For decades, warfarin, a Vitamin K antagonist, was the only oral anticoagulant available to physicians. However, over the last decade, newer agents with different mechanisms of action have become available for the treatment and prevention of thromboembolic events. Physicians must become familiar with the pharmacokinetics, mechanisms of action, indications, risks, and benefits of these agents to become comfortable using them in clinical practice. This review will serve to discuss these aspects of the novel non-Vitamin K oral anticoagulant agents.

Warfarin has been the mainstay of oral anticoagulation. It has been well studied and has proven efficacious in many situations. Its uses include reducing the rate of stroke in atrial fibrillation as well as treatment and prevention of venous thromboembolism (VTE). It is also used to prevent thrombus formation on mechanical valves. A significant advantage of warfarin is that its effect is reliably reversed by Vitamin K, fresh frozen plasma, or prothrombin complex concentrate. However, it has a narrow therapeutic window and a highly unpredictable dose response. It has several interactions with prescription and nonprescription drugs, especially stimulants and inhibitors of the CYP-450 system. Its levels also vary with dietary intake of Vitamin K. Thus, the international normalized ratio must be closely monitored to ensure that patients are within the appropriate therapeutic range. This need for frequent monitoring is a significant deterrent to the use of warfarin, especially in the elderly population.

To address some of the limitations of warfarin, newer oral anticoagulants were developed and introduced.

The two main mechanisms of action of the novel oral anticoagulants (NOACS) are direct inhibition of thrombin and inhibition of factor Xa. Thrombin (factor IIa) is the final enzyme in the clotting cascade that cleaves fibrinogen to fibrin. It also activates other procoagulant factors and activates platelets. Inhibition of thrombin interrupts the final steps in the coagulation pathway. Factor Xa acts one step upstream of thrombin in the clotting cascade, at the convergence point of the intrinsic and extrinsic coagulation pathways. It functions to cleave prothrombin to thrombin. As such, the inhibition of factor Xa prevents thrombin generation, which subsequently prevents clot formation. Four NOACS are licensed currently in the United States: The direct thrombin inhibitor dabigatran, and the factor Xa antagonists: Edoxaban, apixaban, and rivaroxaban. These agents are now acceptable alternatives to warfarin for use in prophylaxis and treatment of VTE and stroke prevention in nonvalvular atrial fibrillation. They have rapid onset and offset of action and fewer interactions with medications and food. They have a more predictable anticoagulant effect which allows fixed dosing without the need for laboratory monitoring. Dabigatran etexilate (Pradaxa) is the only oral direct thrombin inhibitor currently approved for use. It is given as a fixed dose (150 mg twice a day) without monitoring. Dosing can be reduced to 110 mg twice a day in patients...
Table 1: Preprocedure management of the novel oral anticoagulants

| NOAC      | Mechanism                      | Commonly used dose | Preprocedure management |
|-----------|--------------------------------|--------------------|-------------------------|
| Dabigatran (Pradaxa) | Direct thrombin inhibitor | 150 mg twice daily | Give last dose 2-3 days before procedure |
| Rivaroxaban (Xarelto) | Factor Xa inhibitor | 15 mg twice a day for 21 days then 15-20 mg daily | Give last dose 2-3 days before procedure |
| Apixiban (Eliquis) | Factor Xa inhibitor | 2.5-5 mg twice daily | Give last dose 2-3 days before procedure |
| Edoxaban (Savaysa) | Factor Xa inhibitor | 30-60 mg daily | Discontinue 2-3 days before procedure |

NOAC: Novel oral anticoagulants

Dabigatran does not have a reliable effect on coagulation studies. It will prolong the thrombin time and the activated partial thromboplastin time (aPTT), but it will not reliably prolong the pro-thrombin time. Fortunately, monitoring is not required as drug levels are usually predictable for fixed doses.[15] The most commonly reported side effect of dabigatran is dyspepsia.[5] Until recently, dabigatran did not have a specific reversal agent but that changed with the introduction of the monoclonal antibody idarucizumab (Praxbind).

Idarucizumab was studied in the REVERSE AD trial and was able to reverse the effects of dabigatran in over 90% of patients.[18] Praxbind is given intravenously as two separate doses of 2.5 mg about 15 min apart. Of note, it was given accelerated Food and Drug Administration approval and thus, the evidence that supports it is still controversial. Hemodialysis can also be effective in helping to remove dabigatran from the circulation.[6]

There are three oral direct factors X inhibitors available on the market. Rivaroxaban (Xarelto) is a direct factor X inhibitor that is given at a fixed dose of 10–20 mg twice daily depending on the indication. It is metabolized by the liver and the kidneys and has a half-life of 7–13 h. It reaches its peak efficacy 1–4 h after ingestion. It has been studied for VTE prophylaxis following orthopedic surgeries. Four Phase III studies have compared 10 mg/day of rivaroxaban with 40 mg/day of enoxaparin for thromboprophylaxis following hip or knee replacement surgery. In these studies, rivaroxaban was associated with fewer symptomatic VTE events and all-cause mortality. Bleeding events were similar in both groups.[22] Rivaroxaban also demonstrated similar efficacy when compared to low molecular weight heparin followed by warfarin for the treatment of acute VTE in a large prospective randomized controlled trial. EINSTEIN-DVT and EINSTEIN-PE were open-label randomized trials with 8281 patients with acute DVT or PE. They demonstrated the noninferiority of 15 mg BID rivaroxaban for 3 weeks followed by 20 mg once daily to enoxaparin followed by warfarin. Bleeding events were similar in both groups.[10] Rivaroxaban was also studied in a large double-blind trial for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation. It was found to be noninferior to warfarin for this purpose. The major bleeding rates were similar for both drugs but intracranial, and fatal bleeding was less frequent in the rivaroxaban group.[17] Patients with a creatinine clearance of <30 ml/min were not included in these trials. Rivaroxaban is not used in patients with Child-Pugh B or C hepatic dysfunction. Drugs that are dual inhibitors of the CYP-3A4 and P-glycoprotein systems interact with rivaroxaban; therefore, concurrent use is contraindicated. Potent inducers of CYP-3A4 such as St. John’s Wort may reduce the efficacy of rivaroxaban.[16]

Just as with dabigatran, routine monitoring of coagulation times is not required for patients on rivaroxaban. The aPTT and anti-Xa activity can be measured and may be prolonged but are not reliable in determining the efficacy of the drug.[11] Reversal is difficult given the lack of a specific antidote. Dialysis is not effective in clearing rivaroxaban given its high plasma protein binding affinity. Prothrombin complex concentrate and recombinant factor VII can be helpful in case of bleeding.[24] In the case of major bleeding, antifibrinolytic agents such as...
tranexamic acid and epsilon-aminocaproic acid have been suggested for reversal. There is no good clinical data to support the use of any of these agents for reversal of the effect of rivaroxaban and, thus, they are not considered the standard of care.

Apixaban (Eliquis) is an oral factor Xa inhibitor with a half-life of 4–9 h. It reaches peak efficacy 1–4 h after ingestion. It is given as a fixed dose without monitoring. The dose varies according to the clinical indication, age, renal function, and weight and it is approved for use in end-stage renal disease. It is indicated for use in treatment and prevention of VTE’s and stroke prevention in nonvalvular atrial fibrillation. The AMPLIFY study showed that a fixed dose of oral apixaban was as effective as enoxaparin followed by warfarin for the treatment of acute VTE. It was also associated with a clinically significant reduction in bleeding.[1] In the ARISTOTLE study, apixaban was found to be superior to warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation.[13]

As with all novel anti-coagulants, monitoring of coagulation parameters is not required during treatment. Levels may be affected by strong dual CYP3A4 and P-glycoprotein inhibitors; such asazole antifungals or ritonavir. In the case of bleeding, reversal can be achieved with the use of prothrombin complex concentrate or recombinant factor VII. Similar to rivaroxaban, these are not reliable or evidence-based reversal agents.

Edoxaban (Savaysa) is another oral direct factor Xa inhibitor. It achieves peak concentration within 1–2 h. Fifty percent of the elimination of edoxaban occurs via the kidneys. It is given as a fixed dose of 30–60 mg once daily. It was found to be noninferior to warfarin for stroke prevention in patients with atrial fibrillation.[12] Like other NOACs, it was associated with lower rates of bleeding and death from cardiovascular disease. In the setting of VTE, edoxaban given once daily after an initial dose of heparin was found to be noninferior to warfarin given after heparin. It was also associated with significantly less bleeding.[14]

Despite a large amount of evidence demonstrating the efficacy and safety of the factor Xa inhibitors, the lack of a reversal agent is a significant limitation. To that effect, in a very recent study, a recombinant modified human factor Xa decoy protein called Andexanet alfa (andexanet) has been described. Andexanet binds and sequesters factor Xa inhibitors within the vascular space thus restoring the activity of factor Xa.[20] It is a potent and specific antidote to apixaban rivaroxaban and edoxaban. There are currently ongoing studies evaluating this potential reversal agent.

After decades of warfarin being the only anticoagulant available, the NOACS have finally provided physicians and patients with more options. There is a multitude of evidence supporting that they are as efficacious as warfarin. As experience accumulates, it is evident that they are less cumbersome to use and as safe as warfarin. NOACS are slowly but surely becoming the first line for the treatment and prevention of thrombosis in the 21st century.

REFERENCES

1. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
2. Akers RS, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost 2010;104:49-60.
3. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the Vitamin K antagonists: American College of chest physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008;133 [Suppl]: 1605-985.
4. Blech S, Ebner T, Ludwig-Schwellinger E, Stangl J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 2008;36:386-99.
5. Bytzer P, Connolly SJ, Yang S, Ezekowitz M, Formella S, Reilly PA, et al. Analysis of upper gastrointestinal adverse events among patients given dabigatran in the RE-LY trial. Clin Gastroenterol Hepatol 2013;11:246-42.
6. Chai-Adisaksoph C, Hills C, Lim W, Boonsaowat K, Moflat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: A case report and systematic review. J Thromb Haemost 2015;13:1790-8.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
8. Dager WE, Gosselin KC, Kitchen S, Dwyre D. Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: A multicenter, in vitro study. Ann Pharmacother 2012;46:1627-36.
9. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. N Engl J Med 2005;353:1028-40.
10. Einstein Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
11. Freyburger G, Macouillard G, Labrouche S, Sztark F. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing total hip or total knee replacement. Thromb Res 2011;127:457-65.
12. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
13. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
14. Hokusai-VTE Investigators, Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15.
15. Laux V, Perzborn E, Heitmeier S, von Degenfeld G, Dittrich-Wengenroth E, Buchmüller A, et al. Direct inhibitors of coagulation proteins – The end of the heparin and low-molecular-weight heparin era for anticoagulant therapy? Thromb Haemost 2009;102:892-9.
16. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: An update. J Thromb Thrombolysis 2011;31:326-43.
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
18. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Darus间接umab for dabigatran reversal. N Engl J Med 2015;373:51-20.
19. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al.
Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.

20. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-24.

21. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. N Engl J Med 2013;368:1272-4.

22. Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. Thromb Haemost 2011;105:444-53.

23. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. Thromb Haemost 2009;101:77-85.

24. Wong H, Keeling D. Activated prothrombin complex concentrate for the prevention of dabigatran-associated bleeding. Br J Haematol 2014;166:152-3.