# Quick reference guide to the new oral anticoagulants

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**After the commissioning of new oral anticoagulants for the treatment and prevention of thrombosis, these medications are now widely used within clinical settings. Increasing numbers of patients present to the health services on anticoagulant medications, and it is therefore imperative for surgeons to be aware of the new therapeutic treatments available and how patients will benefit from such interventions. This review highlights the most pertinent learning points for surgeons regarding the indications, pharmacokinetics, and perioperative management of these new oral medications, as a quick reference guide. (J Vasc Surg 2016;63:1653-7.)**

During the last 5 years, new anticoagulants, such as dabigatran, rivaroxaban, apixaban, and edoxaban, have been used increasingly in the clinical setting, predominantly for the prevention and treatment of thrombosis. Their added benefits mean they have replaced the use of warfarin in many cases.

The new oral anticoagulant (NOAC) agents not only have the advantage of fast-onset anticoagulation but also have a fixed anticoagulation effect, allowing administration of specified doses and no routine monitoring. Although much ambiguity remains on the efficacy of novel oral anticoagulants, several randomized controlled trials have shown there is no inferiority in their clinical use compared with standard therapy. The landmark studies highlighting these results include: EINSTEIN DVT,[1] EINSTEIN PE,[2] AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy),[3] RE-COVER,[4] ENGAGE AF-TIMI (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48),[5] and Hokusai VTE.[6] Both EINSTEIN studies looked at the use of rivaroxaban compared with enoxaparin in thromboembolic disease, AMPLIFY compared apixaban with enoxaparin, followed by warfarin, RE-COVER reviewed dabigatran compared with warfarin, and ENGAGE AF-TIMI, and Hokusai VTE matched edoxaban therapy to warfarin treatment in the prevention of atrial fibrillation (AF)-related stokes and recurrent venous thromboembolism, respectively.

All these studies show equivocal or reduced rates of stroke[7,8] arterial embolism,[9,10] and bleeding complications with NOACs and significantly reduced rates of intracerebral hemorrhage and overall mortality.[11-13] In light of these results, and their fixed anticoagulation effects, the new anticoagulants have become favorable for use in a variety of patient subsets.

## LICENCES

Currently the new oral anticoagulants hold licences for the following:

- Dabigatran for stroke prevention in patients with AF plus one of reduced ejection fraction, coronary heart disease, diabetes, or age <65 years (150 mg, twice daily [BD]), the treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE) after parenteral anticoagulation for 5 to 10 days (150 mg BD), and prevention of venous thromboembolism in elective hip and knee surgery (110 mg, 1-4 hours after surgery, then 220 mg once daily [OD] for 9/7 days, respectively).
- Rivaroxaban for the prevention of venous thromboembolism in elective hip or knee surgery (10 mg OD for 35/12 days, respectively), stroke prevention in patients with AF plus one of the following risk factors: congestive heart failure, hypertension, age >75 years, diabetes, or prior stroke ($CHADS_2$ [Congestive heart failure, Hypertension {blood pressure consistently >140/90 mm Hg or treated hypertension on medication}, Age ≥75 years, Diabetes mellitus, Prior Stroke or transient ischemic attack or thromboembolism]) (20 mg OD), and treatment of DVT and PE or prophylaxis after recurrent DVT or PE (15 mg BD for 21 days, then 20 mg OD).
- Apixaban for the prevention of stroke in patients with AF plus one $CHADS_2$ risk factor (5 mg BD),

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**Table I.** Comparison of novel anticoagulants: Mode of action and indication for use

| *Variable* | *Dabigatran* | *Rivaroxiban* | *Apixaban* | *Edoxaban* |
|---|---|---|---|---|
| Class | Direct thrombin (IIa) inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Direct inhibitor of factor Xa |
| Mode of action | Direct, competitive inhibition of free and clot bound thrombin | Direct inhibition of free factor Xa and factor Xa bound to prothrombinase complex | Reversible and selectively inhibits free and clot bound factor Xa | Direct inhibition of free factor Xa |
| Indication/FDA licence (in bold) | **Stroke prevention in patients with AF + one of reduced ejection fraction, CHD, diabetes, <65 years (150 mg BD)**<br>**Treatment of DVT or PE after parenteral anticoagulation for 5-10 days (150 mg BD)**<br>**Prevention of venous thromboembolism in elective hip/knee surgery (110 mg 1-4 hours after surgery, then 220 mg OD 9/7)** | **Stroke prevention in patients with AF + one $CHADS_2$ risk factor (20 mg OD)**<br>**Treatment of DVT and PE and prophylaxis after recurrent DVT/PE (15 mg BD for 21 days, then 20 mg OD)**<br>**Prevention of venous thromboembolism in elective hip/knee surgery (10 mg OD for 35/12 days respectively)**<br>**Prevention of atherothrombotic events in adults after acute coronary syndrome (2.5 mg OD)** | **Stroke prevention in patients with AF + one $CHADS_2$ risk factor (5 mg BD)**<br>**Prevention of venous thromboembolism in elective hip/knee surgery (2.5 mg BD for 35/12 days, respectively)**<br>**Treatment of DVT and PE (10 mg BD for 7 days then 5 mg BD), or prophylaxis after recurrent DVT/PE (2.5 mg BD)**<br>**Prevention of venous thromboembolism (2.5 mg BD)** | **Treatment of DVT or PE and prophylaxis after recurrent DVT/PE (60 mg OD)**<br>**Prevention of stroke and systemic embolic events in patients with AF (60 mg OD)** |
| Dosage (mg) | 110-220 | 2.5-20 | 2.5-5 | 30-60 |
| Reversal | Specific reversal not available; consider prothrombin complex concentrate or dialysis | Specific reversal not available; consider prothrombin complex concentrate in emergency setting | Specific reversal not available; consider prothrombin complex concentrate in emergency setting | Specific reversal not available; consider prothrombin complex concentrate in emergency setting |
| Monitoring | No routine monitoring required | No routine monitoring required | No routine monitoring required | No routine monitoring required |
| Periprocedural management | Depends on renal function:<br>CrCl > 80 mL/min: stop 24-48 hours before<br>CrCl 51-80 mL/min: stop 48-72 hours before<br>CrCl 30-50 mL/min: stop 72-96 hours before | Stop at least 24 hours before intervention | Stop at least 24 hours before intervention | Stop at least 24 hours before intervention |

*AF,* Atrial fibrillation; *BD,* twice daily; *$CHADS_2$,* Congestive heart failure, Hypertension (blood pressure consistently >140/90 mm Hg or treated hypertension on medication), Age ≥75 years, Diabetes mellitus, Prior Stroke or transient ischemic attack or thromboembolism; *CHD,* coronary heart disease; *CrCl,* creatinine clearance; *DVT,* deep venous thrombosis; *FDA,* Food and Drug Administration; *OD,* once daily; *PE,* pulmonary embolism.

prevention of venous thromboembolism in elective hip and knee surgery (2.5 mg BD for 35/12 days, respectively), and treatment of DVT and PE (10 mg BD for 7 days then 5 mg BD), or prophylaxis after recurrent DVT/PE (2.5 mg BD).

- Edoxaban for prevention of stroke and systemic embolic events in patients with AF (60 mg OD) and treatment of DVT or PE and prophylaxis after recurrent DVT/PE (60 mg OD).

Dabigatran has also been used in the prevention of venous thromboembolism in elective hip/knee surgery (110 mg 1-4 hours after surgery, then 220 mg OD for 9/7 days, respectively) and rivaroxaban in the prevention of atherosclerotic events after acute coronary syndrome. However, both of these indications are currently off therapeutic licence (Table I).

## CONTRAINDICATIONS

It is important to know the contraindications to NOAC therapy, which include:

- Recent gastrointestinal bleeding
- Malignancy
- Recent brain, spine, or ophthalmic surgery
- Intracerebral hemorrhage
- Varices
- Arteriovenous malformations
- Concurrent use of other anticoagulants

There are further specific contraindications for individual NOACs (Table II).

Dabigatran should not be used in those with renal impairment because it is 85% renally excreted.[14] There are no trials to show its effect with mild hepatic

**Table II.** Comparison of novel anticoagulants: Special populations

| *Variable* | *Dabigatran* | *Ribaroxiban* | *Apixaban* | *Edoxaban* |
|---|---|---|---|---|
| Creatinine clearance <15 mL/min | No | No | No | No |
| Creatinine clearance 15-29 mL/min | No | Reduced dose (50%) | Reduced dose (50%) | Reduced dose (50%) |
| Moderate to severe hepatic impairment | No | No | No | No |
| Mild hepatic impairment | ? Reduced dose | Yes | ? Reduced dose | Yes |
| Weight <60 kg | Yes | Yes | Reduced dose (50%) | Reduced dose (50%) |

**Table III.** Comparison of novel anticoagulants: Pharmacokinetics

| *Variable* | *Dabigatran* | *Rivaroxiban* | *Apixaban* | *Edoxaban* |
|---|---|---|---|---|
| Target | Thrombin (IIa) | Xa | Xa | Xa |
| Prodrug | Yes | No | No | No |
| Half life, hours | 12-14 | 7-11 | 12 | 10-14 |
| Peak levels, hours | 1.5 | 2-4 | 1-2 | 1-2 |
| Doses | BD | OD | BD | OD |
| Excretion | 85% renal | 65% renal | 25% renal | 35% renal |
| Use in pregnancy/ breast feeding | No | No | No | No |
| Interactions | P-gp inducers: rifampicin—increases risk of stroke/embolism<br>P-gp inhibitors: ketoconazole—increases risk of bleeding | CYP3A4 and P-gp inducers: carbamazepine, phenytoin, rifampicin— increases risk of stroke/ embolism<br>CYP3A4 and P-gp inhibitors: HIV protease inhibitors, itraconazole, ketoconazole,<br>Reduced renal function: amiodarone, diltiazem, verapamil, erythromycin— increases risk of bleeding | CYP3A4 and P-gp inducers: carbamazepine, phenytoin, rifampicin − increases risk of stroke/ embolism<br>CYP3A4 and P-gp inhibitors: HIV protease inhibitors, itraconazole, ketoconazole, clarithromycin | CYP3A4 and P-gp inducers: carbamazepine, phenytoin, rifampicin − increases risk of stroke/ embolism<br>CYP3A4 and P-gp inhibitors: HIV protease inhibitors, itraconazole, ketoconazole, clarithromycin<br>Quinidine, verapamil, and dronedarone to increase edoxaban serum levels |

*BD,* Twice daily; *HIV,* human immunodeficiency virus; *OD,* once daily.

impairment, but it is again contraindicated in moderate to severe hepatic impairment. Rivaroxaban is also contraindicated in patients with a creatinine clearance <15 mL/min, but is tolerated in the elderly and those with a weight of <60 kg.

Apixaban should be used with caution in all of the special populations and avoided in those with severe renal and hepatic impairment. A 50% dose reduction should be considered in patients who weigh <60 kg and are aged >80 years.

Edoxaban should be prescribed at 30 mg (50% reduction) in patients with moderate renal impairment and weight <60 kg and avoided in severe renal impairment (creatinine clearance <15 mL/min).

## BLEEDING

Owing to their pharmacokinetics, there are few suitable reversal therapies in the setting of acute bleeding.[15,16] Thus, the same protocol as for major bleeding on warfarin must be adhered to: discontinue the drug, apply manual compression, maintain blood pressure, surgical or radiological intervention, if appropriate, and replace blood products with or without prothrombin complex concentrate.

It is possible to administer activated charcoal if the anticoagulant was taken ≤2 hours of the bleeding, and hemodialysis may be an option with dabigatran only. Tranexamic acid should also be considered after the result of the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial.[17,18]

After increasing use of dabigatran, the United States Food and Drug Administration recently approved Praxbind (idarucizumab; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conn) in October 2015. This is a specific reversal agent licensed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.

Three trials have included 283 patients, and a serum dose reduction of dabigatran was observed in all cases. A fourth trial in 123 patients with uncontrolled bleeding showed that dabigatran was reversed in 89%.[19]

Other target-specific reversal agents are currently being developed, such as "Andexanet Alfa" for the reversal of both apixaban and rivaroxaban. However, idarucizumab is currently the only licensed therapy.[20]

**Table IV.** Monitoring of new oral anticoagulant (NOAC) therapies

| *No* | *Dabigatran* | *Rivaroxiban* | *Apixaban* | *Edoxaban* |
|---|---|---|---|---|
| APTT | Sensitive (concentration − response relationship)<br>At peak levels APTT is increased 1.5-1.8 times | Sensitive (concentration − response relationship)<br>At peak levels APTT increased by 1.5-2 times | Sensitive (concentration − response relationship)<br>At peak levels APTT increased by 1.2 times | Sensitive (concentration − response relationship)<br>At peak levels APTT is increased 1.3 times |
| PT | Insensitive | Quick type PT may be useful, but generally insensitive | Sensitive<br>At peak levels PT increased by 2.9 times | Sensitive<br>At peak levels PT increased by 2 fold |
| TT | Sensitive (concentration − response relationship) | Sensitive through therapeutic range but results extremely variable. | Insensitive | Insensitive |
| Fibrinogen | Levels affected but not relative to dose | N/A | N/A | N/A |
| Antithrombin/ factor X assays | Insensitive | Sensitive to anti-factor Xa; insensitive to antithrombin | Sensitive to anti-factor Xa; insensitive to antithrombin | Sensitive to anti-factor Xa; insensitive to antithrombin |

*APTT,* Activated partial thromboplastin time; *N/A,* not applicable; *PT,* prothrombin time; *TT,* thrombin time.

## SURGERY

Surgical teams are frequently encountering patients on anticoagulant therapy before the intervention. It is therefore important to be fluent with the management of anticoagulation before an operative procedure. Warfarin has a half-life of 20 to 60 hours and, consequently, a very unpredictable profile. This was reproduced in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, where only one in 10 patients was suitable for surgery 48 hours after stopping warfarin.[21] The advantages of using NOACs are their short half-lives and rapid onset of action. They can be discontinued and resumed rapidly in the preoperative and postoperative period, decreasing the window for risk of thromboembolism (Table III).

Understanding the pharmacokinetics will give background and rationale, but in all cases, the NOACs require cessation of treatment 24 hours before surgery, with the exception of dabigatran, which must be adjusted according to renal function (Table I). As long as adequate hemostasis has been achieved postoperatively, novel anticoagulants can be restarted 6 to 8 hours after the intervention.[22]

For those patients at low risk (ie, nonvalvular AF and low $CHADS_2$ score, venous thromboembolism >12 months prior, and bileaflet aortic valve without AF), no bridging therapy is required during the operative period.

## BRIDGING

It may be clinically indicated in moderate to high-risk patients to convert their regular NOAC therapy to a low-molecular-weight heparin (LMWH; enoxaparin) or warfarin. For these cases the following protocol should be followed[23-25]:

- Dabigatran and apixaban should be discontinued 12 hours before the first dose of enoxaparin.
- Rivaroxaban, and edoxaban, should be discontinued 24 hours before the first dose of enoxaparin (ie, enoxaparin should be commenced at the same time as the next scheduled NOAC dose).

After the procedure, enoxaparin can be converted to regular NOAC therapy once adequate hemostasis has been achieved. For this, the enoxaparin must be discontinued and the NOAC therapy recommenced at the same time as the next scheduled LMWH dose.

For conversion to warfarin, the NOAC should be discontinued once the patient's international normalized ratio is in the therapeutic range. Apixaban must also be continued for a further 2 days after the therapeutic range is reached.

In the case of dabigatran, conversion to warfarin however is slightly more complex:

- Creatine clearance ≥50 mL/min—commence warfarin 3 days before discontinuing dabigatran.
- Creatine clearance 30 to 50 mL/min—commence warfarin 2 days before discontinuing dabigatran.

It is, however, important to consider in these cases if bridging therapy is required. Multiple studies have shown there are similar rates of thrombotic complications after bridging and cessation of treatment but up to fivefold increases in major bleeding risk.[26-29] The half-life of LMWH is also similar to that of the NOAC therapies; therefore, bridging therapy may actually be irrelevant.[30]

## MONITORING

Although the new oral anticoagulants provide a more predicable anticoagulant profile and do not require monitoring, it is possible to review their effects with routine laboratory coagulation screens.[31] A summary of these tests can be found in Table IV.

With such value-added benefits, the new oral anticoagulants are here to stay. Consultants and trainees are therefore likely to encounter increasing numbers of patients on NOAC therapies and should be confident in their use. Tables I-III highlight this key information, as a summary guide for future reference.

## AUTHOR CONTRIBUTIONS

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