REVIEW ARTICLE

Management of patients who are receiving warfarin or a new oral anticoagulant and require urgent or emergency surgery

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KEY WORDS

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ABSTRACT

An increasing number of patients are receiving long-term oral anticoagulant therapy and the availability of new oral anticoagulants (OACs), which are easier to use than warfarin, will further expand the population of anticoagulated patients. As a consequence, an increasing number of patients will need perioperative anticoagulant management because of elective or nonelective surgery or procedures. The perioperative management of such patients is pertinent to a broad spectrum of physicians, including anesthesiologists, internists, and surgeons. The objectives of this review are to provide a clinically-focused background on the pharmacology of warfarin and the new OACs and to suggest perioperative anticoagulant management strategies. This review will focus on the perioperative management of warfarin and new OACs who require urgent or emergent surgery or who require rapid anticoagulant reversal because of ongoing bleeding or high bleeding risk.

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Introduction It is estimated that 250,000 patients who are receiving long-term oral anticoagulant therapy present for surgery or invasive procedures on a yearly basis for an assessment of treatment interruption to minimize the risk of hemorrhage.[1] Warfarin, the most widely-used vitamin K antagonist, has been the mainstay of long-term outpatient anticoagulation for the past several decades since its approval by the US Food and Drug Administration (FDA) in 1954. This includes the prevention and treatment of venous thromboembolism (VTE), and the prevention of stroke and systemic embolism in patients with chronic atrial fibrillation (AF). Several studies have demonstrated the efficacy of warfarin in preventing thromboembolic events associated with AF.[2-4] The use of warfarin, however, has inherent drawbacks, including the need for laboratory monitoring, which is needed to ensure appropriate anticoagulation dose adjustments, multiple drug and food interactions, and a long offset and onset of action, which necessitates the need for standardized periprocedural management protocols.

Recently, several new oral anticoagulants (OACs) have been introduced for the prevention and treatment of VTE and stroke prevention from AF that do not require the intensive laboratory monitoring of warfarin. These include dabigatran etexilate (Pradaxa®), a direct thrombin (factor IIa) inhibitor approved for VTE prevention and chronic AF in 2008, and 2011, respectively; rivaroxaban (Xarelto®), a direct factor Xa inhibitor approved for VTE prevention and chronic AF in 2011, and 2012, respectively; and apixaban (Eliquis®), a direct factor Xa inhibitor with expected regulatory approval in 2012. The key indication for the new OACs will be chronic AF, given the increasing number of eligible patients and need for indefinite (or life-long) treatment in such patients. Consequently, there is a need for careful assessment of patient eligibility and drug selection when patients with AF are being considered for long-term anticoagulant therapy.[5]

Previously, the management of perioperative anticoagulation was relatively straightforward. The decisions to reverse anticoagulation and the requirements for bridging have been defined and will not be discussed herein.[6] There are

multiple methods to ensure normalization of the international normalized ratio (INR) prior to surgery, from withholding warfarin to completely reversing its activity, depending on the urgency of the procedure. However, the introduction of the new OACs has necessitated a re-evaluation of previous strategies owing to a variable dependence on renal elimination coupled with a lack of specific antidotes, particularly in the urgent and emergent settings.

As the number of patients who are receiving a new OAC increases, the periprocedural management of such patients will become more relevant to a broad spectrum of physician stakeholders, including anesthesiologists, internists, and surgeons. The objectives of this review are: 1) to provide a clinically-focused background on the pharmacology of warfarin and the new OACs; and 2) to suggest perioperative management strategies in the elective, urgent, or emergent settings. Unlike previous reviews of this topic,[7,8] we will focus on the perioperative management of warfarin and new OACs who require urgent or emergent surgery or who require rapid anticoagulant reversal because of ongoing bleeding or high bleeding risk.

Perioperative anticoagulant management for urgent or emergent surgery

Warfarin Warfarin has been, for decades, the first-line anticoagulant for stroke prevention in patients with chronic nonvalvular AF, particularly in those at high risk for stroke ($CHADS_2 \geq 2$).[9] Two landmark studies demonstrated the efficacy of warfarin in reducing the incidence of stroke in patients with AF when the dose is titrated to an INR of 2.0 to 3.0 (75%–86% risk reduction).[2,10] When administered orally (high bioavailability), warfarin exerts its anticoagulant effect by a dose-dependent inhibition of hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, X, while endogenous anticoagulant synthesis of protein C, S, and Z is also inhibited.[11] Because warfarin is almost exclusively metabolized through the hepatic cytochrome P450 pathway, there exists a significant risk of drug interactions with the potential for excessive anticoagulation.[12,13]

Warfarin treatment results in a dose-dependent increase in the prothrombin time (PT) and INR. The dose is titrated to an INR range between 2.0 and 3.0 in chronic AF and 2.5 and 3.5 in patients with mechanical cardiac valves. Recommendations for the interruption of warfarin in the elective perioperative period are based on a case series of 22 patients and several randomized trials. White et al.[14] demonstrated that holding warfarin for 5 days resulted in 78% (17/22 patients) achieving an INR of less than 1.2.[14] Given that prior to surgery, an INR of less than 1.5 is recommended, warfarin can be withheld for 5 days prior to an elective procedure. The American College of Chest Physicians (ACCP) recommends withholding warfarin without administration of vitamin K if the INR is less than 10 and there is no evidence of hemorrhage.[15] In the urgent setting, stopping warfarin and administering vitamin K (1.0–2.5 mg intravenously or 5–10 mg orally) is sufficient to normalize INR within 24 to 48 hours. If there is ongoing, life-threatening hemorrhage, fresh frozen plasma (FFP) or preferably a prothrombin complex concentrate (PCC) in addition to parenteral vitamin K is necessary. In the emergent or life-threatening situation or if there is a need for immediate surgery, the guidelines from the ACCP recommend the administration of 4-factor PCC and intravenous vitamin K, 5–10 mg, instead of fresh frozen plasma and vitamin K.[15-18]

In regard to PCCs, this blood product is available in 3 formulations: 1) a 3-factor PCC, comprising coagulation factors II, IX, and X; 2) a 4-factor PCC comprising factors II, VII, IX, and X (e.g., Beriplex, Octaplex); and 3) an activated 4-factor PCC (e.g., FEIBA – factor VIII inhibitor bypassing activity), which has a faster onset of action compared with other 4-factor PCCs. The advantages of PCC over FFP include a smaller volume of infusion (i.e., 50 ml vs. 180–230 ml per unit FFP), more rapid administration (i.e., PCC is a lyophilized powder that can be reconstituted within minutes whereas FFP needs to be thawed, which may take 30–60 minutes), and more reliable amounts of vitamin K-dependent coagulation factors transfused. These properties make PCC the agent of choice for reversing warfarin coagulopathy in patients who require urgent/emergent surgery or are actively bleeding and require prompt coagulation factor replacement.

Dabigatran etexilate Dabigatran etexilate (Pradaxa®) is an orally administered direct thrombin inhibitor that is approved for the prevention of VTE after hip or knee replacement surgery, the treatment of acute VTE (RE-COVER trial) , and the prevention of stroke in chronic AF (RE-LY trial).[19-22] When taken orally, dabigatran etexilate is in the form of a prodrug and after rapid intestinal absorption it undergoes hepatic conversion to the active drug, dabigatran.[23] Because conversion to the active metabolite is cytochrome P450 independent, dabigatran has a low risk for drug interactions. Though dabigatran has low bioavailability (6%), necessitating a higher dose,[24,25] peak plasma levels are achieved from 2 to 3 hours after intake, with an elimination half-life of 14 to 17 hours.[25-27]

Dabigatran is primarily eliminated renally (80%) with the remaining portion (20%) by hepatic acylglucuronides to active metabolites with subsequent biliary excretion.[27] A reduced dosage, 75 mg twice-daily, has been recommended by the FDA in the United States for patients with a creatinine clearance (CrCl) of 15 to 30 ml/min, although this recommendation is based on pharmacokinetic studies alone as this dose has not been prospectively investigated in patients with this degree of renal insufficiency.[28] In general, dabigatran should be used with caution in patients

with moderately-to-severely impaired renal function (CrCl ≤50 ml/min) because of the potential for drug bioaccumulation in the setting of acute deterioration of renal function.

The anticoagulant effect of dabigatran is difficult to measure reliably using standard coagulation tests. Though the activated partial thromboplastin time (aPTT) and PT increase with the administration of dabigatran, indicating its effect, these assays do not reliably measure its anticoagulant effect. The aPTT will be elevated for several hours after dabigatran intake and may remain elevated if there is a clinically important residual dabigatran plasma level. Thus, a normal aPTT may indicate the lack of a significant residual dabigatran effect but such measurements are not fully reliable due to interassay variability in dabigatran measurement. The thrombin time (TT) is another test that can indicate the presence of a dabigatran anticoagulant effect but its clinical use is limited because it is overly sensitive to dabigatran plasma levels. Thus, although a normal TT will provide reassurance that there is no residual dabigatran effect present, the TT may be prolonged even in the presence of small, clinically unimportant plasma levels of dabigatran. A dilute TT, which is a commercially available assay (Hemoclot), may be the most reliable method to measure the dabigatran-associated anticoagulant effect, but this test is not available in most laboratories and not approved for clinical use in some countries.[29]

Recommendations for periprocedural interruption of dabigatran are based primarily on its pharmacokinetic and pharmacodynamic properties, and are supported by emerging clinical trial data specifically examining this aspect. A recent substudy of patients in the RE-LY trial demonstrated that the rates of major bleeding among patients having urgent surgery were similar across the 3 study groups when the last dose of dabigatran was given a mean of 49 (range, 35–85) hours prior to the procedure: warfarin (21.6%); dabigatran 110 mg (17.8%); dabigatran 150 mg (17.8%).[30] There were no significant differences in major bleeding between warfarin and the 110 mg dabigatran dose (relative risk [RR], 0.82; 95% confidence interval [CI], 0.48–1.41), and between warfarin and the 150 mg dabigatran dose (RR, 0.82; 95% CI, 0.50–1.35). Where normal hemostasis for elective invasive procedures is required, pharmacokinetic data suggest that between 48 and 72 hours (between 4 and 5 half-lives) should elapse between the last dose of dabigatran and the invasive procedure, and perhaps even longer for intracranial/spinal procedures. Urgent procedures will require discussion between surgeons, anesthesiologists, and internists to determine the most appropriate time to proceed, keeping in mind possible residual dabigatran activity. With respect to emergent (<24 hours) surgery, there are no antidotes available to reverse the action of dabigatran. Both PCCs and recombinant factor VIIa have not demonstrated the ability to reverse the effect of dabigatran in human studies though FEIBA products (i.e., activated PCC) may have some clinical utility in dabigatran-associated bleeding or in such patients who need urgent surgery.[31,32]

The emergent setting is of particular concern because no specific antidote exists for dabigatran. A recent meta-analysis demonstrated that the risk of intracranial hemorrhage (ICH) while on dabigatran was less than that of warfarin (RR, 0.49; 95% CI, 0.36–0.66).[33] Indeed, data from RE-LY demonstrate that, compared with those on warfarin, patients receiving both doses of dabigatran had lower rates of ICH, though rates of extracranial hemorrhage were lower only for the 110 mg dose and comparable in the 150 mg dose.[34] Patients on dabigatran had a lower rate of ICH compared with those on warfarin (0.31% [150 mg dabigatran], 0.23% [110 mg dabigatran], 0.76% [warfarin]).[35] Overall, fewer patients on dabigatran died from ICH than those receiving warfarin.

Expert opinion suggests the use of oral activated charcoal in the setting of recent (<2 hours) ingestion or hemodialysis if there is anticipated prolonged anticoagulant effect, for example in the setting of acute renal failure.[36] While this guidance indicates that there is currently no clear evidence to support use of PCC or FFP in patients with dabigatran-associated bleeding, 4-factor PCC may be considered in life-threatening or intracranial bleeding associated with dabigatran treatment. The uncertainty surrounding the efficacy of PCC for dabigatran-associated bleeding relates to the fact that in dabigatran-treated patients coagulation factor levels are not depleted and, therefore, additional administration of vitamin K-dependent clotting factors may have little impact on the ongoing inhibitory effect of dabigatran on thrombin (factor II). It is possible, though, that PCC may overwhelm such an inhibitory effect, although further clinical studies are needed to support (or refute) this premise. FFP is not recommended for dabigatran-associated bleeding, while the opinion is unclear on the use recombinant factor VIIa and 3-factor PCC.[36]

Rivaroxaban Rivaroxaban (Xarelto®) is an orally administered factor Xa inhibitor that has been approved for the prevention and treatment of VTE (RECORD and EINSTEIN trials) and the prevention of stroke in AF (ROCKET-AF trial).[37,38]

In contrast to dabigatran, rivaroxaban has high oral bioavailability (>60%).[39] Rivaroxaban undergoes primarily hepatic metabolism independent of the cytochrome P450 pathway and has a low risk for drug interactions. Peak plasma levels are achieved rapidly (2–3 hours) while the elimination half-life is from 8 to 10 hours.[39]

Approximately one-third of rivaroxaban is eliminated renally (one-third of the inactive form of rivaroxaban is also cleared by the kidneys) with the remaining portion eliminated by the liver.[26,40] Rivaroxaban, in general, should be

avoided (or used with caution) in patients with severe renal insufficiency (CrCl <30 ml/min), although a reduced treatment dose (15 mg daily) has been studied in patients with a CrCl of 15 to 30 ml/min. While rivaroxaban results in a dose-dependent increase in the PT and, to a lesser extent, the aPTT, the best method to assess its anticoagulant activity is through an antifactor Xa assay that is calibrated according to a rivaroxaban-based standard.[41,42]

Recommendations for the interruption of rivaroxaban are different than those of dabigatran because its elimination half-life is shorter but nonetheless based on similar principles of discontinuing for 4 to 5 half-lives. In the case of rivaroxaban, this is as short as 24 hours or as long as 60 hours. The duration of interruption does need to be adjusted in patients with mild renal impairment but may require adjustment if there is more severe renal insufficiency (e.g., CrCl, 30–50 ml/min). With respect to urgent/emergent situations, there are some data to suggest that PCC, FEIBA, or factor X concentrate may be helpful in rivaroxaban-treated patients with bleeding but, as with dabigatran, clinical studies to support this premise are lacking and such agents should be reserved for life-threatening or intracranial bleeding.[31,32] Moreover, the short half-life of rivaroxaban should obviate the need for administering PCC or other prohemostatic agents in most clinical situations.

In the ROCKET-AF trial, comparing once-daily rivaroxaban (20 mg) to dose-adjusted warfarin, the incidence of all types of bleeding were similar (hazard ratio, 1.03, $P = 0.44$). However, the rates of both ICH (0.5% vs. 0.7%, $P = 0.02$) and fatal hemorrhage (0.2% vs. 0.5%, $P = 0.003$) were reduced in the rivaroxaban group, suggesting a better safety profile than that of warfarin.[38] This is important in light of the limited data on the reversibility of rivaroxaban and case reports describing hemorrhage.[43]

Apixaban Apixaban is another orally administered factor Xa inhibitor with FDA approval expected in 2012. Two separate trials have demonstrated in patients with AF the superiority of apixaban over aspirin (AVERROES) and warfarin (ARISTOTLE) in terms of reducing systemic embolism and stroke as well as reduced hemorrhagic complications.[44,45]

The pharmacokinetic and pharmacodynamic properties of apixaban are similar to rivaroxaban in terms of bioavailability (65%), elimination half-life of 8 to 14 hours, lack of drug interaction, and effects on coagulation tests.[46,47] A potential advantage of apixaban is that only 25% of the drug is eliminated by the kidneys.[47] However, as with both dabigatran and rivaroxaban, apixaban should be used with caution (or avoided) in patients with severe renal insufficiency (CrCl <30 ml/min).

The duration of interruption before invasive procedures, as with rivaroxaban, also does not need to be adjusted in patients with mildly impaired renal function. Management of apixaban in the urgent/emergent setting will likely be similar to rivaroxaban; however, there have been no studies to date assessing the effect of PCC, FEIBA, and recombinant factor VIIa on coagulation status with apixaban.

Summary The new OACs (dabigatran etexilate, rivaroxaban, and apixaban) are major advances for anticoagulation therapy. They have demonstrated ease of use as well as superior efficacy compared with dose-adjusted warfarin in terms of reducing thromboembolic complications in the setting of chronic AF. A recent meta-analysis by Miller et al.[33] confirms this as well as indicates that mortality is reduced and there are fewer hemorrhagic complications, both fatal and nonfatal, compared with warfarin.

Despite this, there is still some concern because of the lack of specific antidotes for all of these agents in the perioperative period. The elective and semi-urgent settings are of less concern because management of anticoagulation in these cases is predicated on the pharmacokinetic properties of each respective therapeutic. In the emergent setting, however, there are few, well-studied, highly effective antidotes to these agents. Thus, even though the incidence of hemorrhage is lower and overall mortality from hemorrhage is correspondingly lower, when it occurs it may be untreatable with potential catastrophic consequences.

Additional research is urgently needed to better define clinical outcomes in patients with life-threatening bleeding during treatment with new OACs and to determine if such bleeding is associated with worse outcomes than with warfarin-associated bleeding. In addition, there is a need for well-designed, prospective management studies to inform best practices for patients receiving a new OAC who require urgent or emergent surgery.

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ARTYKUŁ POGLĄDOWY

Postępowanie z chorymi, którzy otrzymują warfarynę lub nowy doustny antykoagulant i wymagają pilnej lub ratunkowej operacji chirurgicznej

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SŁOWA KLUCZOWE

nowe doustne antykoagulanty, okołooperacyjny, pilna operacja chirurgiczna, warfaryna

STRESZCZENIE

Zwiększająca się liczba chorych otrzymujących długoterminowo doustne leki przeciwkrzepliwe oraz dostępność nowych doustnych antykoagulantów, które się łatwiej stosuje niż warfarynę spowoduje dalsze rozszerzanie się populacji chorych leczonych przeciwkrzepliwie. W następstwie tego coraz większa liczba pacjentów będzie wymagać postępowania okołooperacyjnego w przypadku leczenia przeciwkrzepliwego z powodu planowych i nieplanowych operacji i zabiegów. Okołooperacyjne postępowanie z takimi pacjentami dotyczy szerokiego spektrum lekarzy, w tym anestezjologów, internistów i chirurgów. Celem tego artykułu poglądowego jest dostarczenie klinicznie istotnych podstawowych informacji na temat farmakologii warfaryny i nowych doustnych antykoagulantów oraz zaproponowanie strategii postępowania okołooperacyjnego z chorymi leczonymi przeciwkrzepliwie. W przeglądzie tym skupimy się na postępowaniu okołooperacyjnym u otrzymujących warfarynę lub nowe doustne antykoagulanty, którzy wymagają pilnej lub ratunkowej operacji chirurgicznej lub u których konieczne jest szybkie odwrócenie efektu przeciwkrzepliwego z powodu czynnego krwawienia lub dużego ryzyka krwawienia.

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