Reversal Agents for the New Generation of Oral Anticoagulants: Implications for the Perioperative Physician

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ALTHOUGH HEPARIN AND vitamin K antagonists such as warfarin have dominated anticoagulation therapy for decades, the advent of novel oral anticoagulants (NOACs) has revolutionized the field (Table 1).[1,2] The NOACs currently include dabigatran, a direct thrombin inhibitor, and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, which recently all have been reviewed extensively in this *Journal*.[1-5] Compared with oral vitamin K antagonists, the NOACs have more predictable pharmacodynamic and pharmacokinetic profiles, decreased food and drug interactions, and a wider therapeutic window.[1-3] As a consequence of these pharmacologic advantages, the NOACs typically can be administered at a fixed dose without therapeutic monitoring in most patients.[1-4] Furthermore, their clinical properties may significantly cut healthcare costs due to reductions in laboratory testing, clinic visits, and hospital admissions.[5,6]

The NOACs have become entrenched in clinical practice due not only to these outlined clinical advantages but also because recent clinical trials have demonstrated significant outcome advantages in atrial fibrillation such as reductions in stroke, myocardial infarction, systemic noncerebral embolism, and mortality.[7,8] Furthermore, large meta-analyses of randomized controlled trials have highlighted the significantly safer bleeding profile of the NOACs compared with standard anticoagulation, with marked reductions in the risks for intracranial hemorrhage and mortality.[9,10] These trends for satisfactory outcomes and/or safety in the setting of NOACs have persisted in specialized settings such as heart failure, cardioversion, and intervention for acute ischemic stroke.[11-13]

Despite these positive data, NOACs still have an associated risk of bleeding (Table 2).[14-17] Until recently, a major perioperative disadvantage with the NOACs has been the lack of rapid reversal techniques.[1,2] Reversal agents are readily and effectively available for the traditional anticoagulants such as unfractionated heparin (protamine) and vitamin K antagonists (vitamin K injection, fresh frozen plasma, and/or prothrombin complex concentrates).[1-4] Effective, specific, and safe antidotes for NOACs would represent a major clinical advance in perioperative settings such as emergency surgery and major bleeding.[1-4]

The medical community has recognized this urgency and has developed measures for fast-track approval of target-specific reversal drugs for the NOACs.[18,19] These efforts have included strategies such as extensive discussions among all stakeholders, expanded approval criteria, and tailored trial design to allow antidotes for severe bleeding associated with NOACs to break through into clinical practice in an accelerated fashion.[20,21] The purpose of this expert review is to review the reversal strategies that currently are available for NOACs, with a focus on the current limitations of these agents and emerging specific agents for their reversal.

CLINICAL APPLICATIONS OF THE NOVEL ORAL ANTICOAGULANTS

The current clinical indications for NOACs are similar and have been derived from large, randomized clinical trials (see Table 1).[1-4] These indications include the following: nonvalvular atrial fibrillation, specifically in patients without valve prostheses or more-than-mild mitral stenosis; primary prevention of venous thromboembolism after knee or hip replacement; and treatment of venous thromboembolism.[22] An evolving indication may be in the setting of patients with atrial fibrillation and bioprosthetic heart valves, given that recent data suggest safety and efficacy and that further trials are planned to refine the indications for these agents in valvular atrial fibrillation.[23-25] In the setting of mechanical heart valves, recent high-quality data revealed that NOACs were associated with significantly higher risks of thromboembolism and

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Table 1. Novel Oral Anticoagulants

Characteristics	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Target factor	II (Thrombin)	Xa	Xa	Xa
Clinical indications	1. NVAF 2. PE or DVT treatment	1. NVAF 2. PE or DVT treatment 3. PE or DVT prophylaxis for major hip or knee surgery		1. NVAF 2. PE or DVT treatment
Hepatic metabolism	Yes	Yes	Yes	Yes
Percentage renal clearance	75%-80%	25%-30%	60%-65%	45%-50%
Half-life (hours)	12-17	8-15	9-13	8-10

Abbreviations: DVT, deep vein thrombosis; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism.

bleeding.[26,27] In the case of patients with antiphospholipid syndrome, pilot data have suggested that NOACs may be inferior to vitamin K antagonists, although randomized clinical trials are planned to evaluate this observation further.[28,29]

LABORATORY MONITORING FOR NOVEL ORAL ANTICOAGULANTS

Although routine laboratory monitoring of anticoagulation is not required for patients taking NOACs, there are clinical scenarios that might warrant such testing for precise quantification of activity, although the effects of these agents on routine tests are variable.[30-32] The clinical indications for laboratory testing of anticoagulation in the setting of NOAC therapy include the following[31-33]: (1) Urgent situation: bleeding or thrombotic events occurring while taking the drug, perioperatively for procedures with a bleeding risk, overdose; (2) Routine: chronic kidney disease, suspected drug interactions and factors that alter absorption, suspected noncompliance.

In the urgent situational category, drug monitoring is helpful to estimate the risk of bleeding against that of thrombosis to guide interventions or drug dosing changes to terminate bleeding, treat refractory thrombosis, or perform lifesaving procedures (Fig 1).[31-33] It is important to note that decreased creatinine clearance extends the duration of action of NOACs because they all are cleared renally to some extent, especially dabigatran (see Table 1).[33,34] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, it was shown that patients taking dabigatran with a creatinine clearance of 30 to 50 mL/min had a substantially increased risk of bleeding compared with those taking warfarin.[33] In addition, patients with chronic kidney disease are at high risk for marked variation in effective creatinine clearance in the settings of dehydration or infection, thereby significantly increasing the risk for major bleeding during NOAC therapy.[34,35]

As a clinical rule, NOACs are metabolized to some extent by the cytochrome P450 pathway in the liver and also interact with the intestinal p-glycoprotein absorption pathway (most important for dabigatran due to poor oral bioavailability).[1-4] Both these enzymatic systems have significant drug interactions that may be inducers (such as carbamazepine, phenytoin, and rifampin) and inhibitors (such as azole antifungals, verapamil, diltiazem, and amiodarone).[1-4] Given that concomitant exposure to these drugs is common, in these settings coagulation monitoring of NOACs may be beneficial. The European Heart Rhythm Association has published a guideline that details this topic in depth and the need for additional monitoring of renal function and liver function.[22] Noncompliance with therapy can be a major problem because NOACs have relatively short half-lives (most 12-24 hours) compared with the vitamin K antagonists, leading to the potential for rapid cessation of anticoagulation.[1-4]

Because there are reasonable clinical circumstances for monitoring of anticoagulation due to therapy with NOACs, the next consideration is what laboratory tests are most applicable for the various members of this drug class (Table 3).[30-32] The use of agent-specific assays for drug levels currently are either only available in research settings or do not have rapid delivery of results to guide clinical decision-making in emergencies. Furthermore, many point-of-care coagulation tests are not suitable for monitoring NOACs due to poor correlation with drug levels and the level of clinical anticoagulation.[30-32]

For the direct thrombin inhibitors (eg, dabigatran), a normal activated partial thromboplastin time typically would exclude excessive levels of dabigatran.[30-32] Hence, although this has a robust negative predictive value when normal, it does not further quantify anticoagulation status.[30-32] A thrombin time within the normal range typically rules out clinically relevant dabigatran levels, although this test is not widely available. The dilute thrombin time and ecarin clotting time both correlate even more closely with dabigatran levels, but again they are not widely available clinically.[30-32,36] The prothrombin time and derived international normalized ratio have little role in the setting of dabigatran because they have poor correlation with dabigatran levels and the anticoagulation level.

Table 2. Annual Incidence of Bleeding Complications for Novel Oral Anticoagulants

Anticoagulant	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Major bleeding (%)	3.1%	3.6%	3.6%	3.1%
Intracranial hemorrhage (%)	0.3%	0.5%	0.8%	0.5%
Fatal bleeding (%)	0.33%	0.2%	0.2%	0.2%

NOTE: Data derived from major trials on atrial fibrillation.[14-17]