second dose in the twice daily regimen to allow a longer delay before catheter placement or removal. Consideration should be given to delaying the next dose for at least 4 hours based on individual risk factors. For patients with CrCl < 30 mL/min, elimination of enoxaparin is more prolonged; therefore, consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).

For enoxaparin use associated with PCI, hemostasis at the puncture site should be obtained before sheath removal following percutaneous coronary revascularization.

Enoxaparin has not been adequately studied in pregnant women with mechanical prosthetic heart valves. "Gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including enoxaparin and dalteparin multidose vials. Preservative-free formulations should be used if parenteral anticoagulation is necessary during pregnancy, as well as for neonates and low-birth weight infants.

These agents are primarily eliminated by the kidneys and should be used with caution in patients with renal insufficiency due to increased risk of major bleeding. Fondaparinux (Arixtra) is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min) and may produce prolonged anticoagulation in patients with a CrCl 30 to 50 mL/min. In patients with body weight < 50 kg, fondaparinux is contraindicated when used for prophylaxis therapy with abdominal surgery, hip fracture surgery, or hip or knee replacement surgery and should be used with caution for treatment of PE and DVT due to increased risk of bleeding. Fondaparinux is also contraindicated in patients with bacterial endocarditis due to increased risk of bleeding. Fondaparinux is contraindicated in patients with a serious hypersensitivity reaction (e.g., angioedema, anaphylactoid/anaphylactic reactions) to fondaparinux and in cases of thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux. In addition, the prefilled syringe of fondaparinux contains dry natural latex rubber that may cause allergic reactions in those allergic to latex.

The risk of hemorrhage is increased when using fondaparinux in patients at risk for bleeding including patients who have the following conditions: congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, uncontrolled arterial hypertension, diabetic retinopathy, or shortly after brain, spinal, or ophthalmic surgery. Patients should not receive agents that increase the risk for hemorrhage with fondaparinux unless it is essential for their care; patients should be closely monitored for bleeding.

Oral

Apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), rivaroxaban (Xarelto), and warfarin are contraindicated in patients with hypersensitivity to any component of the product.

Apixaban, dabigatran, edoxaban, and rivaroxaban all carry a boxed warning regarding the increased risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is performed. Epidural or spinal hematomas can result in long-term or permanent paralysis. Patients at highest risk are those with indwelling epidural catheters for administration of analgesics and patients concurrently on non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants. Increased risk is also seen in those with a history of traumatic or repeated epidural or spinal puncture, spinal deformity, or spinal surgery. Frequent monitoring for signs and symptoms of neurologic impairment should be performed. The benefit and risk should be considered before neuraxial intervention in anticoagulated patients or patients to be anticoagulated for thromboprophylaxis. Epidural or intrathecal catheters should not be withdrawn earlier than 12 hours after the last edoxaban dose, 18 hours after the last rivaroxaban dose in patients 20 to 45 years of age and 26 hours in those 60 to 76 years of age (≥ 2 half-lives), or 24 hours after the last apixaban dose. The next dose of rivaroxaban should be held for at least 6 hours, the next dose of apixaban should be held for at least 5 hours, and the next dose of edoxaban should be held for at least 2 hours post catheter removal. Withhold rivaroxaban for 24 hours and apixaban for 48 hours following traumatic epidural or spinal puncture. Specific timing recommendations are not given for dabigatran. The pharmacokinetic profile of dabigatran should be considered; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Due to their rapid onset and offset of action, missing even 1 dose of the newer oral anticoagulant agents could result in a period without protection from thromboembolism. As a result, apixaban, dabigatran, edoxaban, and rivaroxaban carry boxed warnings stating that premature discontinuation of any of these agents can increase the risk of thromboembolism, and coverage with another anticoagulant may be needed. If therapy with any of these agents must be discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider administering another anticoagulant. Afterwards, restart the oral anticoagulant as soon as medically appropriate.

Apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin increase the risk of bleeding and can cause serious and, sometimes, fatal bleeding. Warfarin is contraindicated in patients with bleeding/hemorrhagic tendencies or blood dyscrasias. Apixaban, dabigatran, edoxaban, and rivaroxaban are contraindicated with active major or pathological bleeding. Rivaroxaban should not be used for primary VTE prophylaxis in hospitalized, acutely ill medical patients at high risk of bleeding (e.g., history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer, active gastroduodenal ulcer in the 3 months prior to treatment, history of bleeding in the 3 months prior to treatment, or dual antiplatelet therapy). Concurrent use of the oral agents with drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, selective serotonin reuptake inhibitors [SSRIs], and serotonin norepinephrine reuptake inhibitors [SNRIs], NSAIDs) can increase bleeding risk. Concomitant use of drugs that are known combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors increase rivaroxaban exposure thereby increasing the risk of bleeds. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Reversal of the anticoagulant effect of dabigatran by idarucizumab (Praxbind) may be used for emergency surgery, urgent procedures, and in life-threatening or uncontrolled bleeding in adults.[96] Coagulation factor Xa (recombinant), inactivated–zhzo (Andexxa) is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.[97] The use of procoagulant reversal agents (e.g., PCC, activated prothrombin complex concentrate, recombinant factor VIIa) may be considered for apixaban but has not been evaluated in clinical trials; monitoring with the use of clotting tests or anti-factor Xa (e.g., prothrombin time [PT], INR, aPTT and FXa, respectively) is not recommended. Activated charcoal reduces the absorption of apixaban and lowers the plasma concentrations of the drug. There is no established method to reverse bleeding in patients taking edoxaban.

Regarding the reversal effects of idarucizumab (Praxbind), in the RE-VERSE AD study (n=503) the primary endpoint of reversal of the anticoagulant effect within 4 hours, as measured by diluted thrombin time (dTT) and ecarin clotting time (ECT), was observed in 100% of patients treated with idarucizumab.[98] Onset of complete reversal was immediate and was maintained for 24 hours in most patients. Apixaban and edoxaban effects can be expected to persist for approximately 24 hours after the last dose. Use of procoagulant reversal agents, such as prothrombin complex concentrate, activated prothrombin complex concentrate, recombinant factor VIIa, or concentrates of coagulation factors II, IX, or X, may be considered but has not been evaluated in clinical studies. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban, dabigatran, or rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of PCCs in healthy volunteers given rivaroxaban. Activated charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration.

Bleeding is more likely to occur during warfarin initiation and dose escalation (resulting in a higher INR). Risk factors for bleeding include high intensity anticoagulation (INR > 4), age ≥ 65 years, highly variable INRs, history of gastrointestinal (GI) bleeding, hypertension, cerebrovascular disease, anemia, malignancy, trauma, renal insufficiency, genetic factors, concomitant drugs, and long duration of warfarin therapy.

Warfarin is contraindicated in pregnancy, except in women with mechanical heart valves (where benefit may outweigh risk), as it can cause congenital malformations, fetal hemorrhage, and spontaneous abortion. It is contraindicated in situations of threatened abortion, eclampsia, and preeclampsia. The effects of apixaban, dabigatran, edoxaban, or rivaroxaban during labor and delivery are unknown; however, these agents should be used with caution in pregnancy due to potential obstetric hemorrhage and/or emergent delivery. The risk for significant uterine bleeding in females of reproductive potential or those with abnormal uterine bleeding, possibly requiring surgical intervention, should be evaluated with oral anticoagulants.

Warfarin is also contraindicated in patients with bleeding tendencies associated with central nervous system (CNS) hemorrhages, cerebral aneurysms, dissecting aorta, bacterial endocarditis, pericarditis and pericardial effusions, and active ulceration or overt bleeding of the GI, genitourinary, or respiratory tract. Other warfarin contraindications include recent or contemplated surgery of the CNS or eye, traumatic surgery resulting in large open surfaces, unsupervised patients with potential high levels of non-compliance, spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding, major regional or lumbar block anesthesia, and malignant hypertension.

Although lapses in dabigatran therapy should be minimized, treatment should be stopped 1 to 2 days before elective surgery in patients with CrCl ≥ 50 mL/min or 3 to 5 days prior in patients with CrCl < 50 mL/min, to lessen bleeding risk. Longer lapses of dabigatran therapy may be necessary for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port. Edoxaban should be discontinued at least 24 hours before invasive or surgical procedures because of the risk of bleeding. Edoxaban can be restarted after the procedure as soon as adequate hemostasis has been established.

Based on results from the GALILEO study, rivaroxaban is not recommended in patients with a transcatheter aortic valve replacement (TAVR) due to higher rates of death and bleeding compared to patients receiving an anti-platelet regimen.[99]

The European RE-ALIGN study was stopped because patients on dabigatran were more likely to experience strokes, MI, TIA, and thromboembolism forming on the mechanical heart valves than those on warfarin. There was also more bleeding after valve surgery in the dabigatran users than in patients on warfarin. Therefore, the use of dabigatran in patients with mechanical prosthetic values is contraindicated.

Use of apixaban or rivaroxaban is not recommended in patients with prosthetic heart valves since safety and efficacy have not been studied in this population. The safety and efficacy of edoxaban have not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis and the use of edoxaban in these patients is not recommended.

With regard to warfarin therapy in patients with prosthetic heart valves, INR target is dependent on the type and positioning of the specific valve.

Direct-acting oral anticoagulants including apixaban, dabigatran, edoxaban, and rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS) as the efficacy and safety in patients with APS has not been established. Additionally, in patients that are triple positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies, treatment with DOACs could lead to higher rates of recurrent thrombotic events compared with VKA therapy.

Thrombocytopenia with dabigatran has been identified as an adverse drug reaction during the post-marketing period.

Initiation of apixaban or rivaroxaban is not recommended acutely as an alternative to UFH in patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

P-gp inhibition and renal insufficiency are major independent factors resulting in increased exposure to dabigatran and risk of bleeding. Renal function should be evaluated before initiating dabigatran and periodically throughout therapy. Discontinue dabigatran in patients who develop acute renal failure and consider alternate anticoagulation. Concomitant use of P-gp inhibitors (e.g., rifampin) reduces exposure to dabigatran and should be avoided. Use of P-gp inhibitors in patients with renal impairment is expected to increase exposure to dabigatran above that observed with either factor alone. Dosage adjustments should be considered. Dabigatran should be avoided in pediatric patients with an estimated glomerular filtration rate (eGFR) of < 50 mL/min/1.73m^2. Concomitant use of dabigatran with P-gp-inhibitors has not been studied in pediatric patients but may increase dabigatran exposure.

Concomitant use of other drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan) increases rivaroxaban exposure and may increase bleeding risk. Avoid concomitant use of rivaroxaban with known combined P-gp and strong CYP3A4 inhibitors or drugs that are known combined P-gp and strong CYP3A4 inducers.

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding. Use of concomitant drugs affecting hemostasis, such as aspirin and other antiplatelet drugs, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and NSAIDs, increase the risk of bleeding.

Regular INR monitoring should be performed on all patients on warfarin. Many factors, alone or in combination, including changes in diet, medications, herbal medications, and genetic variations in the CYP2C9 enzymes involved in metabolic clearance of warfarin and VKORC1 enzymes (which recycles vitamin K and is required for gamma carboxylation of vitamin K-dependent coagulation factors), may affect patient response to warfarin. Both endogenous and exogenous factors, alone or in combination, may be responsible for increased PT/INR response. Patients at high risk for bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be educated about methods of reducing the risk of bleeding, as well as immediately reporting signs and symptoms of bleeding to physicians.

Necrosis and/or gangrene of skin and other tissues have been reported (< 0.1%) with warfarin use. Necrosis has, in some cases, resulted in amputation of the affected areas.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms when using warfarin including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys, followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death. Acute kidney injury may occur with warfarin.

Warfarin should not be used as initial therapy in patients with HIT, with or without thrombosis syndrome. Cases of venous limb ischemia, necrosis, and gangrene have been reported in patients with HIT and heparin-induced thrombocytopenia with thrombosis syndrome (HITTS) when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients, sequelae have included amputation of the involved area and/or death. Treatment with warfarin may be considered after the platelet count has normalized.

Warfarin has no direct effect on established thrombus and it does not reverse ischemic tissue damage.

Treatment of each patient with warfarin is a highly individualized matter.

DRUG INTERACTIONS[100,101,102,103,104,105,106,107,108]

Due to the increased risk of bleeding, injectable anticoagulants should be used with caution with oral anticoagulants or platelet inhibitors, including aspirin, salicylates, NSAIDs, dipyridamole, dextran, ticlopidine, clopidogrel (Plavix®), and thrombolytics.

The concomitant use of dabigatran (Pradaxa) with P-gp inducers, such as rifampin, reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone. Exposure to dabigatran is higher when it is administered with dronedarone (Multaq®) or systemic ketoconazole than when it is administered alone. When using dabigatran to reduce the risk of stroke in patients with NVAF, consider reducing the dose of dabigatran to 75 mg twice daily when dronedarone or systemic ketoconazole is co-administered with dabigatran in patients with moderate renal impairment (CrCl 30 to 50 mL/min). The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of dabigatran. These results should not be extrapolated to other P-gp inhibitors. The concomitant use of dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl 15 to 30 mL/min) should be avoided in patients with NVAF. When used for the treatment and reduction in the risk of recurrence of DVT or PE, the concomitant use of dabigatran and P-gp inhibitors should be avoided in patients with CrCl < 50 mL/min. In patients with CrCl ≥ 50 mL/min who are also taking P-gp inhibitors, it may be helpful to separate the timing of dabigatran and the P-gp inhibitor by several hours when indicated for prophylaxis of DVT and PE following hip replacement surgery. Use of dabigatran and P-gp inhibitors in patients with a CrCl < 50 mL/min should be avoided.

Apixaban (Eliquis) is a substrate of both CYP3A4 and P-gp enzymes. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. For patients taking apixaban 5 mg or 10 mg twice daily, the dosage should be decreased by 50% when used with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir). While clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is needed with concomitant administration with apixaban. If a patient is already taking a dose of 2.5 mg daily, avoid concomitant use with combined P-gp and strong CYP3A4 inhibitors. Concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) can decrease the exposure of apixaban and should be avoided. Co-administration of apixaban and antiplatelet agents (e.g., fibrinolytics, heparin, aspirin, and chronic NSAIDs) increases the risk of bleeding.

Edoxaban (Savaysa) is a substrate of the P-gp transporter. The concomitant use of edoxaban with rifampin (a P-gp inducer) should be avoided. There are no dose alterations recommended in patients with NVAF receiving concomitant P-gp inhibitors (e.g., ketoconazole, verapamil, erythromycin, cyclosporine, amiodarone). However, based on the Hokusai VTE study, patients receiving edoxaban for the treatment of DVT and/or PE should have their dose reduced to edoxaban 30 mg once daily if they are receiving specific concomitant P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole).[109] The concurrent use of edoxaban with other drugs that affect hemostasis, such as aspirin, antiplatelet agents, other anticoagulants, and antithrombotic/fibrinolytic agents, or chronic use of NSAIDs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors, may increase the risk of bleeding. Patients requiring low dose aspirin or NSAIDs on a long-term basis should be carefully monitored.

Rivaroxaban (Xarelto) is a substrate of CYP3A4, CYP3A5, CYP2J2, and P-gp and ATP-binding cassette G2 (ABCG2) transporters. Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) as they increase rivaroxaban concentrations. Rivaroxaban should not be used in patients with CrCl 15 to < 80 mL/min who are also taking combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the benefits outweigh the risks. Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Avoid use with other drugs that affect hemostasis, such as anticoagulants, fibrinolytics, NSAIDS/aspirin, antiplatelet drugs, selective serotonin uptake inhibitors, and serotonin norepinephrine reuptake inhibitors unless the benefit outweighs the bleeding risk.

Drug-drug interactions with warfarin can occur through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions include synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin are primarily enzyme induction, enzyme inhibition, and reduced plasma protein binding. Some drugs may interact by more than 1 mechanism.

Caution is recommended when warfarin is administered concomitantly with NSAIDs, anticoagulants, antiplatelets, serotonin reuptake inhibitors, antibiotics, antifungals, and herbal products (e.g., St. John's wort, co-enzyme Q10, ginseng, garlic, ginkgo biloba).

Warfarin is stereoselectively metabolized by hepatic cytochrome P450 (CYP) isoenzymes to inactive, hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols which have minimal anticoagulant activity). The CYP isoenzymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. CYP2C9 is the major enzyme that metabolizes S-warfarin and modulates the *in vivo* activity of warfarin. CYP1A2 and 3A4 metabolize the R-isomer. Inhibitors of CYP1A2, 2C9, and 3A4 may increase the exposure of warfarin and, hence, increase its effect. Inducers of these enzymes may in turn decrease warfarin's effect.

CYP2C9 gene and VKORC1 gene variants generally explain the largest proportion of known variability in warfarin dose requirements. Genetic polymorphism of CYP2C9 may play a role in the interpatient variability of response to warfarin, as well as predisposition to drug interactions. The variant alleles, CYP2C9*2 and CYP2C9*3, result in decreased hydroxylation of S-warfarin and decrease its clearance; the presence of more than 1 of the CYP2C9 variant alleles further decreases clearance. In Caucasians, the frequency of the CYP2C9*2 variant is 8% to 20%, while the frequency of the CYP2C9*3 variant is 6% to 10%. The presence of CYP2C9*2 and *3 variant alleles in Blacks and Asians is much lower (0% to 4%); other CYP2C9 alleles that may decrease warfarin metabolism occur at lower frequencies in all races. Poor CYP2C9 metabolizers are more dependent on the metabolism of S-warfarin by the CYP3A4 pathway. Drugs that affect any of the enzymes involved in the metabolism of warfarin may alter the anticoagulation response. As a result, drugs that preferentially induce S-warfarin metabolism impair coagulation to a greater degree than those that induce the metabolism of R-warfarin.

In addition, variants in the gene encoding VKORC1 may be responsible for approximately 25% to 30% of warfarin dose variances.[110,111] There are 2 main VKORC1 haplotypes: low-dose haplotype group (A) and a high-dose haplotype group (B). African Americans can have a higher proportion of group B haplotypes and are, on average, relatively resistant to warfarin, while Asian Americans may have a higher proportion of group A haplotypes and are generally more sensitive to warfarin.

Exogenous administration of vitamin K, such as enteral feedings, certain multivitamins, and many foods, can decrease or reverse the activity of warfarin. Patient response to warfarin usually returns after stopping the vitamin K-containing agent. Foods that contain large to moderate amounts of vitamin K include green tea, brussels sprouts, leafy greens, asparagus, avocado, broccoli, cabbage, cauliflower, liver, soy products, lentils, peas, and green scallions. Medical products that contain soybean oil, such as intravenous lipid emulsions or propofol, can decrease warfarin anticoagulation. Patients should avoid large amounts/frequent servings of vitamin K-containing foods or maintain a constant vitamin K diet. Some botanicals may have anticoagulant, antiplatelet, and/or fibrinolytic properties (e.g., garlic and ginkgo biloba). These effects may be additive to the anticoagulant effects of warfarin. Conversely, some botanicals may decrease the effects of warfarin (e.g., co-enzyme Q10, St. John’s wort, and ginseng). Some botanicals and foods can interact with warfarin through CYP450 interactions (e.g., echinacea, grapefruit juice, ginkgo, goldenseal, St. John’s wort). In patients treated with warfarin, additional PT/INR determinations are recommended whenever other medications, including botanicals, are initiated, discontinued, or taken irregularly.

ADVERSE EFFECTS[112,113,114,115,116,117,118,119,120]

Parenteral

Drug	Major Bleeding	Thrombocytopenia	Injection Site Reactions
dalteparin (Fragmin)	0-5.6	< 1	4.5-12
enoxaparin (Lovenox)	< 1-4	0.1-1.3	reported
fondaparinux (Arixtra)	1.2-4.8	0.04-3	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts, are not comparative, or all inclusive. All adverse effects are reported for prophylaxis.

Direct comparison of bleeding risks among the injectable anticoagulants is difficult due to different definitions of bleeding in various clinical studies.

Dalteparin and fondaparinux can cause aspartate (AST) and alanine (ALT) aminotransferase elevations. In pediatric patients with symptomatic VTE, the most frequently occurring adverse reactions were injection site bruising (30%), contusion (12%), and epistaxis (10%).

Oral

Most common adverse effects with dabigatran (Pradaxa) in clinical trials were gastritis-like symptoms (> 15%) and bleeding. Gastrointestinal (GI) complaints leading to discontinuation included dyspepsia, nausea, upper abdominal pain, GI hemorrhage, and diarrhea; specific percentages were not reported. Serious bleeding, including intracranial hemorrhage, life threatening bleeding, and major bleeds, were reported in dabigatran and warfarin treatment groups. In trials, the rate for major bleeds was lower in dabigatran-treated patients (0.9% to 3.5%) compared to warfarin-treated patients (1.8% to 3.6%); the percentage of any bleed for dabigatran and warfarin was 16.1% and 19.4% versus 22.7% and 26.2%, respectively. There was a higher rate of major GI bleeds in patients receiving dabigatran 150 mg (1.6%) than in patients receiving warfarin (1%) (hazard ratio [HR] versus warfarin, 1.5; 95% confidence interval [CI], 1.2 to 1.9), and a higher rate of any GI bleeds (6.6% versus 4.2%, respectively). In 2012, after review of new information, the FDA concluded that bleeding rates associated with new use of dabigatran do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the RELY trial.[121] As a follow-up to the ongoing safety review of this issue, the FDA completed a study which looked at data from 134,000 Medicare patients. Compared to warfarin, dabigatran had reduced risk of ischemic stroke, intracranial hemorrhage, and death. Dabigatran was found to have an increased risk of GI bleeding compared to warfarin. No difference was found in the risk of myocardial infarction. These data were consistent with the pivotal RELY trial except RELY had an increased risk of MI. The FDA concluded that the benefits of therapy outweigh the risk and required no changes to dabigatran's labeling.[122] In pediatric patients treated for VTE in the DIVERSITY trial, notable adverse events (reported in comparison to standard of care, respectively) were major bleeding (2.3% versus 2.2%), any bleeding (22% versus 24%), any gastrointestinal bleeds (5.7% versus 1.8%), dyspepsia (9% versus 2%), upper abdominal pain in (5% versus 1%), vomiting in (8% versus 2%), nausea (5% versus 4%), and diarrhea (5% versus 1%). The adverse reaction profile in patients treated with dabigatran for the reduction in risk of recurrent VTE was generally consistent with the profile seen in adults.

The most serious adverse events reported with apixaban (Eliquis) in clinical trials were bleeding related. The safety of apixaban 5 mg (n=11,284) and 2.5 mg (n=602) twice daily was evaluated in the ARISTOTLE and AVERROES studies. Mean duration of apixaban was 89 weeks for the ARISTOTLE and 59 weeks for AVERROES. Major bleeding was reported in 2.1% of patients on apixaban and 3.1% on warfarin (HR, 0.69; 95% CI, 0.6 to 0.8; p<0.0001). Clinically relevant non-major bleeding occurred in 2.1% and 3% of patients on apixaban and warfarin (HR, 0.7; 95% CI, 0.6 to 0.8; p<0.0001). Major bleeding was reported in 1.4% of patients on apixaban versus 0.9% of patients on aspirin (HR, 1.54; 95% CI, 0.96 to 2.45; p=0.07). Discontinuation due to bleeding-related adverse reactions in ARISTOTLE occurred in 1.7% and 2.5% of patients treated with apixaban and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% of patients on apixaban and aspirin, respectively. In the ARISTOTLE study, major bleeding did not differ based on age and weight. Other adverse events reported for apixaban were hypersensitivity reactions and syncope in < 1% of patients. The ARISTOTLE trial also examined the incidence, location, and management of non-major bleeding in patients with AF receiving apixaban (n=18,140). Non-major bleeding was 3 times more common than major bleeding (21.1% versus 3.8%). Non-major bleeding was more frequent with warfarin (9.4 per 100 patient years) than apixaban (6.4 per 100 patient years)(adjusted HR, 0.69; 95% CI, 0.63 to 0.75).

The most common adverse reactions to edoxaban (Savaysa) are bleeding, anemia, rash, and abnormal liver function tests. In the NVAF trial, bleeding led to discontinuation of edoxaban in 3.9% of cases; this was lower than the 4.1% discontinuation rate due to bleeding with warfarin. The most common site of major bleeding with edoxaban was the GI tract. In patients with DVT and/or PE treated with edoxaban, the incidence of clinically relevant bleeding was lower with edoxaban compared to warfarin (HR, 0.81; 95% CI, 0.71 to 0.94; p=0.004]).

The most common adverse event with rivaroxaban (Xarelto) for DVT prophylaxis or treatment, as well as in NVAF, is bleeding. In DVT prophylaxis clinical trials, the risk of bleeding was similar to that of enoxaparin (Lovenox) 40 mg once daily. Major bleeding was seen in < 1% of patients (for both hip and knee replacement surgery) and any bleeding was seen in 5.8% and 5.6% of patients treated with rivaroxaban and enoxaparin, respectively. During rivaroxaban treatment, the majority of major bleeding complications (≥ 60%) occurred during the first week after surgery. The rate of discontinuation due to bleeding events in the treatment of DVT and PE was 1.7% with rivaroxaban and 1.5% with enoxaparin/vitamin K antagonist regimen. Major bleeding occurred in 1% and 1.7% of rivaroxaban and enoxaparin/vitamin K antagonist treated patients, respectively. In the NVAF setting, major bleeding, bleeding into a critical organ (mostly intracranial), fatal bleeding, and GI bleeding was seen in 3.6% versus 3.5%, 0.5% versus 0.7%, 0.2% versus 0.5%, and 2% versus 1.2% of rivaroxaban versus warfarin patients, respectively. The most frequent adverse reactions associated with permanent drug discontinuation were bleeding events: 4.3% for rivaroxaban and 3.1% for warfarin. In the study evaluating acutely ill medical patients at risk for thromboembolism, bleeding resulting in drug discontinuation was 2.5% with rivaroxaban compared to 1.4% with enoxaparin/placebo. In pediatric patients when rivaroxaban was used for the treatment of VTE and reduction in risk of recurrent VTE in the EINSTEIN Junior study, notable adverse events (reported in comparison to standard of care, respectively) were major bleeding (0 versus 1.2%), clinically relevant non-major bleeding (3% versus 0.6%), trivial bleeding (34.3% versus 27.2%), any bleeding (36.2% versus 27.8%), pain in extremity (7% versus 4.3%), fatigue (7% versus 4.3%), and vomiting (10.6% versus 8%). In pediatric patients with congenital heart disease (CHD) who received rivaroxaban as thromboprophylaxis after the Fontan procedure (UNIVERSE study), notable adverse reactions (reported in comparison to aspirin at approximately 5 mg/kg, respectively) were major bleeding (1.6% versus 0), clinically relevant non-major bleeding (6.3% versus 8.8%), trivial bleeding (32.8% versus 35.3%), any bleeding (35.9% versus 41.2%), cough (15.6% versus 8.8%), vomiting (14.1% versus 8.8%), gastroenteritis (12.5% versus 2.9%), and rash (9.4% versus 5.9%).

A 5-year post-marketing observational surveillance study utilized electronic medical records from a US Department of Defense database to evaluate the safety of rivaroxaban in 27,467 patients with NVAF.[123] Major bleeding was reported as 2.86 per 100 person-years. The rate of death due to bleeding was 0.08 per 100 person-years. The most common site of bleeding was gastrointestinal (88.8%) followed by intracranial (7.5%). Major bleeding was reported more frequently in patients who were older, had hypertension, coronary heart disease, heart failure, renal disease, or greater $CHADS_2$ and CHA_2DS_2-VASc scores.

Adverse events with warfarin include fatal or nonfatal hemorrhage, including major bleeding from any tissue or organ. The incidence of major bleeding in the atrial fibrillation trials ranged from 0.6% to 2.7%. Hemorrhagic complications may present as paralysis; paresthesia; headache; chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficulty breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Bleeding can occur when the PT/INR is within the therapeutic range. Necrosis of skin and other tissues has been reported (< 0.1%).

There are no specific reversal agents for edoxaban. Fresh frozen plasma and red blood cells can be used for management of bleeding. Activated prothrombin complex concentrates, recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X may be considered. The use of these agents has not been studied in clinical trials. Activated charcoal to reduce absorption in case of apixaban or rivaroxaban overdose may be considered. Apixaban and rivaroxaban is not expected to be dialyzable, due to high plasma protein binding. Phytonadione (vitamin K1) is the antidote for warfarin. Protamine is used as an antidote for LMWH and UFH. Idarucizumab (Praxbind) may be used to reverse the anticoagulant effects of dabigatran in adults.[124] Dabigatran can be dialyzed; however, data supporting this approach are limited.

A meta-analysis of 11 studies (5 in AF; 6 in VTE; overall n=100,324) evaluated the risk of fatal hemorrhage with the oral anticoagulants, rivaroxaban, dabigatran, apixaban, and edoxaban, compared to VKAs or LMWHs followed by a VKA.[125] Overall, patients treated with newer oral anticoagulants had a lower risk of fatal bleeding compared to VKAs (odds ratio [OR], 0.53; 95% CI, 0.42 to 0.68) and a LMWH followed by a VKA (OR, 0.36; 95% CI, 0.15 to 0.8).

SPECIAL POPULATIONS[126,127,128,129,130,131,132,133,134]

Pediatrics

Safety and effectiveness of dalteparin for the treatment of symptomatic VTE have been established in pediatric patients aged ≥ 1 month based on evidence from well-controlled studies in adults with additional pharmacokinetic, pharmacodynamic, efficacy, and safety data from 2 separate studies in pediatric patients aged ≥ 1 month. The long-term effects of dalteparin in this population, including its effects on growth and bone metabolism, have not been established.

Multiple-dose vials of dalteparin (Fragmin) contain benzyl alcohol as a preservative, which can cause gasping syndrome in neonates and low-birth weight infants. Preservative free formulations should be used in this population.

Safety and effectiveness of LMWH and fondaparinux (Arixtra) in pediatric patients have not been established. Since risk for bleeding during treatment with fondaparinux is increased in adults who weigh < 50 kg, bleeding may be a particular safety concern for use of fondaparinux in the pediatric population.

Despite their unproven efficacy, LMWHs have rapidly become the anticoagulant of choice in many pediatric patients, both for primary prophylaxis and treatment of thromboembolism.[135] Potential advantages of LMWH in children include predictable pharmacokinetics requiring minimal monitoring, which is critically important in pediatric patients with poor or nonexistent venous access; SC administration; lack of drug or food interactions, such as those that exist for VKA; reduced risk of HIT; and probable reduced risk of osteoporosis with long-term use, which occurs with UFH. The guidelines point out that, although they use the term LMWH and present dosing schedules for several different LMWHs, the majority of all clinical data with respect to LMWH use in children is from studies that used enoxaparin.[136]

The safety and effectiveness of dabigatran (Pradaxa) oral capsules have been established to reduce the risk of recurrence of VTE in pediatric patients 8 to < 18 years of age who have been previously treated as well as for the treatment of VTE in patients 8 to < 18 years of age who have been treated with a parenteral anticoagulant for ≥ 5 days. The safety and effectiveness of dabigatran (Pradaxa) oral pellets have been established to reduce the risk of recurrence of VTE in pediatric patients 3 months to < 12 years of age who have been previously treated as well as for the treatment of VTE in patients 3 months to < 12 years of age who have been treated with a parenteral anticoagulant for ≥ 5 days.

The safety and effectiveness of rivaroxaban (Xarelto) have been established in pediatric patients from birth to < 18 years for the treatment of VTE and the reduction in risk of recurrent VTE; however, rivaroxaban was not studied, and dosing has not been determined for use in children < 6 months who were < 37 weeks of gestation at birth; had < 10 days of oral feeding, or with a body weight < 2.6 kg. The safety and effectiveness of rivaroxaban have also been established in pediatric patients ≥ 2 years old with congenital heart disease who have undergone the Fontan procedure. The 2.5 mg tablets of rivaroxaban do not have any safety, efficacy, pharmacokinetic, or pharmacodynamic data for use in pediatric patients and are not recommended for use in these patients.

Safety and effectiveness of apixaban (Eliquis), edoxaban (Savaysa), and warfarin in pediatric patients have not been established. However, warfarin has been used in pediatric patients for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported and more frequent PT/INR monitoring is recommended due to potential varying warfarin requirements.

Pregnancy

Limited human data suggest that enoxaparin (Lovenox) does not increase the risk of major developmental abnormalities; however, it should only be used in pregnancy if "clearly needed".

Limited data have not reported a clear association with fondaparinux (Arixtra) and adverse developmental outcomes. In addition, the limited data suggest low placental transfer of fondaparinux.

Limited data have not reported a clear association with dalteparin (Fragmin) and adverse developmental outcomes; the risks and benefits to both the fetus and the mother (if untreated) should be considered. A substudy of the ongoing Thrombophilia in Pregnancy Prophylaxis study (TIPPS) determined long-term prophylactic dalteparin (Fragmin) in pregnancy did not result in a significant decrease in maternal bone mineral density (BMD).[137] Based on data from 62 patients, there was no difference in mean BMD between the patients receiving dalteparin or the control group.

In general, LMWH and UFH do not cross the placenta and do not have the potential to cause fetal bleeding and/or malformations.[138,139] Pregnant women receiving anticoagulants should be carefully monitored for evidence of bleeding or unexpected changes in coagulation parameters. Use of a shorter acting anticoagulant should be considered as delivery nears.

Multiple-dose vials of dalteparin (Fragmin) and enoxaparin (Lovenox) contain benzyl alcohol as a preservative, which may cross the placenta. Formulations that are free of preservatives should be used in pregnant women.

Limited data is available on use of apixaban (Eliquis) in pregnant women; therefore, the drug-associated risks for major birth defects, miscarriage, or adverse developmental outcomes have not been established. Labeling for edoxaban (Savaysa), rivaroxaban (Xarelto), and dabigatran (Pradaxa) state that available data in pregnant women are insufficient to determine whether there are drug-associated risks for adverse developmental outcomes.

Warfarin is contraindicated in women who are pregnant except in pregnant women with mechanical heart valves who are at risk of thromboembolism, in which the benefits of warfarin use outweigh its risks. Warfarin crosses the placenta and may cause fetal harm; exposure to warfarin in the first trimester of pregnancy caused congenital malformations in approximately 5% of exposed offspring. Adverse pregnancy outcomes have also been reported following warfarin exposure during the second and third trimesters. All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Hemorrhage can occur at any site and may lead to death of mother and/or fetus.

Renal Impairment

The risk of bleeding with LMWH increases with CrCl < 30 mL/min.[140] The dose and/or frequency of administration of enoxaparin (Lovenox) should be reduced to once daily in patients with severe renal insufficiency. In addition, if placement or removal of an epidural catheter is required, the procedure should be delayed at least 24 hours for the lower prescribed dose (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day) in patients with a CrCl < 30 mL/min.

Dalteparin (Fragmin) and fondaparinux (Arixtra) should be used with caution in patients with renal insufficiency. Fondaparinux is contraindicated in patients with severe renal insufficiency (CrCl < 30 mL/min).

The 2016 CHEST guidelines advise that oral anticoagulants and LMWH are contraindicated in patients with severe renal impairment and dosing of oral agents differ between agents and levels of renal dysfunction.[141]

The recommended dose of apixaban (Eliquis) is 2.5 mg twice daily in patients with at least 2 of the following for the reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: age ≥ 80 years old, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL. Clinical efficacy and safety studies with apixaban did not enroll patients with end-stage renal disease (ESRD) on dialysis when treating for reduction of risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In these patients who are on intermittent hemodialysis, apixaban administered at the usual recommended dose will result in drug levels and pharmacodynamic activity as those in the ARISTOTLE study; however, it is unknown whether it will result in similar stroke reduction and bleeding risk. When using apixaban for the prophylaxis of DVT following hip or knee replacement surgery, treatment of DVT or PE, or for the reduction in the risk of recurrence DVT and PE, no adjustment in dose is recommended for patients with renal impairment, including those with ESRD on dialysis. Studies did not enroll patients with ESRD on dialysis or patients with a CrCl < 15 mL/min; therefore, dosages are recommended based on pharmacokinetic and pharmacodynamic data.

Renal function should be evaluated prior to the start of therapy and should be re-assessed in clinical situations associated with declining function. If acute renal failure develops, discontinue dabigatran (Pradaxa). For NVAF, no dose adjustment of dabigatran is recommended in patients with a CrCl > 30 mL/min. Dabigatran dosage should be reduced in patients with CrCl 15 to 30 mL/min. No dosing recommendations are available per the product label for patients with CrCl < 15 mL/min or on dialysis; although hemodialysis can remove dabigatran, data supporting this approach are limited. P-gp inhibition and impaired renal function both result in increased exposure to dabigatran. In patients with a CrCl 30 to 50 mL/min, co-administration with P-gp inhibitors (dronedarone or ketoconazole) may increase exposure similar to that observed in patients with severe renal impairment; consider reducing the dabigatran dosage. Avoid co-administration of dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl 15 to 30 mL/min) using dabigatran for NVAF. For DVT treatment or risk reduction, as well as prophylaxis of DVT and PE following hip replacement surgery, no dosing recommendations are provided for patients with a CrCl < 30 mL/min. Additionally, the concomitant use of P-gp inhibitors in patients with CrCl < 50 mL/min should be avoided in patients using dabigatran for these indications. Due to the lack of data in this population, the use of dabigatran in pediatric patients with an eGFR < 50 mL/min/1.73 m^2 (calculated using the Schwartz formula) should be avoided; it may be used at standard dosing in patients with higher eGFRs.

In the treatment of patients with NVAF, creatinine clearance should be assessed prior to initiating edoxaban (Savaysa) therapy.

In studies, rivaroxaban (Xarelto) exposure increased by approximately 44% to 64% in adults with renal failure. Rivaroxaban is not recommended in adults with CrCl < 15 mL/min for DVT prophylaxis or treatment, reduction in the risk of recurrence of DVT and of PE, or prophylaxis of VTE in acutely ill medical patients. It should be used with caution in adults with CrCl 15 mL/min to < 30 mL/min due to limited clinical data; patients should be observed closely and signs and symptoms of blood loss should be promptly evaluated. Consider dose adjustment or discontinuation of rivaroxaban if acute renal failure develops. In NVAF, rivaroxaban is dosed based on creatinine clearance. Due to high plasma protein binding, rivaroxaban is not expected to be dialyzable. No dosage adjustment is needed in patients ≥ 1 year of age with mild renal impairment (eGFR 50 to ≤ 80 mL/min/1.73 m^2). Data are limited in pediatric patients ≥ 1 year old with moderate or severe renal impairment (eGFR < 50 mL/min/1.73 m^2); avoid use of rivaroxaban in these patients. Data are not available for pediatric patients < 1 year old with serum creatinine > 97.5th percentile; avoid use of rivaroxaban in these patients.

Patients with renal failure have an increased risk of bleeding complications; therefore, patients with moderate renal insufficiency who are taking warfarin should be monitored very closely. In patients with altered glomerular integrity or with a history of kidney disease, warfarin may cause acute kidney injury; therefore, frequent anticoagulation monitoring is advised.

In some patients with and without ESRD on warfarin, serious and often fatal calciphylaxis or calcium uremic arteriolopathy have been reported. Patients must seek treatment for calciphylaxis; discontinue therapy with warfarin immediately and consider switching to a different anticoagulant.

Hepatic Impairment

Patients with hepatic impairment may be particularly vulnerable to bleeding during fondaparinux (Arixtra) therapy. Although not evaluated, enoxaparin (Lovenox) should be used with caution in patients with hepatic impairment.

Use of apixaban is not recommended in patients with severe hepatic impairment (Child Pugh C).

Patients taking dabigatran with mild to moderate hepatic impairment (Child Pugh A and B) demonstrated greater variability in pharmacokinetic parameters; no dosage adjustment information is provided for dabigatran.

The use of edoxaban in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment (Child-Pugh A).

Avoid rivaroxaban in adults with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease with coagulopathy; data are not available regarding use in pediatric patients with hepatic insufficiency.

Anticoagulant response may be enhanced in obstructive jaundice, hepatitis, and cirrhosis. Monitor warfarin patients with moderate hepatic insufficiency more cautiously.

Geriatrics

In clinical trials, patients ≥ 65 years using fondaparinux had similar efficacy compared to patients < 65 years old. However, there was an increase in serious adverse events (e.g., major bleeds). Elderly patients also are more likely to have decreased renal function which places them at a higher risk for adverse reactions since fondaparinux is significantly excreted by the kidneys.

In the major dabigatran clinical trial (RELY), 82% of patients were older than 65 years of age, while 40% were 75 years or older. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups.

In both the NVAF trial as well as the DVT/PE treatment trials, the efficacy and safety of edoxaban in elderly (65 years or older) and younger patients were similar.

In rivaroxaban clinical trials, no overall differences in effectiveness or safety were reported between patients < 65 years and those > 65 years of age. However, the elderly subjects exhibited an increase in drug exposure that may be caused by age-related changes in renal function.

Patients aged 60 years or older have a greater than expected PT/INR response to warfarin. Therefore, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation, with increasing age.

Race

Asian patients may require lower initiation and maintenance doses of warfarin. Refer to the Drug Interactions section for further information. Healthy Japanese subjects were found to have 20% to 40% higher rivaroxaban exposures compared to other ethnicities, including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Pharmacogenomics

When available, the patient's CYP2C9 and VKORC1 genotype information may assist in selection of the starting warfarin dose. Trials comparing genotype-guided dosing versus standard dosing have produced conflicting results and the utility of genotype-guided dosing to result in better outcomes is lacking at this time.[142,143] In all patients, subsequent dosage adjustments must be made based on the results of INR determinations. Please see Dosage and Administration section for more information.

DOSAGES[144,145,146,147,148,149,150,151,152]

Parenteral

Drug	DVT prophylaxis					DVT Treatment (outpatient)*
	Hip Replacement**	Knee Replacement**	Hip Fracture Surgery**	Abdominal Surgery	Medical	
dalteparin (Fragmin)	5,000 units once daily for 5 to 10 days (up to 14 days given in clinical trials)	--	--	2,500 to 5,000 units once daily for 5 to 10 days	5,000 units once daily for 12 to 14 days	--
enoxaparin (Lovenox)	30 mg every 12 hours OR 40 mg once daily for 7 to 10 days (up to 14 days given in clinical trials)	30 mg every 12 hours for 7 to 10 days (up to 14 days given in clinical trials)	--	40 mg once daily for 7 to 10 days (up to 12 days given in clinical trials)	40 mg once daily for 6 to 11 days (up to 14 days given in clinical trials)	1 mg/kg every 12 hours
fondaparinux (Arixtra)	2.5 mg daily for 5 to 9 days (up to 11 days given in clinical trials)	2.5 mg daily for 5 to 9 days (up to 11 days given in clinical trials)	2.5 mg daily for 5 to 9 days and up to 24 days (a total of 32 days [peri-operative and extended prophylaxis] was administered in clinical trials)	2.5 mg daily for 5 to 9 days (up to 10 days given in clinical trials)	--	Based on patient's weight: 5 mg (< 50 kg); 7.5 mg (50-100 kg); 10 mg (> 100 kg) daily for 5 to 9 days (up to 26 days given in clinical trials)

All dosages are given subcutaneously; refer to drugs' package inserts for dosing tables and timing of administration.

* Given for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2 to 3).

** CHEST recommends at least 10 to 14 days and an extended thromboprophylaxis of up to 35 days after major orthopedic surgery in patients undergoing total hip replacement, hip fracture, or knee replacement surgery (Grade 2B).[153]u

dalteparin (Fragmin)

When extending treatment in patients with cancer and symptomatic venous thromboembolism, dalteparin therapy begins with the initial VTE treatment and continues for 6 months. For the first 30 days, dalteparin 200 IU/kg SC is administered once daily. Dosage should not exceed 18,000 IU. For months 2 through 6, dalteparin is given as 150 IU/kg once daily, not to exceed 18,000 IU daily. The daily dose of dalteparin should be reduced by 2,500 IU for patients who have reduced platelet counts (50,000/mm^3 to 100,000/mm^3) until the platelet count ≥ 100,000/mm^3. Patients with platelet counts < 50,000/mm^3 should not receive dalteparin until platelet count is > 50,000/mm^3. In patients with severe renal impairment (CrCl < 30 mL/min), anti-Xa levels should be monitored to determine the appropriate dose of dalteparin.

The recommended dose of dalteparin is 120 IU/kg of body weight (not to exceed 10,000 IU) SC every 12 hours with concurrent oral aspirin (75 mg to 165 mg once daily) until patient is clinically stable when dalteparin is needed for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The usual duration of administration is between 5 and 8 days.

Alternatively, when using dalteparin for abdominal surgery in patients with malignancy, 2,500 IU can be used 1 to 2 hours prior to surgery then 2,500 IU administered 12 hours later followed by 5,000 IU once daily postoperatively for 5 to 10 days.

For the treatment of symptomatic VTE in pediatric patients, the recommended starting dose is weight-based, according to the patient's age. The starting dose in patients ages 4 weeks to < 2 years is 150 IU/kg twice daily; in patients 2 years to < 8 years is 125 IU/kg twice daily; and in patients 8 years to < 17 years is 100 IU/kg twice daily. Measure anti-Xa level prior to the fourth dose and adjust doses in increments of 25 IU/kg to achieve target anti-Xa level between 0.5 and 1 IU/mL. In pediatric patients who experience thrombocytopenia, discontinue dalteparin if the platelet count is ≤ 50,000/mm^3. It may be restarted when the platelet count recovers to > 50,000/mm^3. For platelet counts of 50,000 to 100,000/mm^3, reduce the daily dalteparin dose by 50% until the platelet count recovers to ≥ 100,000/mm^3.

fondaparinux (Arixtra)

When treating acute symptomatic PE, the recommended dose is 5 mg (weight < 50 kg), 7.5 mg (weight 50 to 100 kg), or 10 mg (weight > 100kg) SC once daily. Treatment ranges from 5 to 9 days, until a therapeutic oral anticoagulant effect is obtained; however, clinical trials have used the medication up to 26 days.

Oral

Drug	Indications			
	Patients with Nonvalvular Atrial Fibrillation*	Prophylaxis of DVT/PE for Knee or Hip Replacement Surgery*	Treatment of DVT/PE*	To Prevent Recurrence of DVT/PE*
apixaban (Eliquis)	5 mg twice daily	2.5 mg twice daily	10 mg twice daily x 7 days; 5 mg twice daily thereafter	2.5 mg twice daily
dabigatran (Pradaxa)	150 mg twice daily	110 mg on first day, then 220 mg once daily	150 mg twice daily after 5 to 10 days of parenteral anticoagulant (adults)	150 mg twice daily (adults)
edoxaban (Savaysa)	60 mg once daily	--	60 mg once daily after 5 to 10 days of parenteral anticoagulant	--
rivaroxaban (Xarelto)	20 mg once daily	10 mg once daily	15 mg twice daily for 21 days; 20 mg once daily thereafter (adults)	10 mg daily after at least 6 months of standard treatment (adults)
warfarin	typical dose may be 2 mg to 10 mg once daily but dose must be individualized based on INR	typical dose may be 2 mg to 10 mg once daily but dose must be individualized based on INR	typical dose may be 2 mg to 10 mg once daily but dose must be individualized based on INR	typical dose may be 2 mg to 10 mg once daily but dose must be individualized based on INR

*Doses listed are based on patients with normal renal function; please see comments below for individualizing doses of some medications based on altered renal function and dosages for additional indications not listed in the table.

apixaban (Eliquis)

The recommended dose of apixaban to reduce the risk of stroke and systemic embolism in patients with NVAF is 5 mg twice daily. A reduced dose of 2.5 mg twice daily is recommended in patients with at least 2 of the following: serum creatinine ≥ 1.5 mg/dL, age ≥ 80 years, and weight ≤ 60 kg. In addition, dosage reductions are recommended for those also on strong dual CYP3A4 and P-gp inhibitors (for patients taking 5 mg twice daily, reduce dose by 50%). The recommended dose for patients with ESRD maintained on hemodialysis is 5 mg twice daily.

For prophylaxis of DVT following hip or knee replacement surgery, the recommended dose of apixaban (Eliquis) is 2.5 mg twice daily. The initial dose should be taken 12 to 24 hours after surgery and should be continued for 12 days in patients undergoing knee replacement and 35 days in patients undergoing hip replacement surgery.

As described above, dosage reductions are recommended for those also on strong dual CYP3A4 and P-gp inhibitors who are taking apixaban for treatment of DVT or PE (for patients taking 5 mg or 10 mg twice daily, reduce dose by 50%). The recommended dose of apixaban to reduce the risk of recurrence of DVT and PE is 2.5 mg twice daily after a minimum 6 months of treatment for DVT or PE.

If a scheduled dose of apixaban is missed, the dose should be taken as soon as possible on the same day and twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose. Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Discontinue apixaban at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Apixaban should be restarted after the procedure as soon as an adequate hemostasis has been established.

When switching from warfarin to apixaban, warfarin should be discontinued and apixaban started when the INR is < 2. Apixaban affects INR; therefore, when switching from apixaban to warfarin, INR measurements during co-administration may not be useful for determining the appropriate dose of warfarin; if continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range. When switching between apixaban and anticoagulants other than warfarin, discontinue apixaban/non-warfarin anticoagulant and begin taking the new anticoagulant at the usual time of the next dose.

For patients who are unable to swallow whole tablets, apixaban tablets may be crushed and suspended in water, or apple juice, or mixed with applesauce and promptly administered orally. For patients with nasogastric (NG) tubes, apixaban 2.5 mg and 5 mg tablets may be crushed and suspended in 60 mL of water and immediately administered through the NG tube. Crushed apixaban tablets are stable in water, apple juice, and applesauce for ≤ 4 hours.

dabigatran (Pradaxa)

The recommended dabigatran dose administered to patients with CrCl > 30 mL/min to reduce the risk of stroke and systemic embolism in patients with NVAF is 150 mg orally twice daily. For NVAF patients with renal impairment, defined as CrCl 15 to 30 mL/min, dabigatran dose should be reduced to 75 mg orally twice daily. Dosage recommendations for the treatment of patients with NVAF and a CrCl < 15 mL/min or on dialysis cannot be provided. In patients with moderate renal impairment (CrCl 30 to 50 mL/min), concomitant use of the P-gp inhibitors, dronedarone or systemic ketoconazole, can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Reduce the dose of dabigatran to 75 mg twice daily in patients receiving these P-gp inhibitors. Avoid use of dabigatran in patients with severe renal impairment (CrCl 15 mL/min to 30 mL/min) when taking P-gp inhibitors.

For the treatment of DVT and PE, or to reduce the risk of recurrence of DVT and PE, patients with a CrCl > 30 mL/min should receive dabigatran 150 mg twice daily after 5 to 10 days of parenteral anticoagulation. For prophylaxis of DVT and PE following hip replacement surgery, patients with a CrCl > 30 mL/min should receive dabigatran 110 mg once 1 to 4 hours following surgery and after hemostasis has been achieved followed by 220 mg once daily for 28 to 35 days. If not started on the day of surgery, after hemostasis has been achieved, start treatment with 220 mg once daily.

In pediatric patients, the dabigatran dose for the treatment of VTE is weight-based, administered twice daily following ≥ 5 days of parenteral anticoagulant. In pediatric patients, the dabigatran dose for the reduction in the risk of recurrence of VTE also is weight-based, administered twice daily following the prior treatment. Oral capsules and oral pellets are not interchangeable on a mg-to-mg basis; they should not be substituted for one another or combined for a total dose. Administration with food is recommended, as needed, to improve tolerability of dabigatran capsules.

Pediatric Dabigatran (Pradaxa) Dosages

Actual Weight (kg)	Dose (mg) – Administered Twice Daily	Dosage Form – Administered Twice Daily
Dosage for Capsules (8 years to < 18 years of age)		
11 kg to < 16 kg	75 mg	1 x 75 mg capsule
16 kg to < 26 kg	110 mg	1 x 110 mg capsule
26 kg to < 41 kg	150 mg	2 x 75 mg capsules; or 1 x 150 mg capsule
41 kg to < 61 kg	185 mg	1 x 75 mg capsule plus 1 x 110 mg capsule
61 kg to < 81 kg	220 mg	2 x 110 mg capsules
≥ 81 kg	260 mg	1 x 150 mg capsule plus 1 x 110 mg capsule; or 2 x 75 mg capsules plus 1 x 110 mg capsule
Dosage for Pellets (2 years to < 12 years of age)		
7 kg to < 9 kg	70 mg	1 x 30 mg plus 1 x 40 mg packet
9 kg to < 11 kg	90 mg	1 x 40 mg plus 1 x 50 mg packet
11 kg to < 13 kg	110 mg	1 x 110 mg packet
13 kg to < 16 kg	140 mg	1 x 30 mg plus 1 x 110 mg packet
16 kg to < 21 kg	170 mg	1 x 20 mg plus 1 x 150 mg packet
21 kg to < 41 kg	220 mg	2 x 110 mg packets
≥ 41 kg	260 mg	1 x 110 mg plus 1 x 150 mg packet

Pediatric Dabigatran (Pradaxa) Dosages (continued)

Actual Weight (kg)	Age (months)	Dose (mg) – Administered Twice Daily	Dosage Form – Administered Twice Daily
Dosage for Pellets (3 months to < 2 years of age)			
3 to < 4 kg	3 to < 6 months	30 mg	1 x 30 mg packet
4 to < 5 kg	3 to < 10 months	40 mg	1 x 40 mg packet
5 kg to < 7 kg	3 to < 5 months	40 mg	1 x 40 mg packet
	5 to < 24 months	50 mg	1 x 50 mg packet
7 kg to < 9 kg	3 to < 4 months	50 mg	1 x 50 mg packet
	4 to < 9 months	60 mg	2 x 30 mg packets
	9 to < 24 months	70 mg	1 x 30 mg packet plus 1 x 40 mg packet
9 kg to < 11 kg	5 to < 6 months	60 mg	2 x 30 mg packets
	6 to < 11 months	80 mg	2 x 40 mg packets
	11 to < 24 months	90 mg	1 x 40 mg packet plus 1 x 50 mg packet
11 kg to < 13 kg	8 to < 18 months	100 mg	2 x 50 mg packets
	18 to < 24 months	110 mg	1 x 110 mg packet
13 kg to < 16 kg	10 to < 11 months	100 mg	2 x 50 mg packets
	11 to < 24 months	140 mg	1 x 30 mg packet plus 1 x 110 mg packet
16 kg to < 21 kg	12 to < 24 months	140 mg	1 x 30 mg packet plus 1 x 110 mg packet
21 kg to < 26 kg	18 to < 24 months	180 mg	1 x 30 mg packet plus 1 x 150 mg packet

Avoid use of concomitant P-gp inhibitors (ketoconazole, amiodarone, dronedarone, verapamil, quinidine) in patients with CrCl < 50 mL/min for the treatment of DVT and PE, risk reduction of recurrent of DVT and PE, and prophylaxis of DVT and PE following hip replacement surgery. Dosing recommendations for the treatment of DVT and PE, to reduce the risk of recurrence of DVT and PE, and prophylaxis of DVT and PE following hip replacement surgery in patients with a CrCl ≤ 30 mL/min or on dialysis cannot be provided.

Renal function assessment should be done with the initiation of dabigatran and periodically thereafter. Dabigatran should be discontinued in patients who develop acute renal failure and consideration given to alternative anticoagulant therapy. Dabigatran capsules should not be broken, chewed, or opened before administration as the oral bioavailability increases by 75% when the pellets are administered without the capsule shell. Patients should be instructed to take dabigatran with a full glass of water. Patients should also be counseled on what to do in the event they miss a dose. If the dose is not taken at the scheduled time, the dabigatran dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of dabigatran should not be doubled to make up for a missed dose. Temporarily discontinue (1 to 2 days [CrCl ≥ 50 mL/min] or 3 to 5 days [CrCl < 50 mL/min]) dabigatran in adults before invasive or surgical procedures when possible; restart promptly. In pediatrics undergoing an elective surgery, discontinue dabigatran 24 hours prior to the surgery (eGFR > 80 mL/min/1.73m^2) or 2 days prior (eGFR 50 to 80 mL/min/1.73m^2). If emergency surgery is required and cannot be delayed, there is an increased risk of bleeding; the risk of bleeding should be weighed against the urgency of the intervention.

If reversal of dabigatran's anticoagulant effects is needed for emergency surgery, urgent procedures, or in life-threatening or uncontrolled bleeding, idarucizumab (Praxbind) is available as a reversal agent for adults. The recommended dose of idarucizumab is 5 g as an intravenous (IV) infusion.[154] Efficacy and safety of this agent in pediatric patients have not been established. Restart dabigatran as soon as medically appropriate.

Dosing instructions for converting patients from warfarin to/from dabigatran appear in the prescribing information. To switch from warfarin to dabigatran in adults and pediatrics, discontinue warfarin and start dabigatran when the INR is < 2. When switching from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows: for CrCl ≥ 50 mL/min, start warfarin 3 days before discontinuing dabigatran. For CrCl 30 mL/min to 50 mL/min, start warfarin 2 days before discontinuing dabigatran. For CrCl 15 to 30 mL/min, start warfarin 1 day before discontinuing dabigatran. For CrCl < 15 mL/min, no recommendations can be made. Because dabigatran can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days. In pediatric patients when converting to warfarin, start warfarin 3 days before discontinuing dabigatran capsules or pellets.

For patients converting from parenteral anticoagulation therapy, dabigatran should be started 0 to 2 hours before the time the next parenteral drug would have been scheduled or at the time of the discontinuation of a continuously administered parenteral drug. For patients being switched from dabigatran to a parenteral anticoagulant, wait 12 hours (adults, CrCl ≥ 30 mL/min; pediatrics) or 24 hours (adults, CrCl < 30 mL/min) after the last dabigatran dose before starting parenteral anticoagulant therapy.

edoxaban (Savaysa)

In the treatment of patients with NVAF, creatinine clearance should be assessed prior to initiating therapy. The recommended dose is edoxaban 60 mg once daily in patients with CrCl > 50 to ≤ 95 mL/min. Edoxaban should not be used in patients with a CrCl > 95 mL/min and should be reduced to 30 mg once daily in patients with CrCl 15 to 50 mL/min.

The recommended dose for the treatment of DVT and/or PE is 60 mg once daily. A reduced dose of 30 mg once daily is recommended for patients with CrCl 15 to 50 mL/min or those with a body weight ≤ 60 kg or patients who are taking certain P-gp inhibitors (verapamil, quinidine, or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, or itraconazole or oral ketoconazole).

When switching from warfarin to edoxaban, discontinue warfarin and start edoxaban when the INR is less than or equal to 2.5. When switching from LMWH or any oral anticoagulant other than warfarin to edoxaban, discontinue the current anticoagulant and start edoxaban at the time of the next scheduled dose of the other anticoagulant. When switching from UFH to edoxaban, start edoxaban 4 hours after discontinuation of the heparin infusion. When switching from edoxaban to a parenteral anticoagulant, edoxaban should be discontinued and the parenteral anticoagulant should be started at the time of the next edoxaban dose. For patients transitioning from edoxaban to warfarin, edoxaban should be discontinued. Both warfarin and a parenteral anticoagulant may be given at the time of the next edoxaban dose with the parenteral anticoagulant continued until the INR is ≥ 2. Alternately, the edoxaban dose may be reduced by 50% with warfarin concomitant warfarin. The INR should be measured at least weekly just prior to the daily dose of edoxaban to minimize the influence on INR measurements. Once a stable INR (≥ 2) is achieved, edoxaban should be discontinued and warfarin continued.

For patients who are unable to swallow tablets, edoxaban tablets may be crushed and mixed with 2 to 3 ounces of water then administered by mouth or through a gastric tube. The crushed tablets may also be mixed into a small amount of applesauce and administered orally.

rivaroxaban (Xarelto)

The recommended dose of rivaroxaban for the reduction of risk of major CV events (CV death, MI, and stroke) in patients with chronic CAD is 2.5 mg twice daily in combination with aspirin (75 mg to 100 mg once daily).

The recommended dose of rivaroxaban for the reduction of risk of major thrombotic vascular events (MI, stroke, acute limb ischemia, major amputation of a vascular etiology) in patients with PAD, is 2.5 mg twice daily in combination with aspirin (75 mg to 100 mg once daily). It should only be initiated in patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD once hemostasis has been established.

The recommended dosage of rivaroxaban for DVT prophylaxis following hip or knee replacement surgery is 10 mg orally once daily without regard to food, starting 6 to 10 hours post-op, after hemostasis has been established. The duration of treatment for hip and knee replacement is 35 days and 12 days, respectively. Missed doses should be taken as soon as possible on the same day; for patients taking 15 mg twice daily, the patient should take the medication immediately to ensure 30 mg is received for the day (two 15 mg tablets may be taken at once) and should continue with their regular 15 mg twice daily the next day; for patients taking 10 mg, 15 mg, or 20 mg once daily, the patient should take the missed dose immediately.

The recommended dosage of rivaroxaban for treatment of DVT and/or PE is 15 mg twice daily with food, for 21 days, followed by 20 mg once daily with food, for the remaining treatment. For the reduction of recurrence of DVT and/or PE, rivaroxaban dosage is 20 mg once daily with food. Please see the Pharmacokinetics section regarding rivaroxaban bioavailability with and without concomitant food intake. The 15 mg and 20 mg tablets should be taken with food, while the 10 mg tablet can be taken with or without food. Use of rivaroxaban for the treatment of DVT and/or PE treatment and for the reduction in risk of recurrence of DVT and/or PE in patients with continued risk should be avoided if the CrCl is < 15 mL/min.

For NVAF for adults with CrCl > 50 mL/min, administer rivaroxaban 20 mg once daily with the evening meal. For NVAF for patients with CrCl ≤ 50 mL/min, the recommended rivaroxaban dosage is 15 mg once daily with the evening meal.

When switching from warfarin to rivaroxaban, discontinue warfarin and start rivaroxaban as soon as an INR < 3 in adults and < 2.5 in pediatric patients is achieved to avoid periods of inadequate anticoagulation. There is no guide for converting adults from rivaroxaban to warfarin. Rivaroxaban affects INR, so INR measurements made during concomitant warfarin therapy may not be useful for determining the appropriate dose of warfarin. One approach may be to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken. An increased rate of stroke was observed during the transition from rivaroxaban to warfarin in clinical trials in atrial fibrillation patients. For pediatric patients transitioning from rivaroxaban to warfarin, continue rivaroxaban for ≥ 2 days after the first dose of warfarin; following 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban. Co-administration of rivaroxaban and warfarin should continue until the INR is ≥ 2; once rivaroxaban is discontinued, INR testing can be conducted 24 hours after the last dose. When switching adults or pediatric patients from rivaroxaban to an anticoagulant with rapid onset, give the first dose of the other anticoagulant (oral or parenteral) at the time when the next rivaroxaban dose would have been taken. For adults and pediatric patients receiving an anticoagulant other than warfarin that are to be switched to rivaroxaban, start rivaroxaban 0 to 2 hours prior to the next scheduled administration of the drug (e.g., LMWH). For UFH being administered via a continuous infusion, stop the infusion and start rivaroxaban at the same time.

The absorption of rivaroxaban is dependent on the site of drug release in the GI tract. Avoid administration of rivaroxaban distal to the stomach as it can result in reduced absorption and drug exposure. If a feeding tube is used for administration, confirm gastric placement. For patients who are unable to swallow whole tablets, rivaroxaban tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. Crushed rivaroxaban tablets are stable in water and in applesauce for up to 4 hours. With the exception of the 2.5 mg and 10 mg tablets, after the administration of a crushed rivaroxaban tablet, the dose should be immediately followed by food or an enteral feeding, if being administered through a nasogastric (NG) or gastric feeding tube. When rivaroxaban is administered through an NG tube or gastric feeding tube, rivaroxaban tablets may be crushed and suspended in 50 mL of water for administration. An *in vitro* study has confirmed there is no adsorption of rivaroxaban suspended in water to polyvinyl chloride (PVC) or silicone NG tubing.

The recommended dose of rivaroxaban for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding is 10 mg once daily during hospitalization and after discharge. It can be taken with or without food for a total recommended duration of therapy of 31 to 39 days. Use should be avoided in patients with CrCl < 15 mL/min.

In pediatric patients, the rivaroxaban dose for the treatment of VTE and reduction in risk of recurrent venous thromboembolism is weight-based and should be initiated following ≥ 5 days of initial parenteral anticoagulation therapy. Additionally, patients < 6 months old should meet the following criteria: at birth were ≥ 37 weeks of gestation, have had ≥ 10 days of oral feeding, and weigh ≥ 2.6 kg at the time of dosing. All doses for this use in pediatric patients should be taken with feeding or with food to increase absorption since drug levels align with that of 20 mg daily dose used in adults. To ensure a therapeutic dose is prescribed, pediatric patient's weight should be monitored and the dose reviewed periodically, particularly if the child is < 12 kg. For all pediatric patients with thrombosis (except < 2 years old with catheter-related thrombosis), rivaroxaban should be continued for ≥ 3 months; treatment can be extended up to 12 months, if needed, depending on the risk for recurrent thrombosis compared to the risk for bleeding. For pediatric patients < 2 years old with catheter-related thrombosis, rivaroxaban should be continued for ≥ 1 month; treatment can be extended up to 3 months, if needed, depending on the risk for recurrent thrombosis compared to the risk for bleeding.

Pediatric Rivaroxaban (Xarelto) Dosages for Treatment of VTE and Reduction in Risk of Recurrent VTE

Dosage Form	Body Weight	Dosage			Total Daily Dose
		Once per day	2-times a day	3-times a day	
Oral suspension only (1 mg rivaroxaban = 1 mL suspension)	2.6 kg to 2.9 kg			0.8 mg	2.4 mg
	3 kg to 3.9 kg			0.9 mg	2.7 mg
	4 kg to 4.9 kg			1.4 mg	4.2 mg
	5 kg to 6.9 kg			1.6 mg	4.8 mg
	7 kg to 7.9 kg			1.8 mg	5.4 mg
	8 kg to 8.9 kg			2.4 mg	7.2 mg
	9 kg to 9.9 kg			2.8 mg	8.4 mg
	10 kg to 11.9 kg			3 mg	9 mg
	12 kg to 29.9 kg		5 mg		10 mg
Oral Suspension or Tablets	30 kg to 49.9 kg	15 mg			15 mg
	≥50 kg	20 mg			20 mg

In pediatric patients with congenital heart disease (CHD), the rivaroxaban dose for thromboprophylaxis after the Fontan procedure is weight-based. All doses can be taken with or without food since drug levels align with use of a 10 mg daily dose in adults.

Pediatric Rivaroxaban (Xarelto) Dosages for Thromboprophylaxis after Fontan Procedure

Dosage Form	Body Weight	Dosage		Total Daily Dose
		Once per day	2-times a day	
Oral suspension only (1 mg rivaroxaban = 1 mL suspension	7 kg to 7.9 kg		1.1 mg	2.2 mg
	8 kg to 9.9 kg		1.6 mg	3.2 mg
	10 kg to 11.9 kg		1.7 mg	3.4 mg
	12 kg to 19.9 kg		2 mg	4 mg
	20 kg to 29.9 kg		2.5 mg	5 mg
	30 kg to 49.9 kg	7.5 mg		7.5 mg
Oral Suspension or Tablets	≥ 50 kg	10 mg		10 mg

warfarin

Warfarin dosing should be individualized by monitoring the PT/INR; dose adjustment is based on the patient's INR, condition in which they are being treated for, and target INR range. Some of the factors influencing warfarin dose variability include clinical (age, race, body weight, sex, concomitant medications, and comorbidities) and genetic (CYP2C9 and VKORC1 genotypes).

Warfarin loading doses are not recommended due to increase in hemorrhagic and other complications. In addition, the loading dose does not offer more rapid protection against clot formation. If the patient's CYP2C9 and VKORC1 genotypes are unknown, a typical initial dose is 2 mg to 5 mg per day. PT/INR response determines maintenance doses and interval; a typical maintenance dose is between 2 mg and 10 mg once daily. If the patient's CYP2C9 and VKORC1 genotypes are known, dosing ranges for initial therapy and maintenance therapy are provided in the medication prescribing guide. If large daily doses of warfarin are required to maintain a patient's PT/INR within a normal therapeutic range, acquired or inherited warfarin resistance (although rare) should be suspected. Lower initiation and maintenance doses should be considered for elderly and debilitated patients.

Duration of therapy should be individualized and followed according to current treatment guidelines. An INR > 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

PT/INR should be done daily after the initial dose of warfarin and until results stabilize in the therapeutic range. Intervals between subsequent PT/INR should be based upon the physician's judgment of the patient's reliability and response to warfarin to maintain therapeutic range. Acceptable intervals for PT/INR determinations are within the range of 1 to 4 weeks once a stable dosage has been determined. However, PT/INR should be checked when other warfarin products are used or when other medications are started, discontinued, taken irregularly, or have dosing changes. Studies suggest that patients in usual care monitoring are in therapeutic range only 33% to 64% of the time. Time in therapeutic range is higher at 56% to 93% in patients managed by anticoagulation clinics, among self-testing/self-monitoring patients, and in patients managed with the help of computer programs.[155]

Oral or parenteral vitamin K1 reverses the anticoagulant effects of warfarin. Idarucizumab (Praxbind) reverses the effects of dabigatran (Pradaxa) in adults.[156] Coagulation factor Xa (recombinant), inactivated–zhzo (Andexxa) reverses the effects of apixaban (Eliquis) and rivaroxaban (Xarelto).[157] A specific antidote for edoxaban (Savaysa) is not currently available.

Availability

Drug	Availability
Injectable	
dalteparin (Fragmin)	2,500 units, 5,000 units, 7,500 units, 10,000 units, 12,500 units, 15,000 units, 18,000 units single-dose, pre-filled syringes; 95,000 units MDV
enoxaparin (Lovenox)	30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 150 mg single-dose, pre-filled syringes; 300 mg MDV
fondaparinux (Arixtra)	2.5 mg, 5 mg, 7.5 mg, 10 mg single-dose, pre-filled syringes
Oral	
apixaban (Eliquis)	2.5 mg, 5 mg tablets; 30-day Starter Pack (DVT-PE; 5 mg tablets)
dabigatran (Pradaxa)	75 mg, 110 mg (brand only), 150 mg capsules*
edoxaban (Savaysa)	15 mg, 30 mg, 60 mg tablets
rivaroxaban (Xarelto)	2.5 mg, 10 mg, 15 mg, 20 mg tablets; 30-day Starter Pack (DVT-PE; 42 x 15 mg and 9 x 20 mg tablets); 1 mg/mL oral suspension†
warfarin‡	1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg tablets

MDV = multiple-dose vial

* Dabigatran capsules should not be chewed or broken open as this increases bioavailability by 75%. Dabigatran must be kept in original bottles to protect from moisture. Open bottles of dabigatran must be used within 4 months of being opened. An oral pellet formulation of dabigatran in the following strengths per packet has been FDA-approved: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg. This formulation is intended for twice daily use within 30 minutes of mixing with certain soft foods at room temperature or 1 to 2 ounces of apple juice. It may also be directly administered into the patient's mouth. It should

not be administered via a syringe or feeding tube or with any soft food or liquid containing milk products. Notably, the oral pellet formulation is not interchangeable on a mg per mg basis with the oral capsule.

† For children unable to swallow 10 mg, 15 mg, or 20 mg whole tablets, the rivaroxaban oral suspension should be used. The 2.5 mg tablets are not recommended for use in pediatric patients.

‡ Jantoven®, manufactured by Upsher Smith, is a branded generic of warfarin.158

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class for the FDA-approved indications used in the outpatient setting. Randomized, controlled trials comparing agents for either the treatment or prophylaxis of DVT/PE in the outpatient setting or NVAF are considered the most relevant in this category. Comparative trials are the most important, but when comparative trials were unavailable, placebo-controlled trials were considered relevant. In comparisons with UFH, studies utilizing weight-based dosing of UFH with adjustments according to laboratory parameters were considered most useful. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

VTE Prophylaxis

apixaban (Eliquis) versus enoxaparin (Lovenox)

Apixaban was compared to enoxaparin in 3 randomized, double-blind, double dummy phase 3 trials. These trials were Apixaban Dosed orally Vs. ANtiCoagulation with Enoxaparin (ADVANCE)-1, ADVANCE-2, and ADVANCE-3.[159,160,161] In ADVANCE-1 and ADVANCE-2, the studies were conducted in patients undergoing knee replacement surgery and ADVANCE-3 studied patients undergoing hip replacement surgery. ADVANCE-2 and ADVANCE-3 compared apixaban to enoxaparin 40 mg subcutaneously (SC) once daily, a dosing schedule used in Europe but that is not a FDA-approved dosing regimen. ADVANCE-1 compared apixaban with the FDA-approved dosing regimen of enoxaparin 30 mg SC twice daily for DVT prophylaxis in patients undergoing knee or hip replacement surgery. All 3 trials were funded by Bristol-Myers Squibb and Pfizer.

ADVANCE-1 was a double-blind, double-dummy, non-inferiority trial (n=3,195) that compared apixaban 2.5 mg orally twice daily with enoxaparin 30 mg SC every 12 hours in patients undergoing total knee replacement. Both medications were started 12 to 24 hours after surgery and continued for 10 to 14 days. The primary efficacy outcome was a composite of asymptomatic and symptomatic DVT, nonfatal PE, and death from any cause for up to 60 days after the end of anticoagulation therapy. The primary safety outcome was bleeding during the treatment period or within 2 days after the last dose of anticoagulant therapy. The primary efficacy outcome occurred in 104 (9%) patients randomized to apixaban and in 100 (8.8%) of patients randomized to enoxaparin. The statistical criterion for noninferiority was not met (relative risk, 1.02; 95% CI, 0.78 to 1.32; p=0.06 for non-inferiority). Major bleeding occurred in 11 (0.7%) patients who received apixaban and in 22 (1.4%) patients who received enoxaparin (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49 to 0.14; p=0.053). The authors concluded the primary efficacy outcome was much lower than expected in the enoxaparin arm and, therefore, it was difficult to demonstrate apixaban noninferiority.

ADVANCE-2 was a multicenter, double-blind, phase 3 trial comparing apixaban 2.5 mg orally twice daily with enoxaparin 40 mg SC once daily in 3,057 patients undergoing elective total knee replacement. Apixaban was started 12 to 24 hours after surgery and enoxaparin was started 12 hours before surgery; both drugs were continued for 10 to 14 days. Primary efficacy outcome was identical to ADVANCE-1. The primary outcome was reported in 147 (15%) apixaban-treated patients and 243 (24%) enoxaparin-treated patients (relative risk 0.62; 95% CI, 0.51 to 0.74; p<0.0001 when tested for noninferiority and superiority). Major or clinically relevant non-major bleeding occurred in 53 (4%) apixaban-treated patients and 72 (5%) enoxaparin-treated patients (p=0.09)

ADVANCE-3 was a randomized, double-blind, double-dummy phase 3 study comparing apixaban 2.5 mg orally twice daily with enoxaparin 40 mg SC once daily in 5,407 patients undergoing total hip replacement. Initiation schedule for both medications was identical to ADVANCE-2 but the duration of therapy was continued for 35 days after hip replacement surgery. The primary efficacy outcome was identical to ADVANCE-1 and -2. The primary efficacy outcome occurred in 27 (1.4%) patients in the apixaban group and in 74 patients (3.9%) in the enoxaparin group (relative risk with apixaban, 0.36; 95% CI, 0.22 to 0.54; p<0.001 for both noninferiority and superiority; absolute risk reduction, 2.5%; 95% CI, 1.5 to 3.5). The composite outcome of major and clinically relevant non-major bleeding occurred in 129 (4.8%) patients receiving apixaban and 134 (5%) patients receiving enoxaparin (absolute difference in risk, -0.2%; 95% CI, -1.4 to 1).

dabigatran (Pradaxa) versus enoxaparin (Lovenox)

RE-NOVATE, a multinational, multicenter, double-blind, randomized, non-inferiority trial, compared the efficacy of oral dabigatran 150 mg (n=1,174) or 220 mg (n=1,157) once daily, both starting with a half-dose 1 to 4 hours following surgery, to SC enoxaparin 40 mg once daily (n=1,162) starting the evening before surgery in adults for VTE prophylaxis following total hip replacement surgery.[162] The median treatment duration was 33 days. The primary outcome was the composite of total VTE (venographic or symptomatic) and all-cause death during treatment (non-inferiority margin set at 7.7%). The primary outcome occurred in 6.7% (60/897) of patients in the enoxaparin group compared to 8.6% (75/874) of patients in the 150 mg dabigatran group (treatment difference, 1.9%; 95% CI, -0.6 to 4.4) and 6% (53/880) of patients in the 220 mg dabigatran group (treatment difference, -0.7%; 95% CI, -2.9 to 1.6). Both doses of dabigatran were found to be non-inferior to enoxaparin (150 mg dose not FDA-approved for this use), and bleeding rates with both doses of dabigatran were similar to those of enoxaparin (p=0.6 for 150 mg, p=0.44 for 220 mg).

RE-NOVATE II, also a multinational, multicenter, double-blind, randomized, non-inferiority trial, compared the efficacy of dabigatran 220 mg once daily, starting with a half-dose 1 to 4 hours following surgery, to SC enoxaparin 40 mg once daily starting the evening before surgery in 2,055 adults for VTE prophylaxis following total hip arthroplasty.[163] Treatment duration ranged from 28 to 35 days. The primary outcome was the composite of total VTE (venographic or symptomatic) and all-cause death during treatment (non-inferiority margin set at 7.7%). The primary outcome occurred in 8.8% of patients in the enoxaparin group compared to 7.7% of patients in the dabigatran group (treatment difference, -1.1%; 95% CI, -3.8 to 1.6; p<0.0001). The key secondary composite outcome was major VTE (proximal DVT or non-fatal PE) and VTE-related death. This secondary outcome occurred in 4.2% of patients in the enoxaparin group compared to 2.2% of patients in the dabigatran group (treatment difference, -1.9%; 95% CI, -3.6 to -0.2; p=0.03). Bleeding rates were similar between groups (p=0.4).

dabigatran (Pradaxa) in pediatrics

The safety of dabigatran for the prevention of recurrent VTE was assessed in an open-label, single-arm study in 214 pediatric patients from birth to < 18 years of age.[164,165] Patients needing further anticoagulation following an initial 3-month treatment for confirmed VTE following or following completion of the DIVERSITY study for VTE treatment were included. Patients received age- and weight-based dosing of dabigatran (capsules, oral pellets) until prophylaxis was no longer needed, up to 12 months. The primary endpoints were the recurrence of VTE, major and minor bleeding, and mortality at 6 and 12 months. At 3, 6, and 12 months, the probabilities of being free from recurrence of VTE were 0.99 (95% CI, 0.96 to 0.997), 0.984 (95% CI, 0.95 to 0.995), and 0.984 (95% CI, 0.95 to 0.995), respectively. At 3, 6, and 12 months, the probabilities of being free from bleeding events were 0.849 (95% CI, 0.792 to 0.891), 0.785 (95% CI, 0.718 to 0.838), and 0.723 (95% CI, 0.645 to 0.787), respectively.

dalteparin (Fragmin) use in pregnancy

The Efficacy of Thromboprophylaxis as an Intervention during Gravidity (EThIG) was a prospective trial of 810 pregnant women assigned to 1 of 3 management strategies according to predefined VTE risk factors.[166] The low risk (group I) received dalteparin 50 to 100 IU/kg body weight for 14 days postpartum. The high (group II) or very high risk (group III) received dalteparin 50 to 100 IU/kg/day and 100 to 200 IU/kg/day, respectively, from enrollment until 6 weeks postpartum. Symptomatic VTE occurred in 5 of 810 women (0.6%; 95% CI, 0.2 to 1.5) (group I, 0 of 225; II, 3/469; III, 2/116). Serious bleeding occurred in 3% (95% CI; 1.9 to 4.4); 1.1% (95% CI, 0.5 to 2.2) was possibly dalteparin-related. There was no evidence of HIT and 1 case of osteoporosis was reported. Risk-stratified heparin prophylaxis was associated with a low incidence of symptomatic VTE and few clinically important adverse events.

dalteparin (Fragmin) versus fondaparinux (Arixtra)

The Pentasaccharide in General Surgery Study (PEGASUS) enrolled 2,297 surgical patients who were randomized in double-blind fashion to receive either fondaparinux 2.5 mg or dalteparin 5,000 units SC daily.[167] Fondaparinux was initiated 6 hours after high-risk abdominal surgery. Dalteparin was initiated as 2,500 units given 2 hours preoperatively and repeated 12 hours later. There was no difference between the 2 treatment arms in occurrence of VTE up to post-operative day 10 (4.6% versus 6.1% for fondaparinux and dalteparin, respectively), a relative risk reduction of 24.6% (95% CI, -9 to 47.9; p=0.144); this met the pre-determined criterion for non-inferiority of fondaparinux. No difference was detected in the primary safety outcome, major bleeding, during the initial treatment period. The rate of major bleeding was 3.4% in the fondaparinux group and 2.4% in the dalteparin group.

dalteparin (Fragmin) versus warfarin

In the double-blind, North American Fragmin trial, 1,472 patients were randomized to dalteparin given once daily immediately or early after surgery or post-operative warfarin for DVT prophylaxis in patients undergoing hip arthroplasty.[168] Venograms were performed 5 days after surgery. The dalteparin group had 10.7% positive for any DVT whereas the warfarin group had 24% positive for any DVT (p<0.001). Proximal DVTs were identified in 0.8% of dalteparin patients and 3% of the warfarin patients (p=0.03 and p=0.04). Serious bleeding was similar in both groups. Pre-operative dalteparin patients experienced more major surgical site bleeding than did the warfarin patients (p=0.01). When evaluating extended out-of-hospital use for up to 35 days with dalteparin or placebo, new proximal DVT rates were 0.7% to 1.3% of dalteparin patients and 4.8% for the inpatient warfarin group.[169] Overall, the cumulative incidence of all DVT was 17.2% to 22.2% with dalteparin and 36.7% with in-hospital warfarin/out-of-hospital placebo group. Cumulative proximal DVT rates were 2% to 3.1% for dalteparin and 9.2% for the warfarin/placebo groups. No major bleeding occurred during the extended prophylaxis time period.

enoxaparin (Lovenox) versus fondaparinux (Arixtra)

A multicenter, randomized, double-blind trial compared enoxaparin and fondaparinux in patients undergoing elective knee surgery.[170] Patients (n=1,049) were randomized to receive enoxaparin 30 mg SC twice daily or fondaparinux 2.5 mg SC once daily. Both drugs were started postoperatively. The primary efficacy endpoint, incidence rate of VTE, was determined by day 11. The primary safety outcome was major bleeding. Incidence of VTE by day 11 was significantly lower in the fondaparinux group (12.5%) than the enoxaparin group (27.8%; p<0.001). The rate of symptomatic venous thrombosis was similar between the groups. More major bleeding was observed in the fondaparinux group (p=0.006).

In a multicenter, randomized, double-blind trial, enoxaparin 40 mg and fondaparinux 2.5 mg, each given SC once daily, were compared in 1,711 patients undergoing hip fracture surgery.[171] Enoxaparin therapy was initiated pre-operatively whereas fondaparinux was initiated post-operatively; treatment continued for at least 5 days in both groups. The primary efficacy endpoint was the rate of VTE up to day 11; the primary safety outcomes were major bleeding and all-cause mortality through 6 weeks. In the study, the incidence of VTE was significantly lower in the fondaparinux group (8.3%) than the enoxaparin group (19.1%; p<0.001). Symptomatic venous thrombosis was similar between the groups. There were no significant differences between the 2 groups in the incidence of death or rate of clinically relevant bleeding.

In the double-blind European Pentasaccharide Hip Elective Surgery Study (EPHESUS), 2,309 consecutive adult patients undergoing elective hip replacement surgery were randomly assigned in a double-blind manner to fondaparinux 2.5 mg SC daily, starting postoperatively, or enoxaparin 40 mg SC daily, starting preoperatively.[172] The primary efficacy outcome was VTE up to day 11; primary safety outcomes were bleeding and death through 6 weeks. Primary efficacy analysis was performed in 908 fondaparinux patients and 919 enoxaparin patients. By day 11, 4% of fondaparinux patients experienced VTE whereas 9% of enoxaparin patients had positive findings for VTE (55.9% relative risk reduction; p<0.0001). The 2 groups did not differ significantly in incidence of death or rate of clinically relevant bleeding.

In the similarly designed PENTATHLON 2000 study, 2,275 consecutive adult patients who were undergoing elective hip replacement surgery were randomized in a double-blind manner to receive either fondaparinux 2.5 mg SC once daily or enoxaparin 30 mg SC twice daily.[173] The primary efficacy of the presence of VTE was assessed to day 11 in 1,584 patients. VTE was reported in 6% of patients on fondaparinux and 8% of patients receiving enoxaparin (p=NS). The 2 groups did not differ in the number of patients who died or in the number who had clinically relevant bleeding.

rivaroxaban (Xarelto) versus aspirin

A randomized, double-blind study was conducted in 3,365 patients with venous thromboembolism over nearly 12 months to assess whether it is better to use full (20 mg once daily) or lower (10 mg once daily) intensity rivaroxaban or aspirin (100 mg daily).[174] All patients were equipoise regarding the need for continued anticoagulation. The primary efficacy outcome was symptomatic recurrent fatal or non-fatal VTE; the primary safety outcome was major bleeds. The primary efficacy outcome occurred in 17 of the 1,107 patients treated with rivaroxaban 20 mg daily; 13 of the 1,127 patients treated with rivaroxaban 10 mg daily; and 50 of the 1,131 patients taking aspirin 100 mg daily (HR, 0.34; 95% CI, 0.20 to 0.59 [rivaroxaban 20 mg daily versus aspirin]; HR 0.26; 95% CI, 0.14 to 0.47 [rivaroxaban 10 mg daily versus aspirin]; p< 0.001). The rates of major bleeding were 0.5%, 0.4%, and 0.3% for rivaroxaban 20 mg, rivaroxaban 10 mg, and aspirin 100 mg daily, respectively. The study concluded that for patients with VTE in equipoise for continued anticoagulation, the risk for a recurrent event was higher with aspirin compared to rivaroxaban (10 mg or 20 mg daily) without significant difference in bleeding rates.

rivaroxaban (Xarelto) versus enoxaparin (Lovenox)

Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) 1 and 2 for elective total hip replacement and RECORD 3 for elective total knee replacement were all randomized, double-blind, multinational trials that compared oral rivaroxaban 10 mg once daily started 6 to 8 hours after wound closure to subcutaneous (SC) enoxaparin 40 mg once daily started 12 hours pre-op.[175] Enoxaparin 40 mg once daily is not the FDA-approved dose in knee replacement. In all these trials, rivaroxaban was superior in preventing total VTE (a composite endpoint of DVT, nonfatal PE, and death from any cause) and major VTE (a composite endpoint of proximal DVT, nonfatal PE, and venous thromboembolic death).

In RECORD 1 and 2, a total of 6,727 patients were randomized and 6,579 received study drug. In RECORD 1, the mean exposure duration (± standard deviation [SD]) to rivaroxaban and enoxaparin was 33.3 + 7 days and 33.6 + 8.3 days, respectively. In RECORD 2, the mean exposure duration to rivaroxaban and enoxaparin was 33.5 + 6.9 days and 12.4 + 2.9 days, respectively. After day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration.

In RECORD 1, the occurrence of the primary efficacy outcome of total VTE at 36 days was 1.1% for rivaroxaban and 3.7% for enoxaparin (p<0.001; absolute risk reduction, 2.6%; 95% CI, 1.5 to 3.7; number needed to treat [NNT]=38).[176] The main secondary outcome of major VTE occurred in 0.2% of patients in the rivaroxaban group and in 2% of patients in the enoxaparin group (p<0.001; absolute risk reduction, 1.7%; 95% CI, 1 to 2.5). The primary safety outcome of major bleeding occurred in 0.3% and 0.1% of patients in the rivaroxaban and enoxaparin groups respectively (p=0.18).

In RECORD 2, the occurrence of the primary efficacy outcome of total VTE in the rivaroxaban versus enoxaparin groups was 2% versus 8.4% (p<0.001; absolute risk reduction, 7.3%; 95% CI, 5.2 to 9.3; NNT=14).[177]

In RECORD 3 (n=2,531), the mean exposure duration (± SD) to rivaroxaban and enoxaparin was 11.9 + 2.3 days and 12.5 + 3 days, respectively.[178] The primary outcome of total VTE 13 to 17 days after surgery occurred in 9.6% and 18.9% of patients treated with rivaroxaban and enoxaparin, respectively (p<0.001; absolute risk reduction, 9.2%; 95% CI, 5.9 to 12.4; NNT=11). The secondary outcome of major VTE occurred in 1% of patients in the rivaroxaban group and 2.6% of patients in the enoxaparin group (p=0.01; absolute risk reduction, 1.6%; 96% CI, 0.4 to 2.8). The primary safety outcome of major bleeding occurred in 0.6% and 0.5% of rivaroxaban- and enoxaparin-treated patients, respectively.

RECORD 4 (n=3,148) was a randomized, double-blind study comparing oral rivaroxaban 10 mg once daily to SC enoxaparin 30 mg every 12 hours (FDA-approved dose for knee replacement) in patients undergoing total knee replacement surgery.[179] The primary outcome, composite of DVT, PE, or death from any cause up to day 17 after surgery, occurred in 6.9% compared to 10.1% patients on rivaroxaban and enoxaparin, respectively (p=0.0118; absolute risk reduction, 3.19%; 95% CI, 0.71 to 5.67; NNT=31). Major bleeding occurred in 0.7% of rivaroxaban patients compared with 0.3% of enoxaparin patients (p=0.1096).

The Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Medically Ill Patients (MAGELLAN) study evaluated the safety and efficacy of rivaroxaban compared to enoxaparin during hospitalization and following discharge in adult patients at risk of VTE due to moderate or severe immobility who had additional risk factors for VTE. [180,181] In this double-blind study, patients were randomized to receive 10 mg once daily rivaroxaban for 35 ± 4 days (n=4,050) or 40 mg once daily SC enoxaparin for 10 ± 4 days (n=4,051). At day 35, the primary composite endpoint evaluating asymptomatic proximal DVT in lower extremity, symptomatic proximal or distal DVT in the lower extremity, symptomatic non-fatal PE, and death related to VTE was found to be significantly reduced with rivaroxaban (4.4%) compared to enoxaparin (5.7%) (95% CI, 0.62 to 0.96; absolute risk reduction, 1.3%; NNT=77). After removal of patients at high risk of bleeding from the analysis, the treatment difference favoring rivaroxaban (3.9%) over enoxaparin (5.7%) was more pronounced (95% CI, 0.53 to 0.88; absolute risk reduction 1.8%; NNT=56).

VTE Treatment (Outpatient)

apixaban (Eliquis) versus enoxaparin (Lovenox)/warfarin

Apixaban, at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months, was compared to SC enoxaparin followed by adjusted dose warfarin (conventional therapy) in patients with acute VTE.[182] The AMPLIFY trial (n=5,395) was a randomized, double-blind study sponsored by Bristol-Myers Squibb and Pfizer. The primary efficacy outcome was the incidence of the composite of recurrent symptomatic VTE or death related to VTE. The primary efficacy outcome occurred in 59 of 2,609 patients (2.3%) in the apixaban group and in 71 of 2,635 patients (2.7%) in the conventional-therapy group, for a relative risk with apixaban of 0.84 (95% CI, 0.6 to 1.18; p<0.001 for noninferiority). The primary safety outcome was major bleeding. Major bleeding occurred in 15 of 2,676 patients (0.6%) in the apixaban group and in 49 of 2,689 patients (1.8%) in the conventional-therapy group, for a relative risk of 0.31 (95% CI, 0.17 to 0.55; p<0.001 for superiority).

dabigatran (Pradaxa) versus warfarin

Dabigatran 150 mg orally twice daily was compared to adjusted-dose warfarin in patients with acute VTE who had been treated with parenteral anticoagulation for 5 to 11 days. RE-COVER (n=1,274) and RE-COVER II (n=2,589) were 2 multicenter, randomized double-blind trials conducted with identical study designs. A pooled analysis of both studies was reported.[183,184] Funding was provided by Boehringer Ingelheim for both trials. The studies were designed as non-inferiority trials and examined the 6-month incidence of recurrent, symptomatic, objectively-confirmed VTE and related deaths as their primary outcome measure. The pooled analysis of patients from both trials yielded a hazard ratio (HR) for recurrent VTE of 1.09 (95% CI, 0.76 to 1.57) for dabigatran compared with warfarin. Both trials independently, as well as the pooled analysis, indicated a trend toward less clinically relevant bleeding episodes with dabigatran compared to placebo, but the safety endpoint of major bleeding was not statistically significantly different (HR, 0.73; 95% CI, 0.48 to 1.11 for pooled analysis group).

dabigatran (Pradaxa) versus warfarin or placebo - extended treatment

Two randomized, double blind trials examined the use of dabigatran for extended treatment in patients who had already received a minimum of 3 months of anticoagulant therapy.[185] The RE-SONATE trial (n=1,343) compared dabigatran with placebo in patients who had received initial treatment for 6 to 18 months prior to being enrolled. The RE-MEDY trial (n=2,856) compared dabigatran to adjusted dose warfarin in patients who had previously received 3 to 12 months of anticoagulant therapy. The patients in the RE-MEDY trial were considered to be at an increased risk for recurrent VTE on the basis of the site investigator's assessment. Many of the patients in these trials were recruited from the population of patients who had been enrolled in the RE-COVER and RE-COVER II trials. Patients were followed for up to 36 months in the active control group and up to 12 months in the placebo group. In both studies, the primary outcome measure was recurrent symptomatic and objectively-verified VTE or death associated with VTE (or unexplained death in the placebo-controlled study). Safety outcomes included major bleeding and clinically relevant non major bleeding. In the placebo-controlled group (RE-SONATE trial), recurrent VTE occurred in 3 patients (0.4%) in the dabigatran group and 37 patients (5.6%) in the placebo group (p<0.001). No patients in the placebo group experienced major bleeding versus 2 patients in the dabigatran group. In the RE-MEDY trial, recurrent VTE occurred in 26 (1.8%) of the dabigatran patients and 18 (1.3%) of the warfarin patients (HR with dabigatran, 1.44; 95% CI, 0.78 to 2.64; p=0.01 for non-inferiority). Major bleeding occurred in 13 (0.9%) patients in the dabigatran group and in 25 (1.8%) of the patients receiving warfarin (HR 0.52; 95% CI, 0.27 to 1.02). Major or clinically relevant non major bleeding occurred less frequently with dabigatran (HR, 0.54; 95% CI, 0.41 to 0.71; p<0.001). Acute coronary syndromes occurred in 0.9% of patients in the dabigatran group and 0.2% in the warfarin group (p=0.02). These studies were funded by the manufacturer of dabigatran.

dabigatran (Pradaxa) in pediatrics

DIVERSITY: The safety and efficacy of dabigatran for the treatment of VTE in pediatric patients from birth to < 18 years of age were assessed in an open-label, randomized, parallel-group, noninferiority study.[186,187,188] Eligible patients (n=328) were stratified by age and randomized 2:1 to age- and weight-based dabigatran capsules, oral pellets, or oral solution (based on age) following 5 to 21 days of treatment with a parenteral anticoagulant or to standard of care (LMWH, VKA, fondaparinux). Those assigned to dabigatran received a possible titration following a drug concentration on before the 7th dose to target levels of 50 to 250 ng/mL. If the single titration did not result in target drug concentrations, the patient was removed from the study (occurred in 6.8%). Included patients were treated for a median duration of 85 days and were predominantly White (91.8%). Efficacy was assessed via a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Eighty-one of 177 patients (45.8%) in the dabigatran group compared to 38 of 90 (42.2%) in the standard of care group met the composite endpoint (difference in rate, -0.04; 95% CI, -0.14 to 0.07), meeting the predefined noninferiority margin of 20% (p<0.0001). Bleeding events occurred in 24% and 22% of standard of care- and dabigatran-treated patients, respectively (HR, 1.15; 95% CI, 0.68 to 1.94; p=0.61). Major bleeding events occurred in 2% of both groups (HR, 0.94; 95% CI, 0.17 to 5.16; p=0.95). Serious adverse events occurred in 20% of those treated with standard of care compared to 13% treated with dabigatran. No notable outliers were found following key subgroup analyses.

dalteparin (Fragmin) in pediatrics

A single-arm, open-label, clinical trial was conducted in 38 pediatric patients (ages < 2 years to ≤ 18 years) with (n=26) or without (n=12) cancer and symptomatic DVT and/or PE.[189] This study included 26 patients with an active malignancy and 12 patients without cancer. Patients were treated with dalteparin for up to 3 months, with the starting dose based on age and weight. The efficacy was based on achievement of therapeutic anti-Xa levels by day 7 of the dose adjustment period and supported by the number of patients with lack of VTE progression or new VTE. A total of 34 patients achieved a therapeutic anti-Xa level (0.5 to 1 IU/mL) in the 7-day dose adjustment period. The mean time to achieve a therapeutic anti-Xa level was 2.6 days (range, 1 to 7 days). At study end, 21 patients (62%) achieved resolution of the qualifying VTE, 7 patients (21%) showed regression, 2 patients (6%) showed no change, and no patients showed progression of the qualifying VTE. One patient (3%) experienced a new VTE during the study while on treatment.

edoxaban (Savaysa) versus warfarin

Hokusai-VTE was a randomized, double-blind, noninferiority study in 8,240 patients diagnosed with either DVT or PE who had initially received heparin (either LMWH or UFH).[190] Patients were randomized to edoxaban 60 mg daily or warfarin (target INR of 2 to 3) and followed for 12 months. Patients randomized to edoxaban who had a CrCl < 50 mL/min or a body weight < 60 kg or who were receiving verapamil, quinidine, or short-term concomitant therapy with azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole had their dose reduced to edoxaban 30 mg daily. The primary efficacy outcome was recurrent symptomatic VTE and the primary safety outcome was major or clinically relevant non-major bleeding. In the edoxaban group, 130 patients (3.2%) experienced a recurrent symptomatic VTE compared to 146 patients in the warfarin group (3.5%) (HR, 0.89; 95% CI, 0.7 to 1.13; p<0.001 for noninferiority). There were 349 (8.5%) patients in the edoxaban group who experienced major or clinically relevant non-major bleeding compared to 423 (10.3%) patients in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; p=0.004 for superiority).

enoxaparin (Lovenox) in pediatrics

A study with 27 children evaluated enoxaparin for the treatment of DVT.[191] Neonates through adolescents were included. Doses of enoxaparin administered were 1.5 mg/kg twice daily for neonates and infants, and 1 mg/kg twice daily for children. Mean duration of treatment was 16.5 days followed by a mean prophylaxis period of 9.8 months. Anti-Xa activity treatment goals were achieved in 85% of patients. Re-thrombosis and HIT were not observed in any patient in the study.

Children over 3 months old with DVT were treated with enoxaparin to a target 4-hour anti-factor Xa activity between 0.5 to 0.8 IU/mL.[192] In the open-label trial of 80 children, the patients were stratified to receive once daily or twice daily doses of enoxaparin for a median duration of 5 months. Endpoints were post-thrombotic syndrome, re-thrombosis, bleeding, and therapy-related death. No significant differences were observed between treatment groups. No bleeding or therapy-related deaths occurred. The median follow-up was 24 months.

enoxaparin (Lovenox) versus fondaparinux (Arixtra)

MATISSE DVT trial was a multicenter, double-blind study including 2,205 patients with acute symptomatic DVT. The patients were randomized to receive enoxaparin 1 mg/kg SC twice daily or fondaparinux 7.5 mg SC once daily for at least 5 days and until the INR was above 2.[193] Vitamin K antagonist therapy was initiated within 72 hours of either randomized therapy. Doses for fondaparinux were adjusted for patients weighing less than 50 kg (fondaparinux 5 mg SC daily) and more than 100 kg (fondaparinux 10 mg SC daily). The rates of recurrent thromboembolic events (primary outcome) were similar in the enoxaparin and fondaparinux groups (4.1% and 3.9%, respectively; p=NS). Major bleeding occurred in 1.2% of patients receiving enoxaparin and 1.1% of patients receiving fondaparinux (p=NS).

rivaroxaban (Xarelto) versus enoxaparin (Lovenox)/VKA

Rivaroxaban therapy was compared to enoxaparin/VKA therapy for the treatment of DVT and/or PE and for the reduction in the risk of recurrence of DVT and/or PE in the EINSTEIN DVT (n=3,449) and EINSTEIN PE (n=4,832), open-label, non-inferiority studies.[194,195,196] Rivaroxaban was administered orally at an initial dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily; enoxaparin 1 mg/kg twice daily was administered subcutaneously for at least 5 days with VKA and VKA was continued once target INR (2 to 3) was achieved. Rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE (EINSTEIN DVT HR, 0.68; 95% CI, 0.44 to 1.04); EINSTEIN PE HR, 1.12; 95% CI, 0.75 to 1.68). Primary endpoint occurred in 2.1% of patients in the rivaroxaban groups for both EINSTEIN DVT and EINSTEIN PE and occurred in 3% and 1.8% of patients in the rivaroxaban and enoxaparin/VKA groups, respectively. In a pooled analysis of EINSTEIN DVT and PE trials, nonfatal major bleeding was seen in 1% versus 1.7% of rivaroxaban versus enoxaparin/VKA group, with the same rate of intracranial hemorrhage, and comparable clinically relevant non major bleeding. A superiority extension study evaluated the risk of recurrence of DVT or PE in a double-blind fashion, comparing rivaroxaban (20 mg daily) to placebo in patients (n=1,196) who had completed 6 to 14 months of treatment for DVT and/or PE. The primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE was reported in 1.3% and 7.1% of patients on rivaroxaban and placebo, respectively (HR, 0.18; 95% CI, 0.09 to 0.39; p<0.0001). Nonfatal major bleeding was reported in 0.7% of rivaroxaban versus 0% of placebo patients, respectively (p=0.11).

rivaroxaban (Pradaxa) in pediatrics

The safety and efficacy of rivaroxaban for the treatment of VTE and reduction in the risk of recurrent VTE was assessed in a multicenter, open-label, active-controlled, randomized, phase 3 study (EINSTEIN Junior; NCT02234843) conducted in 500 pediatric patients from birth to < 18 years old with confirmed VTE.[197,198] The majority of children (n=276) were 12 to < 18 years old, 101 children were 6 to < 12 years, 69 children were 2 to < 6 years, and 54 children were < 2 years old. Following initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for ≥ 5 days, children were randomized 2:1 to either weight-based dosing of rivaroxaban (to align with 20 mg daily dose in adults) or comparator of UFH, LMWH, fondaparinux, or VKA for a 3- month treatment period (with the exception of children < 2 years with central venous catheter-related [CVC] VTE who received 1 month of therapy). When deemed clinically needed, therapy was extended for up to 12 months (up to 3 months for children < 2 years old with CVC-VTE). Following a median follow-up of 91 days in children with a treatment period of 3 months (n=463) and 31 days for children with a study treatment period of 1 month (n=37), the primary efficacy outcome of symptomatic recurrent VTE occurred in 1.2% (4/335; 95% CI, 0.4 to 3) of children receiving rivaroxaban compared to 3% (5/165; 95% CI, 1.2 to 6.6) of children in the standard anticoagulant arm (HR, 0.4; 95% CI, 0.11 to 1.41). Based on repeat imaging, thrombotic burden was significantly improved in children receiving rivaroxaban compared with standard anticoagulation (p=0.012). In terms of major or clinically relevant non-major bleeding, 3% (10/329; all non-major bleeding) of patients in the rivaroxaban arm compared with 2% (3/162; 2 major, 1 non-major) of patients in the standard anticoagulant arm (HR, 1.58; 95% CI, 0.51 to 6.27). Authors concluded treatment with rivaroxaban lead to a comparable low risk for recurrence and decreased thrombotic burden without an increased bleeding risk, compared to standard anticoagulant therapy.

Nonvalvular AF

Warfarin was approved in the US in 1954.[199] It has established itself as a highly effective strategy for the treatment of VTE and is often used with UFH, LMWH, or fondaparinux.[200] Adjusted-dose warfarin has also demonstrated efficacy for the long-term prevention of VTE recurrence in most patients.[201,202] The 2014 American Academy of Neurology (AAN) guidelines for the prevention of stroke in NVAF state warfarin dosing resulting in an INR of 2 to 3 likely reduces the frequency and severity of ischemic stroke as compared to anticoagulation resulting in lower INR levels.[203] Adjusted-dose warfarin has consistently established itself in randomized trials for prevention of stroke in younger (averaging about 70 years old) patients with NVAF.[204,205] Adjusted-dose warfarin has shown superiority to aspirin by demonstrating 54% relative risk reduction of stroke in older NVAF patients (≥ 75 years) with similar bleeding rates.[206]

dabigatran (Pradaxa) versus warfarin

Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial:[207] Dabigatran and warfarin were compared in a randomized, blinded, non-inferiority trial with 18,113 patients with atrial fibrillation and a risk for stroke over 2 years. Risk factors considered in the trial included previous stroke or TIA, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Patients were randomized to dabigatran 110 mg or 150 mg twice daily (blinded) or adjusted-dose warfarin (INR target 2 to 3; unblinded). In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range (INR 2 to 3) was 64%. The rate of stroke or systemic embolism, the primary outcome measure, was 1.69% in the warfarin group and 1.53% for dabigatran 110 mg group (relative risk: 0.91; 95% CI, 0.74 to 1.11; p<0.001 for non-inferiority) and 1.11% for dabigatran 150 mg group (relative risk, 0.66; 95% CI, 0.53 to 0.82; p<0.001 for superiority). Both doses of dabigatran were non-inferior to warfarin (p<0.001). Rates of major bleeding were 3.36%, 2.71%, and 3.11% for the warfarin, dabigatran 110 mg group (p=0.003), and dabigatran 150 mg group (p=0.31 versus warfarin), respectively. The rates of hemorrhagic stroke were 0.38% per year in the warfarin group, 0.12% per year with dabigatran 110 mg (p<0.001), and 0.1% per year with dabigatran 150 mg (p<0.001). Mortality rates were 4.13% per year in the warfarin group, 3.75% per year with dabigatran 110 mg (p=0.13), and 3.64% per year with dabigatran 150 mg (p=0.051). Both doses of dabigatran had a small but significantly higher rate of myocardial infarction (MI) versus warfarin, 0.72% per year for dabigatran 110 mg, 0.74% per year for dabigatran 150 mg, and 0.53% per year for warfarin. However, after study re-evaluation for adverse event under reporting, the MI rate was not significant.[208] The rate of reporting clinical myocardial infarction was 0.7 per 100 patient-years for dabigatran versus 0.6 per 100 patient-years for warfarin.

Dyspepsia was more common in the dabigatran 110 mg (11.8%) and 150 mg (11.3%) groups compared to the warfarin group (5.8%; both p<0.001). Follow up analysis of the data showed a lower rate of all-cause death with dabigatran 150 mg versus warfarin (3.6% versus 4.1%/year).[209] The rate of vascular death was lower on dabigatran versus warfarin (2.3%/year versus 2.7%/year). Non-vascular death rates were similar.

Previous warfarin exposure does not appear to influence the benefits of dabigatran.[210] An analysis of the RELY study found that, regardless of the individual center's quality of INR control, dabigatran maintained its benefits over warfarin.[211] However, these advantages were greater at centers with poor INR control. According to a pre-defined analysis, most effects of both doses of dabigatran versus warfarin were consistent in the subgroup of patients with previous stroke or TIA.[212,213] In an analysis that compared bleeding risks in the RELY trial, at both doses dabigatran compared to warfarin had lower risks of intracranial and extracranial hemorrhage in patients less than 75 years old (p<0.001 for all).[214] In patients 75 years of age and older, intracranial bleeding risk was lower for dabigatran versus warfarin but extracranial bleeding risk was similar or higher.

This study further examined the effects of dabigatran, compared to warfarin, on bleeding, stroke, and mortality in patients with AF by age since the risk of stroke and bleeding vary by age.[215] Patients were stratified by age: < 75 years (n=10,855), 75 to 79 years (n=4,231), 80 to 84 years (n=2,305), and ≥ 85 years (n=722). The benefits of dabigatran compared to warfarin regarding stroke (HR range, 0.63 [95% CI, 0.46 to 0.86] to 0.7 [95% CI, 0.31 to 1.57] for dabigatran 150 mg twice daily; HR range, 0.52 [95% CI, 0.21 to 1.29] to 1.08 [95% CI, 0.73 to 1.6] for dabigatran 110 mg twice daily) and intracranial bleeding were maintained throughout the age groups (p interaction values not significant). Compared to warfarin, both doses of dabigatran in younger adults was associated with lower rates of extracranial major bleeds (HR, 0.78 [95% CI, 0.62 to 0.97] for 150 mg twice daily; HR, 0.72 [95% CI, 0.57 to 0.9] for 110 mg twice daily) but similar (HR, 1.5 [95% CI, 1.03 to 2.18] for 110 mg twice daily) or higher rates (HR, 1.68 [95% CI, 1.18 to 2.41] for 150 mg twice daily) in patients ≥ 80 years (p< 0.001).

edoxaban (Savaysa) versus warfarin

ENGAGE AF-TIMI 48:[216] This was a randomized, double-blind, double dummy, international trial, with a median of 2.8 years, comparing 2 doses of edoxaban (30 mg or 60 mg) or warfarin (dose adjusted to achieve an INR of 2 to 3) in patients (n=21,105) with atrial fibrillation who were at moderate to high risk for stroke. Enrolled patients had either experienced a prior stroke (ischemic or unknown type), TIA, or a non-central nervous system embolism, or they had 2 or more of the following risk factors: age ≥ 75 years, hypertension, heart failure, or diabetes. The primary efficacy endpoint was the time to first occurrence of stroke or other systemic embolic event. The secondary endpoint was ischemic stroke, hemorrhagic stroke, systemic embolism, and a composite of deaths due to CV causes. The principal safety endpoint was major bleeding during treatment. During the treatment period, a stroke or systemic embolic event occurred in 232 patients in the warfarin group (representing a rate of 1.5% per year) as compared with 182 patients in the edoxaban 60 mg/day group (a rate of 1.18% per year; HR versus warfarin, 0.79; 97.5% CI, 0.63 to 0.99; p<0.001 for noninferiority, p=0.02 for superiority) and 253 patients in the edoxaban 30 mg/day group (a rate of 1.61% per year; HR versus warfarin, 1.07; 97.5% CI, 0.87 to 1.31; p=0.005 for noninferiority, p=0.44 for superiority). The annualized rate of hemorrhagic stroke was 0.47% with warfarin, as compared with 0.26% with edoxaban 60 mg daily (HR, 0.54; 95% CI, 0.96 to 1.34, p=0.1) and 0.16% with edoxaban 30 mg daily (HR, 0.33; 95% CI, 0.22 to 0.5; p<0.001). The rate of ischemic stroke was 1.25% with warfarin as compared with 1.25% with edoxaban 60 mg daily (HR, 1; 95% CI, 0.83 to

1.19; p=0.97) and 1.77% with edoxaban 30 mg daily (HR, 1.41; 95% CI, 1.19 to 1.67; p<0.001). Treatment with edoxaban was associated with lower annualized rates of death from CV causes than was warfarin: 3.17% with warfarin, as compared with 2.74% with edoxaban 60 mg daily (HR, 0.86; 95% CI, 0.77 to 0.97; p=0.01) and 2.71% with edoxaban 30 mg daily (HR, 0.85; 95% CI, 0.76 to 0.96; p=0.008). In the safety analysis, the annualized rate of major bleeding events was 3.43% with warfarin, as compared with 2.75% with edoxaban 60 mg daily (HR, 0.8; 95% CI, 0.71 to 0.91; p<0.001) and 1.61% with edoxaban 30 mg daily (HR 0.47; 95% CI, 0.41 to 0.55, p<0.001). The annualized rate of major GI bleeding was higher with edoxaban 60 mg daily than with warfarin (1.51% versus 1.23%). A sub-group analysis revealed that in patients with CrCl > 95 mL/min, the rate of ischemic stroke was higher in the edoxaban 60 mg group compared to warfarin (HR, 2.16; 95% CI, 1.17 to 3.97).

During the ENGAGE AF-TIMI 48 trial, reduced cardiovascular mortality was observed in edoxaban patients versus warfarin patients.[217] During the trial, there were 839 total deaths (4.35%/y) in warfarin-treated patients, 773 (3.99%/y, p= 0.08) with higher-dose edoxaban-treated patients, and 737 (3.8%/y, p=0.006) in the lower-dose edoxaban-treated patients. There were 124 fatal bleeds (65 warfarin patients, 35 higher-dose edoxaban-treated patients [p= 0.003], and 24 lower-dose edoxaban-treated patients [p<0.001]). There were 101 bleeding events with warfarin that were fatal or aided in death and 59 and 54 bleeding events leading to death in high- and lower-dose edoxaban therapy, respectively. There were no significant differences between treatments relating to the 3 most common causes of cardiovascular deaths, fatal malignancies, or other noncardiovascular deaths. Fewer total and cardiovascular deaths were observed with edoxaban-treated patients compared to warfarin-treated patients.

In the FDA-approved cohort of ENGAGE AF-TIMI 48, patients were older with higher $CHADS_2$ and HAS-BLED scores, and more were female as compared with patients not included in the FDA label.[218] The primary endpoint of stroke or systemic embolism occurred in 1.63%/year with edoxaban versus 2.02%/year with warfarin (HR, 0.81; 95% CI, 0.67 to 0.97, p=0.023). Edoxaban significantly reduced the rate of hemorrhagic stroke (HR, 0.47; 95% CI, 0.31 to 0.72; p<0.001) and cardiovascular death (HR, 0.84; 95% CI, 0.73 to 0.97; p=0.015). Ischemic stroke rates were similar between both the groups (1.31%/year versus 1.39%/year, p=0.97). The safety endpoint of major bleeding was also significantly lower in the edoxaban group (3.16%/year versus 3.77%/year; HR, 0.84; 95% CI, 0.72 to 0.98; p=0.023).

The ENGAGE AF-TIMI 48 study also explored outcomes in patients with AF with and without valvular heart disease (VHD).[219] Comparisons were made with the rates of stroke/systemic embolic event (SSEE), major bleeding, and additional efficacy and safety. The study concluded that non-VHD patients (n=18,222) compared to VHD patients (n=2,824) had higher rates of death but a similar rate of SSEE (HR, 1.4; 95% CI, 1.26 to 1.56; p<0.001), major adverse cardiovascular events (HR, 1.29; 95% CI, 1.16 to 1.43; p<0.001), and major bleeding (HR, 1.21; 95% CI, 1.03 to 1.42; p=0.02). The higher edoxaban regimen had similar efficacy to warfarin in patients with VHD for SSEE (HR, 0.69; 95% CI, 0.44 to 1.07 [VHD patients] and HR, 0.91; 95% CI, 0.77 to 1.07 [patients without VHD]; p interaction=0.2226) and for less major bleeding (HR, 0.74; 95% CI, 0.53 to 1.02 [VHD patients] and HR, 0.82; 95% CI, 0.71 to 0.94 [patients with no VHD]; p interaction=0.57). The risk of death, major adverse cardiovascular events, and major bleeding were increased in the presence of VHD but did not impact the relative efficacy and safety of higher dose edoxaban versus warfarin in atrial fibrillation.

In a prespecified subgroup analysis of the ENGAGE AF-TIMI 48 trial, the study compared warfarin with edoxaban in AF patients with and without previous ischemic stroke (IS)/TIA due to their high risk of recurrent cerebrovascular events despite anticoagulation.[220] Of the 5,973 patients with previous IS/TIA, 67% had CHADS (congestive heart failure, hypertension, age, diabetes, prior stroke/TIA) >3 and 36% of patients were ≥ 75 years old. Patients with previous IS/TIA were at a higher risk of thromboembolism and bleeding compared with the 15,132 patients without a previous IS/TIA (p <0.001). Annualized intracranial hemorrhage rates were lower in high-dose edoxaban than with warfarin in patients with previous IS/TIA (0.63% versus 1.09%; HR 0.57; 95% CI, 0.36 to 0.92; p= 0.02). Patients with AF and previous IS/TIA are at a high risk of recurrent thromboembolism and bleeding; high dose edoxaban is as effective as warfarin but safer regardless of previous IS/TIA status.

A detailed analysis of the ENGAGE AF-TIMI 48 trial also examined AF pattern and whether it modifies the risk/benefit of anticoagulation.[221] Patients (n=21,105) were grouped as having paroxysmal (< 7 days duration), persistent (≥ 7 days to < 1 year), or permanent (≥ 1 year or failed cardioversion) AF at randomization and monitored for 2.8 median years. The stroke/systemic embolic event was lower in patients with paroxysmal AF (1.49%/year) compared to persistent (1.83%/year; p-adj=0.015) and permanent (1.95%/year; p-adj= 0.004) AF. All-cause mortality was also lower with paroxysmal (3%/year) compared with persistent (4.4%/year; p-adj < 0.001) and permanent (4.4%/year, p-adj < 0.001) AF. Patients with paroxysmal AF had fewer thromboembolic events compared to persistent and permanent AF patients. The efficacy and safety of edoxaban compared to warfarin were consistent across the 3 AF pattern groups.

rivaroxaban (Xarelto) versus warfarin

Rivaroxaban Once-daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF):[222] This was a randomized, double-blind, multinational, phase 3 trial in 14,264 patients with NVAF at increased risk for stroke. Patient risk factors included either 2 or more of the following: CHF, hypertension, age ≥ 75 years, diabetes; or a history of 1 of the following: stroke, TIA, or systemic embolus. The study compared once daily rivaroxaban to warfarin for the primary endpoint of non-inferiority for prevention of stroke and systemic embolism in NVAF. The median duration of the study was 590 days. Rivaroxaban was given at a dose of 20 mg once daily with the evening meal in patients with CrCl ≥ 50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to <50 mL/min. Warfarin was titrated to INR 2 to 3. Mean time in therapeutic range with warfarin was 55%.[223] Although in the as-treated safety population, the p-value was significant (p<0.02) for rivaroxaban versus warfarin, in the intention-to-treat analysis, the composite primary endpoint was demonstrated for non-inferiority, but not for superiority to warfarin; composite primary endpoint of 3.8% compared to 4.3% for rivaroxaban compared to warfarin (p<0.001 for non-inferiority; HR, 0.88; 95% CI, 0.74 to 1.03; p=0.12 for superiority). Major and non-major bleeding was 14.9%/year versus 14.5%/year for rivaroxaban versus warfarin (HR, 1.03; 95% CI, 0.96 to 1.11; p=0.44). There was no difference in overall major and other clinically relevant bleeding between groups. Major bleeding was seen in 5.6% versus 5.4% of rivaroxaban versus warfarin, respectively. More events were observed with transfusion hemorrhage (2.6% versus 2.1%; p<0.045) and GI bleed (3.1% versus 2%; p<0.02). Fewer events were observed with hemorrhage into a critical organ, mostly intracranial (1.3% versus 1.9%; p=0.007) and fatal bleeds (0.4% versus 0.8%; p=0.003), for rivaroxaban versus warfarin, respectively. Intracranial bleeds alone were observed in 0.8% versus 1.2% of rivaroxaban and warfarin patients, respectively (p<0.02).

A pre-specified secondary analysis of the ROCKET-AF trial compared the safety and efficacy outcomes of rivaroxaban with warfarin in patients aged less than 75 years to those 75 years and older.[224] Forty-four percent of patients in this analysis were at least 75 years of age. In both treatment arms, older patients experienced more stroke and systemic embolism (2.57 versus 2.05%/100 patient-years; p-0.0068) and major bleeding (4.63 versus 2.74%/100 patient-years; p<0.0001) as compared to younger patients. However, rates of stroke/systemic embolism (SE) and major bleeding were consistent among older and younger patients; for ≥75 years stroke/SE rate of 2.29% on rivaroxaban and 2.85% on warfarin per 100 patient-years (HR, 0.8; 95% CI, 0.76 to 1.19); for < 75 years stroke/SE rate of 2% on rivaroxaban versus 2.1% on warfarin per 100 patient-years (HR, 0.95; 95% CI, 0.75 to 1.19; for ≥ 75 years major bleeding rates of 4.86% for rivaroxaban and 4.4% for warfarin per 100 patient-years (HR, 1.11; 95% CI, 0.92 to 1.34); for < 75 years major bleeding rates of 2.69% on rivaroxaban and 2.79% on warfarin per 100 patient-years. Hemorrhagic stroke rates were similar in both age groups.

apixaban (Eliquis) versus warfarin

The ARISTOTLE trial was a randomized, double-blind study that compared apixaban 5 mg twice daily with dose-adjusted warfarin (target INR 2 to 3) in 18,201 patients with AF and at least 1 additional risk factor for stroke (age ≥ 75 years; previous stroke, TIA, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction (LVEF) ≤ 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment).[225,226] The dose of apixaban was reduced (2.5 mg twice daily) in patients with at least 2 of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. The median duration of follow-up was 1.8 years. Mean age was 69 years. The primary outcome of ischemic or hemorrhagic stroke or systemic embolism occurred in 1.27% per year in the apixaban group, and 1.6% per year in the warfarin group (HR for apixaban 0.79; 95% CI, 0.66 to 0.95; p<0.001), or a 21% relative risk reduction (RRR) for apixaban compared to warfarin. The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (HR, 0.51; 95% CI, 0.35 to 0.75; p<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74 to 1.13; p=0.42). Apixaban was found to be superior to warfarin in preventing stroke or systemic embolism, primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs. The primary safety outcome of major bleeding occurred in 2.13% per year in the apixaban arm, and 3.09% per year in the warfarin arm, or a 31% RRR for apixaban compared to warfarin. Apixaban resulted in an 11% RRR in the secondary endpoint of all-cause mortality compared to warfarin primarily due to a reduction in CV death and particularly stroke deaths (3.52% to 3.94%; HR, 0.89; 95% CI, 0.8 to 0.99; p=0.047). The ARISTOTLE trial was funded by the manufacturers of apixaban.

The AVERROES study randomized 5,599 patients with AF who were at increased risk for stroke and who were not candidates for warfarin therapy, to receive apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 mg to 324 mg daily. Mean duration of follow-up was 1.1 years. The primary outcome was occurrence of stroke or systemic embolism.[227,228] A total of 51 primary outcome events (1.6% per year) occurred in the apixaban group and 113 events (3.7% per year) in the aspirin group. Forty-four cases (1.4% per year) of major bleeding were reported with apixaban use, and 39 (1.2% per year) with aspirin use (HR with apixaban, 1.13; 95% CI, 0.74 to 1.75; p=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin (p=0.69). The risk of a first hospitalization for CV causes was reduced with apixaban compared with aspirin (12.6% per year versus 15.9% per year, p<0.001). AVERROES was stopped early based on a prespecified interim analysis that reported a significant reduction in stroke and systemic embolism for apixaban compared to aspirin that was associated with a modest but not statistically significant increase in major bleeding. The AVERROES trial was funded by the manufacturers of apixaban.

Coronary Artery Disease (CAD) and Peripheral Artery Disease (PAD)

rivaroxaban plus aspirin versus aspirin

COMPASS:[229,230] Safety and efficacy of rivaroxaban to reduce the risk of stroke, MI, or CV death in patients with CAD or PAD was assessed in 27,395 patients randomized to rivaroxaban 2.5 mg twice daily plus aspirin (100 mg daily), rivaroxaban 5 mg twice daily alone, or aspirin 100 mg once daily alone. Mean follow-up duration was 23 months. The rivaroxaban 5 mg alone was not superior to aspirin 100 mg alone. In the included population, 91% had CAD, and 27% had PAD (18% had both). Rivaroxaban 2.5 mg plus aspirin reduced the incidence of the composite of CV death, MI, or stroke compared to aspirin alone (4.1% versus 5.4%, respectively; HR, 0.76; 95% CI, 0.66 to 0.86). Looking at each component, reductions were seen for CV death (HR, 0.78; 95% CI, 0.64 to 0.96) and stroke (HR, 0.58; 95% CI, 0.44 to 0.76) but not for MI (HR, 0.86; 95% CI, 0.7 to 1.05). Major bleeding events were reported more often in the combination group than those who received aspirin alone (3.1% versus 1.9%, respectively; HR, 1.7; 95% CI, 1.4 to 2.05), but no difference in intracranial or fatal bleeding were reported. In the COMPASS-CAD population (n=16,574), rivaroxaban 2.5 mg twice daily plus aspirin reduced the incidence of the composite of CV death, MI, or stroke compared to aspirin alone (annual event rate, 2.2% versus 2.9%, respectively; HR, 0.74; 95% CI, 0.65 to 0.86). Looking at each component in the COMPASS-CAD population, reductions were seen for CV death (HR, 0.75; 95% CI, 0.6 to 0.93) and stroke (HR, 0.56; 95% CI, 0.42 to 0.75) but not for MI (HR, 0.86; 95% CI, 0.7 to 1.05). In the COMPASS-PAD population (n=4,996), rivaroxaban 2.5 mg plus aspirin reduced the incidence of the composite of major thrombotic events (MI, ischemic stroke, CV death, acute limb ischemia, and major amputation of a vascular etiology) compared to aspirin alone (annual event rate, 3.4% versus 4.8%, respectively; HR, 0.71; 95% CI, 0.57 to 0.87). Looking at each component in the COMPASS-PAD population, reductions were seen for stroke (HR, 0.55; 95% CI, 0.33 to 0.93), acute limb ischemia (HR, 0.56; 95% CI, 0.32 to 0.99), and major amputation of a vascular etiology (HR, 0.4; 95% CI, 0.2 to 0.79) but not for MI (HR, 0.76; 95% CI, 0.53 to 1.09) and CV death (HR, 0.82; 95% CI, 0.59 to 1.14).

VOYAGER:[231,232] Safety and efficacy of rivaroxaban to reduce the risk of MI, ischemic stroke, CV death, acute limb ischemia, and major amputation of a vascular etiology in patients undergoing a lower extremity infrainguinal revascularization procedure due to symptomatic PAD was assessed in 6,564 patients randomized 1:1 to rivaroxaban 2.5 mg twice daily plus aspirin (100 mg daily) or aspirin 100 mg once daily alone. Included patients were ≥ 50 years of age with documented moderate to severe symptomatic lower extremity atherosclerotic PAD. Patients were followed for a median duration of 30.8 months, and the mean age was 67 years (20% ≥ 75 years). Rivaroxaban 2.5 mg twice daily plus aspirin reduced the incidence of the composite of major thrombotic events (MI, ischemic stroke, CV death, acute limb ischemia, and major amputation of a vascular etiology) compared to aspirin alone (annual event rate, 6.8% versus 8%, respectively; HR, 0.85; 95% CI, 0.76 to 0.96; p=0.0085). Regarding individual components, a reductions was seen for acute limb ischemia (HR, 0.67; 95% CI, 0.55 to 0.82) but not for MI (HR, 0.88; 95% CI, 0.7 to 1.12), ischemic stroke (HR, 0.87; 95% CI, 0.63 to 1.19), CV death (HR, 1.14; 95% CI, 0.93 to 1.4), and major amputation of a vascular etiology (HR, 0.89; 95% CI, 0.68 to 1.16). In addition, rivaroxaban 2.5 mg plus aspirin reduced the incidence of hospitalization for a coronary or peripheral cause of a thrombotic nature (HR, 0.72; 95% CI, 0.62 to 0.85; p<0.0001). Thrombolysis in

Myocardial Infarction (TIMI) major bleeding occurred in 2.65% of patients in the rivaroxaban group compared to 1.87% in the placebo group (HR, 1.43; 95% CI, 0.97 to 2.1; p=0.07).

Thromboprophylaxis in Congenital Heart Disease Patients

rivaroxaban (Pradaxa) in pediatrics

The efficacy and safety of rivaroxaban used for thromboprophylaxis following the Fontan procedure in pediatric patients with congenital heart disease was evaluated in a prospective, open-label, active-controlled, multicenter, phase 3 study (UNIVERSE; NCT02846532).[233,234] The first part of the study evaluated the single and multiple-dose pharmacokinetics of rivaroxaban and the second part assessed use as thromboprophylaxis for 12 months compared to aspirin. Patients 2 to 8 years old with single ventricle physiology who had received the Fontan procedure were randomized 2:1 to either weight-based dosing of rivaroxaban (to align with drug levels of 10 mg daily dose in adults) or aspirin at approximately 5 mg/kg. In part-1 of the study, 12 patients received rivaroxaban to determine the pharmacokinetic/pharmacodynamic and safety of the drug; the median time to initiation of rivaroxaban following the Fontan procedure was 4 days (range, 2 to 61 days). In part-2 of the study, patients were randomized to rivaroxaban (n=64, including 10 patients from part 1) or aspirin (n=34); the median time until initiation of rivaroxaban was 34 days (range, 2 to 124 days); the median time to starting aspirin was 24 days (range, 2 to 117 days). The primary efficacy outcome was any thrombotic event which occurred in 1.6% (1/64; 95% CI, 0.1 to 7.8) of patients in the rivaroxaban study group compared with 8.8% (3/34; 95% CI, 2.4 to 22.2) of patients in the aspirin arm, resulting in a risk difference of -7.3% (95% CI, -21.7 to 1.1). In terms of safety, 1 patient in the rivaroxaban group experienced a major bleeding event, epistaxis requiring transfusion, and clinically relevant non-major bleeding occurred in 6% of patients in the rivaroxaban arm compared to 9% who received aspirin. Trivial bleeding was similar between study arms (33% versus 35%, respectively). Authors concluded children who received rivaroxaban demonstrated comparable safety and less thrombotic events, although this different was not statistically significant, compared to thromboprophylaxis with aspirin.

Efficacy of Injectable Anticoagulants[235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267]

Drug	Prophylaxis: Development of post-operative DVT (%)				Treatment: Recurrent VTE (%)
	Hip Replacement	Knee Replacement	Hip Fracture Surgery	Abdominal Surgery	
enoxaparin (Lovenox)	6-38	19-37	*19.1	9.7	3.3-4.1
fondaparinux (Arixtra)	1.7-5.6	12.5	8.3	4.2	3.9

*off-label

Review of overall occurrence of DVT in patients undergoing orthopedic surgery does not reveal any significant advantage of one LMWH over another for prophylaxis. While fondaparinux (Arixtra) has been shown to reduce the development of post-operative DVT to a greater extent than enoxaparin, this risk reduction can be accompanied by an increase in risk of bleeding. Administration of fondaparinux before 6 hours after surgery has been associated with an increased risk of major bleeding.[268] After hemostasis has been established, the recommended timing of the first fondaparinux injection is 6 to 8 hours after surgery.

Examination of data from VTE treatment trials reveals similar overlap in frequency of events, as well as between-study variability.

META-ANALYSES

Prevention or Treatment of VTE

Two different meta-analyses evaluated the randomized, controlled trials of LMWH versus UFH in the treatment of acute DVT.[269,270] The LMWHs were shown to reduce mortality rates after acute DVT and appeared as safe as UFH and provide similar efficacy. Initial therapy of PE with LMWH also appears as effective as UFH.

A Cochrane database systemic review evaluated the safety and efficacy of 3 types of anticoagulants: LMWH, UFH, and fondaparinux (Arixtra) for the initial treatment of VTE in cancer patients.[271] A meta-analysis of 11 studies showed a statistically significant mortality reduction at 3 months of follow-up in patients treated with LMWH compared with those treated with UFH (relative risk [RR], 0.71; 95% CI, 0.52 to 0.98). A meta-analysis of 3 studies comparing LMWH with UFH in reducing recurrent VTE showed no statistically significant reduction (RR, 0.78; 95% CI, 0.29 to 2.08). The overall quality of evidence was low for LMWH compared to UFH due to imprecision and potential publication bias. There were no statistically significant differences between UFH and fondaparinux for death (RR, 1.27; 95% CI, 0.88 to 1.84), recurrent VTE (RR, 0.95; 95% CI, 0.57 to 1.6), major bleeding (RR, 0.79; 95% CI, 0.39 to 1.63), or minor bleeding (RR, 1.5; 95% CI, 0.87 to 2.59). The study results support LMWH over UFH in the initial treatment of VTE cancer patients.

A meta-analysis of 4 randomized, double-blind, multicenter trials for prevention of VTE in 7,344 patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture compared SC fondaparinux 2.5 mg daily starting 6 hours after surgery to SC enoxaparin regimens.[272] Fondaparinux significantly reduced the primary efficacy outcome of VTE by day 11 compared with enoxaparin, 6.8% versus 13.7%, respectively (common odds reduction of 55.2%; 95% CI, 45.8 to 63.1%; p<0.001). Fondaparinux as compared to enoxaparin resulted in increased risk of major bleeding, 2.7% versus 1.7%, respectively (p=0.008). However, the incidence of clinically relevant bleeding (leading to death or re-operation or occurring in a critical organ) did not differ between groups. In a post-hoc efficacy and safety analysis, the incidence of major bleeding was significantly less in patients receiving fondaparinux ≥ 6 hours versus < 6 hours following surgery (e.g., skin closure), 2.1% versus 3.2%, respectively.[273] There was no significant difference in the incidence of VTE at these different time points.

A systematic review evaluated randomized controlled trials of dabigatran (150 mg and 220 mg daily) and rivaroxaban (10 mg daily) compared with enoxaparin (40 to 60 mg daily) in elective orthopedic surgery.[274] Hemorrhagic events were defined as major and clinically relevant non-major bleeds. Rivaroxaban was superior to enoxaparin for the prevention of VTE (RR, 0.56; 95% CI, 0.43 to 0.73; p<0.0001), with a non-significant trend for increased hemorrhage (RR, 1.26; 95% CI, 0.94 to 1.69; p=0.13). Dabigatran was not superior to enoxaparin for prevention of VTE (RR 1.12, 95% 0.97-1.29, p=0.12). Dabigatran did not reduce hemorrhage risk (RR, 1.1; 95%, 0.9 to 1.35; p=0.32). Adjusted indirect comparison for the pooled relative risks showed that rivaroxaban was superior to dabigatran in preventing VTE (RR, 0.5; 95% CI, 0.37 to 0.68) but with a slight trend towards increased hemorrhage RR, 1.14 (95% CI, 0.8 to 1.64).

A meta-analysis was conducted to compare the efficacy and safety of anticoagulants for the extended treatment of VTE, especially since alternatives (apixaban, dabigatran, edoxaban, rivaroxaban) to warfarin and aspirin are now available.[275] Eleven phase 3, randomized, controlled trials were included in the meta-analysis. The risk of VTE and VTE-related death was statistically significantly lower with NOAC and warfarin (INR 2 to 3) therapy compared to aspirin; however, there were no significant differences between the NOACs noted. Compared to warfarin (INR 2 to 3), apixaban (relative risk [RR] 0.23; 95% credible interval [Crl] 0.10 to 0.55) and dabigatran (RR, 0.55; 95% CrI, 0.43 to 0.71) were associated with a statistically significant risk reduction in major or clinically relevant non-major bleed. Apixaban also showed a significantly reduced risk compared to rivaroxaban (RR, 0.23; 95% CrI, 0.09 to 0.59) and dabigatran (RR, 0.42; 95% Crl, 0.18 to 0.97). NOACs are effective in preventing VTE or VTE-related death for extended therapy but the bleeding risk differs between therapies. Apixaban had the most favorable profile compared to other NOACs, aspirin, or warfarin (INR 2 to 3).

A meta-analysis of 5 randomized, controlled clinical trials evaluated the efficacy and safety of rivaroxaban versus enoxaparin in patients who underwent total knee arthroplasty (TKA).[276] Rivaroxaban was associated with lower rates of symptomatic VTE (RR, 0.55; 95% CI, 0.35 to 0.86; p=0.009), symptomatic DVT (RR, 0.44; 95% CI, 0.25 to 0.8; p=0.007), asymptomatic DVT (RR, 0.57; 95% CI, 0.37 to 0.89; p=0.01), distal DVT (RR, 0.62; 95% CI, 0.45 to 0.85; p=0.003), and proximal DVT (RR, 0.42; 95% CI, 0.24 to 0.75; p=0.004). However, the incidence of symptomatic PE (RR, 0.48; 95% CI, 0.19 to 1.24; p=0.13) in the rivaroxaban group was not significantly different than the enoxaparin group. No statistical difference was seen in all-cause death (RR, 0.38; 95% CI, 0.03 to 4.92; p=0.46) or major bleeding (RR, 1.59; 95% CI, 0.77 to 3.27; p=0.21).

A meta-analysis compared the efficacy of VTE prophylaxis with LMWH versus factor Xa inhibitors and direct thrombin inhibitors in patients undergoing TKA or total hip arthroplasty (THA).[277] Thirty-two randomized, controlled clinical trials were included in the meta-analysis. Patients undergoing TKA or THA who were treated with LMWH had a higher major VTE rate than those treated with factor Xa inhibitors (TKA: OR, 1.88; 95% CI, 1.27-2.77; p=0.002) (THA: OR, 3.32, 95% CI, 1.77 to 6.2; p<0.001). The major VTE rate for TKA patients receiving LMWH and direct thrombin inhibitors was similar (p>0.05) while THA patients receiving LMWH had a higher major VTE rate compared to direct thrombin inhibitors (OR, 1.51; 95% CI, 1.05 to 2.18; p=0.025). The DVT rate was similar for TKA patients who received LMWH versus factor Xa inhibitors or direct thrombin inhibitors and for THA patients who received LMWH versus direct thrombin inhibitors (p>0.05). THA patients who were treated with LMWH had a higher DVT rate than those treated with factor Xa inhibitors (OR, 2.31; 95% CI, 1.42 to 3.76; p=0.001). No differences were seen in major bleeding rate (p>0.05).

A network meta-analysis compared the efficacy of venous thromboembolism prophylaxis strategies in patients undergoing total knee replacement.[278] Twenty-five randomized, controlled trials were included. Rivaroxaban was ranked the most effective strategy for prevention of DVT (RR 0.12; 95% CI, 0.06 to 0.22) followed by apixaban (RR 0.15; 95% CI, 0.07 to 0.26), then LMWH (RR 0.18; 95% CI, 0.1 to 0.3).

A network meta-analysis compared the efficacy and safety of 9 anticoagulants for VTE prophylaxis in patients undergoing TKA or THA.[279] Thirty-five randomized, controlled clinical trials were included in the meta-analysis. Fondaparinux (88.89% ± 10.9%), edoxaban (85.87% ± 13.34%), and rivaroxaban (86.08%

± 10.23%) were ranked as the most effective anticoagulants for DVT prevention using the Bayesian methods for ranking probability of efficacy. In terms of safety, fondaparinux (14.53% ± 15.25%), ximelagatran (18.93% ± 17.49%), and rivaroxaban (23.86% ± 15.14%) were associated with the lowest rates of clinically relevant bleeding events.

Reduction in Risk of Stroke or Systemic Embolism in Nonvalvular Atrial Fibrillation Patients

A meta-analysis evaluated 7 trials (n=30,514) of dabigatran that reported on MI or ACS as secondary outcomes, including 2 stroke prophylaxis in atrial fibrillation studies, 1 in acute VTE, 1 in ACS, and 3 short-term prophylaxis of DVT.[280] In the studies, dabigatran was compared to control arms (warfarin, enoxaparin, or placebo). Dabigatran was significantly associated with a higher risk of MI or ACS compared with the controls (dabigatran, 1.19% versus control, 0.79%; OR, 1.33; 95% CI, 1.03 to 1.71; p=0.03). The risk of MI or ACS was similar when using revised RELY trial results (OR, 1.27; 95% CI, 1 to 1.61; p=0.05) or after exclusion of short-term trials (OR, 1.33; 95% CI, 1.03 to 1.72; p=0.03).

A recent meta-analysis evaluated 42,411 atrial fibrillation patients who were receiving a new anticoagulant and 29,272 atrial fibrillation patients who received warfarin across 4 large trials, RELY (dabigatran), ROCKET AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF-TIMI 48 (edoxaban).[281] Edoxaban is not FDA-approved for this use. The primary efficacy outcome examined was stroke or systemic embolic events and the primary safety outcome examined was major bleeding. The authors calculated relative risks (RRs) and corresponding 95% confidence intervals for each outcome. Data collected from the individual trials included stroke and systemic embolic events, ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial hemorrhage (including hemorrhagic stroke, epidural, subdural, and subarachnoid hemorrhage), and GI bleeding. Median follow-up ranged from 1.8 years to 2.8 years. Important clinical subgroups examined included age (< 75 versus > 75 years), gender, history of previous stroke or TIA, history of diabetes, renal function (CrCl < 50 mL/min, 50 to 80 mL/min, > 80 mL/min), vitamin K antagonist status at study entry (naïve or experienced), and center-based time in the therapeutic INR range (mean time in therapeutic INR range at each enrolling center for patients randomized to warfarin). The results indicated that allocation to a new oral anticoagulant significantly reduced the composite of stroke or systemic embolic events by 19%, mainly driven by a large reduction in hemorrhagic stroke (RR, 0.49; 95% CI, 0.38 to 0.64; p<0.0001). New oral anticoagulants were also associated with a significant reduction in all-cause mortality (RR, 0.9; 95% CI, 0.85 to 0.95; p<0.0003]). Randomization to a new oral anticoagulant (at therapeutic doses) was associated with a 14% non-significant reduction in major bleeding. There was a substantial reduction in intracranial hemorrhage (RR, 0.48; 95% CI, 0.39 to 0.59; p<0.0001) with the newer anticoagulants compared to warfarin but the new oral anticoagulants were associated with an increased rate of GI bleeding (RR, 1.25; 95% CI, 1.01 to 1.55; p=0.043). The benefit of new oral anticoagulants compared with warfarin in reducing stroke or systemic embolic events was consistent across all subgroups described above. For the prevention of ischemic stroke, the new oral anticoagulants had similar efficacy to warfarin. These results concluded the newer anticoagulants have similar efficacy to warfarin (prevention of ischemic stroke) but have a better safety profile (less incidence of hemorrhagic strokes or intracranial bleeding) despite the increased incidence of GI bleeding with the newer anticoagulants. Taken as a whole, the new oral anticoagulants, as a class, reduced all-cause mortality by about 10% in the study population.

A meta-analysis from data involving 4 randomized, controlled trials of non-vitamin K antagonist oral anticoagulants (NOACs) (apixaban, rivaroxaban, dabigatran, edoxaban) was performed to assess the efficacy and safety of treating with both NOACs and aspirin or other antiplatelet drugs for stroke prevention.[282] The studies included 42,411 patients and of those patients 14,148 patients were also on aspirin or another antiplatelet medication. The number of thrombotic and bleeding events was compared between patients taking combination NOAC plus aspirin/antiplatelet to NOAC alone. These results were then compared with therapy with warfarin plus aspirin/antiplatelet or warfarin alone. In the nonrandomized comparison, there was an initial trend towards higher thromboembolic rates with NOAC users also on aspirin/antiplatelet medications (relative risk [RR] 1.16; 95% CI, 1.05 to 1.29) versus NOAC alone which was likely contributed to the higher CHADS2 score in patients on aspirin/antiplatelets. The analysis was also limited to studies that only included aspirin rather than other antiplatelet medications and no difference was seen in thromboembolic rates comparing NOAC alone to combination therapy (RR 1.02; 95% CI, 0.90 to 1.15). Patients on dual therapy had higher bleeding rates. There was no greater risk of thromboembolism in NOAC alone versus NOAC and aspirin/antiplatelet dual therapy and there was no additional benefit seen for stoke between the 2 groups. However, there was an increased risk of bleeding.

Another meta-analysis was performed that examined the data on efficacy and safety of NOACs after cardioversion when risk of thromboembolic events is elevated.[283] NOACs are proven alternatives to vitamin K antagonists (VKAs) for the prevention of thromboembolism in patients with nonvalvular AF. This meta-analysis examined the RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, and X-VeRt trials with patients who underwent both electrical and pharmacological cardioversion for AF. The trials included 3,949 patients who went through 4,900 cardioversions. When comparing VKA and NOAC therapy, a similar risk of stroke/systemic embolism (relative risk [RR] 0.84; 95% CI, 0.34 to 2.04) and major bleeds (RR 1.12; 95% CI, 0.52 to 2.42) occurred. However, no statistically significant heterogeneity was found among studies (Cochrane Q p=0.59; I^2=0% for stoke/systemic embolism; p= 0.47; I^2=0% for major bleeding). When comparing NOACs to dose-adjusted VKA therapy, short-term thromboembolic and major hemorrhage were low and comparable.

A meta-analysis was designed to assess the relative efficacy of several clinical events with anticoagulants in patients with AF. Clinical data from 37 studies involving several anticoagulants for AF were reviewed.[284] The studies revealed patients treated with apixaban and rivaroxaban have a reduced risk of stroke compared to patients treated with warfarin (odds ratio [OR] 0.68; 95% Crl, 0.48 to 0.91; OR 0.72; 95% Crl, 0.53 to 0.88). Rivaroxaban was the most preferable medication in respect to vascular events (surface under the cumulative ranking curve [SUCRA]=0.712). Apixaban and rivaroxaban are preferred to other medications with respect to stroke, SUCRA= 0.72 and 0.678, respectively. When examining mortality (SUCRA=0.695), hemorrhage events (SUCRA=0.747), and MI (SUCRA=0.62), dabigatran outperforms other medications. The meta-analysis concluded that apixaban may be the best medication for preventing stroke; rivaroxaban may be the best for preventing cardiovascular events; and dabigatran had a notable and comprehensive advantage to other medications in preventing hemorrhage, MI, and mortality.

A meta-analysis was conducted evaluating data from 6 randomized, controlled clinical trials evaluating the efficacy and safety of dabigatran compared with warfarin in 20,086 patients with NVAF.[285] No significant difference was found between dabigatran 110 mg and warfarin in the incidence of stroke (RR, 0.9; 95% CI, 0.71 to 1.12; p=0.34) or embolic events (RR, 0.89; 95% CI, 0.71 to 1.12; p=0.32); however, dabigatran 110 mg was associated with a lower incidence of bleeding (RR, 0.81; 95% CI, 0.69 to 0.95; p=0.01) compared to warfarin. Warfarin was associated with a no statistical different in rate of stroke (RR, 0.96; 95% CI, 0.83 to 1.12; p=0.62) or bleeding (RR, 0.67; 95% CI, 0.53 to 0.86; p=0.001), but it was associated with fewer embolic events (RR, 0.67; 95% CI, 0.53 to 0.86; p=0.001) compared to dabigatran 150 mg. Dabigatran 150 mg is the approved dose in NVAF.

A systematic review and meta-analysis compared the efficacy and safety of DOACs to warfarin stratified by time in goal INR range (n=71,681; 4 RCTs [RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE-AF-TIMI]).[286] INR results were categorized based on time in range as low, intermediate, and high. The authors determined that DOAC-treated patients had lower hazard ratios (statistically significant) compared to warfarin-treated patients, regardless of time in INR goal range. In addition, the risk of intracranial hemorrhage was lower in DOAC-treated patients compared to warfarin-treated patients, regardless of time in INR goal range. Major bleeding risk was similar in those in the high degree of time in goal INR range between both groups, but the risk was lower with DOAC-treated patients compared to those treated with warfarin in the low or intermediate time in goal INR range groups.

Comparison of Novel Oral Anticoagulants in the Initial and Long-Term Treatment and Prevention of VTE

Another meta-analysis conducted in July 2014 systematically searched electronic databases to identify randomized controlled trials evaluating apixaban, dabigatran, edoxaban, and rivaroxaban versus LMWH and VKAs. Eligibility criteria included adult patients with confirmed DVT, PE, or both.[287] A total of 6 phase 3 randomized controlled trials met the inclusion criteria: apixaban (1 RCT; n=5,395); rivaroxaban (2 RCTs; n=3,423/4,832); dabigatran (2 RCTs; n=2,539/2,568); edoxaban (1 RCT; n=8,240). A fixed-effect Bayesian network meta-analysis (NMA) was then performed to compare the efficacy and safely of oral anticoagulants used for both initial and long-term treatment of VTE. Among the 6 trials (AMPLIFY, RE-COVER, RE-COVER II, Hokusai-VTE, EINSTEIN DVT and EINSTEIN PE) that met the inclusion criteria, there were found to be no statistically significant differences between the new oral agents with respect to the risk reduction of VTE or VTE-related death. Treatment with apixaban was significantly safer with respect to risk reduction of major or clinically relevant non-major bleed compared to the other agents. Additionally, dabigatran was found to be associated with a lower bleeding risk in comparison to rivaroxaban and edoxaban.

SUMMARY

The injectable anticoagulants, low molecular weight heparins (LMWHs) and fondaparinux (Arixtra), are important treatment options in deep vein thrombosis (DVT) and pulmonary embolism (PE) management. They offer advantages over unfractionated heparin (UFH) including lack of need for laboratory coagulation monitoring, ease of dosing, and reduced risk of heparin-induced thrombocytopenia (HIT). LMWHs have been shown to reduce mortality rates after acute DVT and provide similar efficacy as UFH. Initial therapy of PE with LMWH also appears as effective as UFH. When used in equipotent dosages, all the LMWHs will provide a therapeutic anticoagulant effect. While subcutaneous (SC) anticoagulants have subtle differences in methods of preparation, pharmacokinetic parameters, and anti-Xa activity, the clinical characteristics are similar.

The appropriate duration of treatment for venous thromboembolism (VTE) is usually a minimum of 3 months and may be extended for a much longer period depending on the indication and the patient's individual risk factors. After initial treatment for a minimum of 5 days with a parenteral anticoagulant (UFH, LMWH, fondaparinux [Arixtra]), current evidence supports the use of either a parenteral agent, warfarin, dabigatran (Pradaxa), or edoxaban (Savaysa) for the remaining duration of the anticoagulation therapy. Evidence also supports the use of rivaroxaban (Xarelto) or apixaban (Eliquis) for the treatment of DVT without the requirement for initial treatment with a parenteral anticoagulant.

Dalteparin (Fragmin) is also approved for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients ≥ 1 month of age. Dabigatran (Pradaxa) is approved for the treatment of VTE in pediatric patients ≥ 3 months old who have been treated with a parenteral anticoagulant for ≥ 5 days (approval age based on formulation), and rivaroxaban (Xarelto) is approved for treatment of VTE in pediatric patients from birth to < 18 years after ≥ 5 days of initial parenteral anticoagulant treatment.

Fondaparinux (Arixtra) has shown a reduction in preventing post-operative VTE compared to enoxaparin (Lovenox) following major orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). Fondaparinux (Arixtra) has been associated with an increased risk of bleeding; however, the timing of administration can affect the risk of bleeding. Fondaparinux (Arixtra) has been shown to be non-inferior to dalteparin (Fragmin) in preventing post-operative VTE in patients undergoing major abdominal surgery.

The 2012 American College of Chest Physicians (CHEST) Antithrombotic Therapy and Prevention of Thrombosis (9th Edition) recommends anticoagulant thromboprophylaxis with a LMWH, low-dose UFH, or fondaparinux (Arixtra) as injectable options for the prevention of thrombosis for acutely ill hospitalized medical patients at increased risk of thrombosis. Rivaroxaban has received approval for use as prophylaxis of VTE and VTE-related death during hospitalization and post-hospital discharge in adults admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors and who are not at high risk of bleeding. This agent can be considered a viable treatment option due to clinical trial data demonstrating an improvement in thromboembolic events when compared with enoxaparin. Dabigatran (Pradaxa) has also received approval to reduce the risk of recurrence of VTE in pediatric patients 3 months to < 18 years of age who have been previously treated (approval age based on formulation). Rivaroxaban (Xarelto) has also received approval to reduce the risk of recurrent VTE in pediatric patients from birth to < 18 years.

The CHEST Evidence-Based Clinical Practice Guidelines recommend LMWH, fondaparinux (Arixtra), UFH, warfarin, aspirin, apixaban (Eliquis), dabigatran (Pradaxa), or rivaroxaban (Xarelto) for DVT prophylaxis in patients undergoing total hip or knee replacement surgery. LMWH is recommended over the other alternatives. The newer oral agents, apixaban (Eliquis) and rivaroxaban (Xarelto), have shown superiority to enoxaparin in prevention of DVT/PE, with a similar safety profile for this indication. Dabigatran (Pradaxa) has also received approval for prophylaxis of DVT/PE following hip replacement surgery based on 2 studies demonstrating non-inferiority to enoxaparin. For VTE prophylaxis in patients undergoing hip fracture surgery, CHEST recommends LMWH, fondaparinux, low dose unfractionated heparin, warfarin, aspirin, or an intermittent pneumatic compression device.

The American Society of Clinical Oncology (ASCO) published evidence-based clinical practice guidelines for the prophylaxis and treatment of VTE in cancer patients. In general, LMWH is preferred over UFH or vitamin K antagonists (VKA) in most settings when prophylaxis or treatment is indicated for cancer patients. The 2019 guideline update includes apixaban or rivaroxaban alongside LMWH as prophylactic options for certain high-risk patients in whom prophylaxis is indicated. Initial anticoagulation for treatment of VTE in patients with cancer may include LMWH, UFH, fondaparinux, or rivaroxaban. There is strong evidence to support a recommendation for long-term anticoagulation with a LMWH, edoxaban or rivaroxaban for at least 6 months rather than a VKA.

The American Society of Hematology (ASH) has also provided guidance on the management of VTE, including detailed guidance considering patient-specific factors. For the initial management of DVT and/or PE, ASH suggests the use of direct oral anticoagulants (DOACs) over VKAs, except in select populations, but does not suggest one DOAC over another.

The newer oral anticoagulants (dabigatran [Pradaxa], apixaban [Eliquis], edoxaban [Savaysa], rivaroxaban [Xarelto]) show comparable efficacy and superiority or non-inferiority to warfarin for stroke prevention in NVAF with similar to lower overall rates of major bleeding; however, long-term safety data are limited for these agents. Warfarin has been established for prevention of stroke in atrial fibrillation; however, it is associated with significant adverse events, genetic polymorphisms, drug-drug, and drug-food interactions, as well as laboratory monitoring. In the 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines focused update on the management of patients with atrial fibrillation, all NOACs are now preferred over warfarin in NOAC-eligible patients with AF. Apixaban is preferred in patients with end-stage renal disease or on dialysis, while the other NOACs are not recommended in this population due to lack of evidence.

The 2018 CHEST guidelines recommend that patients with AF without valvular heart disease who are at low risk for stroke receive no antithrombotic therapy. Patients with AF who have 1 non-gender stroke risk factor are suggested to receive oral anticoagulation while patients considered at high risk of stroke are recommended to receive oral anticoagulation. Where oral anticoagulation is recommended or suggested, CHEST suggests using a novel oral anticoagulant (NOAC) rather than adjusted-dose vitamin K antagonist therapy.

A meta-analysis found the newer oral anticoagulants to have an approximately 10% reduction in all-cause mortality compared to warfarin in patients with nonvalvular atrial fibrillation. This was largely due to a decreased incidence of hemorrhagic stroke in the patients assigned to the newer oral anticoagulants compared to patients receiving warfarin. Another study, a network meta-analysis, reported statistically similar reductions in the risk of VTE or VTE-related death for all newer oral anticoagulants; apixaban fared better with respect to the safety profile in terms of reduction in major or clinically relevant non-major bleed compared to rivaroxaban, dabigatran, and edoxaban.

Apixaban, dabigatran, edoxaban, and rivaroxaban do not require laboratory monitoring and the associated dose adjustments required with warfarin therapy. Dabigatran, apixaban, and rivaroxaban now have a corresponding reversal agent; however, there are no established methods to reverse bleeding in patients taking edoxaban. Nonetheless, ACC has provided guidance on the management of bleeding in patients on oral anticoagulants.

Rivaroxaban is the only NOAC approved to reduce risk of major cardiovascular (CV) events (CV death, myocardial infarction, and stroke) in patients with coronary artery disease (CAD) when used in combination with aspirin. It is also approved to reduce risk of major thrombotic vascular events (MI, stroke, acute limb ischemia, major amputation of a vascular etiology) in patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD, when used in combination with aspirin. In clinical trials, rivaroxaban 2.5 mg plus aspirin 100 mg reduced the composite risk of these events compared to aspirin alone.

Rivaroxaban is also approved for thromboprophylaxis in pediatric patients ≥ 2 years old with congenital heart disease after the Fontan procedure.

Ongoing trials are evaluating emerging oral therapies with comparable to better efficacy and improved safety, interactions, genetics, and therapeutic monitoring profiles.

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