New oral anticoagulants – a review

BACKGROUND Dabigatran, rivaroxaban and apixaban are three new oral anticoagulants that have recently been approved in Norway. The aim of this article is to provide an overview of the mechanisms of action, the most important indications and practical advice on the use of these drugs.

METHOD The review is based on published phase 3 studies, a literature search in PubMed and the authors' clinical experience.

RESULTS Indications for use of the new anticoagulants include thromboprophylaxis after total hip and knee replacement surgery (all three), prevention of stroke and systemic embolism in non-valvular atrial fibrillation (all three), treatment of acute venous thrombosis and secondary prophylaxis after venous thrombosis (currently only rivaroxaban). For the aforementioned indications, these drugs have proven to be non-inferior to standard established anticoagulation therapy. For atrial fibrillation, all three drugs have also shown a lower incidence of intracranial bleeding compared with standard treatment.

INTERPRETATION It is important to limit the use of these drugs to approved indications, to select patients who show good compliance, to rule out contraindications and to identify drug interactions. Monitoring of coagulation is not required, but patients should be followed up regularly to detect conditions that may lead to changes in the expected efficacy or safety.

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MAIN POINTS

The new oral anticoagulants inhibit activated coagulation factor II (thrombin) or activated factor X directly

Use must be restricted to approved indications and drug interactions must be checked before starting

Monitoring of anticoagulation effect is not necessary because of predictable dose-response ratio

Patients must be followed up to evaluate compliance, kidney function and risk of bleeding

Good compliance is important for achieving the desired effect

Anticoagulation treatment is necessary for preventing and treating a number of thromboembolic conditions. It is well known that warfarin treatment provides effective protection against thrombosis, but the treatment is made difficult by the small therapeutic window, wide dose-response variation, many interactions and need for INR measurement.

Extensive research has therefore been devoted to developing oral anticoagulants that can be administered in a fixed dose without it being necessary to monitor the coagulation effect. Large-scale drug trial programmes are either in progress or have already been completed (1). At present, there are Norwegian marketing authorisations for the drugs dabigatran, rivaroxaban and apixaban.

The purpose of this article is to provide an overview of the mechanisms of action, trial status and indications and to provide practical information regarding the use of these drugs.

Method

The paper is based on published phase 3 trials of the drugs dabigatran, rivaroxaban and apixaban and clinical experience with them. We also performed a literature search in PubMed to ensure that we had found all phase 3 trials.

Mechanisms of action

Dabigatran, rivaroxaban and apixaban are small molecules that have been developed to inhibit either activated coagulation factor II (thrombin) or activated factor X directly (Fig. 1). Table 1 provides an overview of the most important pharmacokinetic and pharmacodynamic properties (2).

All three drugs result in a predictable and dose-dependent plasma concentration after oral intake. Food intake seems to have little effect on their absorption. Maximum plasma concentration is reached rapidly (after 1–4 hours), while the half-life varies from eight to 17 hours (1).

Clinical studies

Major clinical studies have been made of the efficacy and safety of using the new oral anticoagulants. The studies deal with thromboprophylaxis against post-operative thrombosis following total hip and knee replacement surgery (3–13), prophylaxis against stroke and systemic emboli in patients with non-valvular atrial fibrillation (14–16), treatment of acute deep vein thrombosis and/or pulmonary embolism (17–19), secondary prophylaxis after venous thrombosis (19–21), treatment of acute coronary disease (22–24), and thromboprophylaxis for medical patients (25, 26).

One general principle of the clinical studies has been to show that the clinical efficacy of the new oral anticoagulants is non-inferior to the current treatment with warfarin and/or low-molecular heparin. This principle is often used in trials with an active control arm in order to show that a new treatment is not inferior with regard to effect or safety than the established one. Since it is not possible to show that the two treatments have exactly the same effect, the treatment is thus regarded as non-inferior if the difference in efficacy is within a predefined range.

Dabigatran etexilate

All in all, the clinical trials to investigate post-operative thromboprophylaxis with

dabigatran after total hip (9, 11) or knee replacement (4, 10) have covered more than 10 000 patients. Dabigatran was administered for 28–35 days after hip replacement and for 6–10 days after knee replacement and compared with enoxaparin. In these trials, dabigatran was non-inferior to enoxaparin (40 mg daily) in preventing asymptomatic or symptomatic venous thrombosis and deaths. However, dabigatran *was* inferior to enoxaparin 30 mg × 2 daily – a dose that is largely used in the USA (4). There were no significant differences between dabigatran and enoxaparin in the incidence of major bleeding in these trials.

In patients with non-valvular atrial fibrillation, dabigatran was compared with warfarin as prophylaxis against stroke and systemic embolism (15). Two different dabigatran doses were administered (Table 2) (14–16, 27). The high dose (150 mg × 2) resulted in a significantly reduced incidence of end-points and approximately the same risk of bleeding as warfarin. The low dose (110 mg × 2) was non-inferior to warfarin in preventing stroke and systemic embolism, while causing significantly fewer haemorrhages than warfarin (15). There were fewer life-threatening and intracranial haemorrhages in the dabigatran groups than in the warfarin group, but more gastrointestinal haemorrhages in the group with high dose dabigatran.

Dabigatran was compared with warfarin in patients with acute deep vein thrombosis and/or pulmonary embolism after all the patients had initially been treated with enoxaparin for 5–10 days. Dabigatran treatment was non-inferior to warfarin treatment (17). Dabigatran was also tested in two studies as long-term prophylaxis after initial treatment for acute venous thrombosis (18). In the one study (RE-SONATE) dabigatran was compared with a placebo after an initial 6–18 months of conventional anticoagulation treatment. Dabigatran resulted in a significantly lower risk of recurrence compared with a placebo, but without an increase in major bleeding. In the other trial (RE-MEDY) an active control group was given warfarin, and the participants were randomised after 3–12 months of conventional anticoagulation treatment (20). Here dabigatran was non-inferior to warfarin, but resulted in fewer major bleeding events (Table 3) (17–21, 28).

Half of all haemorrhages in the clinical trials of dabigatran were in the gastrointestinal tract. Dyspepsia was more common in the group that received dabigatran (17).

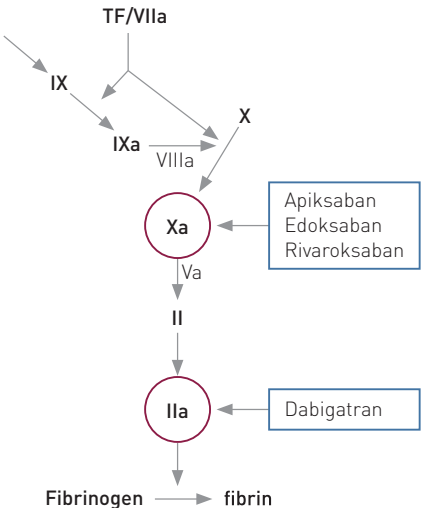

Figure 1 *The coagulation system is activated when the tissue factor (TF) comes into contact with the blood and binds to coagulation factor VII. Factor VII is a proenzyme that is activated to VIIa when VII binds to TF. The TF/VIIa complex then activates coagulation and leads to the formation of factor Xa and factor IIa (thrombin). The new oral anticoagulants are small molecules that inhibit the enzyme activity of factor Xa or thrombin. Three factor Xa inhibitors have been developed – apixaban, edoxaban and rivaroxaban – and one thrombin inhibitor (dabigatran). Edoxaban has not been approved in Norway as yet*

Table 1 The most important properties of the new anticoagulants. The table was prepared by the authors on the basis of the booklet *Informasjon om de nye perorale antikoagulasjonsmidlene dabigatran, rivaroksaban og apiksaban* [Information about the new oral anticoagulants dabigatran, rivaroxaban and apixaban] (2).

Drug	Dabigatran etexilate[1]	Apixaban	Rivaroxaban
Target enzyme	Thrombin	Factor Xa	Factor Xa
Bioavailability (%)	6–7	50	80–100 (with a dose of 10 mg) 66 (with a dose of 20 mg)
Protein binding (%)	35	87	92–95
Time to maximum concentration (h)	1–2	3–4	2–4
Proportion metabolised (%)	10	25	60–70
CYP metabolism	None	CYP3A4	CYP3A4
P-glycoprotein (P-gp)	ER substrate	ER substrate	ER substrate
Secretion in urine (%)	80	27[2]	67[3]
Half-life for different GFR (h)			
> 80 ml/min	14	15	8
50–79 ml/min	17	15	9
30–49 ml/min	19	17	9
< 30 ml/min	28	17	10
Duration of anticoagulation effect (days)	1–3 Dependent on GFR	1–2	1–2

[1] Dabigatran is the active substance. The etexilate group is necessary for absorption in the bowel, but is split off in the liver after absorption
[2] The remainder is metabolised or secreted unaltered into the bowel
[3] Half unchanged and half metabolised

Table 4 Preliminary approved indications for new oral anticoagulants (2). If anticoagulation treatment is needed for conditions where these drugs are not indicated, warfarin or heparins must be used

Indication	Dabigatran etexilate	Apixaban	Rivaroxaban
Non-valvular atrial fibrillation	Yes	Yes	Yes
Post-operative prophylaxis for knee and hip surgery	Yes	Yes	Yes
Deep vein thrombosis – acute	No	No	Yes
Pulmonary embolism – acute	No	No	Yes
Venous thrombosis – secondary prophylaxis	No	No	Yes

Rivaroxaban

The clinical trials to investigate post-operative thromboprophylaxis with rivaroxaban after total hip or knee replacement surgery covered a total of 12 500 patients (3, 5, 12, 13). In all the trials, rivaroxaban prophylaxis was significantly superior to enoxaparin prophylaxis. There were no significant differences in the incidence of major bleeding, although for all the trials combined there was a tendency towards an increase in the number of major bleeding events (1), Extended thromboprophylaxis with rivaroxaban for 31–39 days was significantly superior to 10–14 days of prophylaxis with enoxaparin, which has been general practice following hip replacment (3).

Rivaroxaban treatment of patients with non-valvular atrial fibrillation was non-inferior to warfarin treatment for preventing stroke and systemic embolism (14), and there was no significant difference in the incidence of major bleeding, although there were fewer intracranial and fatal haemorrhages in the rivaroxaban group (Table 2) (14).

Rivaroxaban treatment of patients with pulmonary embolism with/without deep vein thrombosis (18) and deep vein thrombosis without pulmonary embolism (19) was non-inferior to conventional anticoagulation (2). Rivaroxaban was also tested as long-term prophylaxis after anti-coagulation treatment of acute deep vein thrombosis and/or pulmonary embolism and gave a significant reduction in the risk of recurrence compared to a placebo, without a significantly higher incidence of major bleeding (19).

In cases of acute coronary syndrome, low-dose rivaroxaban administered as a supplement to conventional anti-platelet therapy led to a reduction in cardiovascular mortality, myocardial infarction or stroke compared with supplementary treatment with a placebo. At the same time, however, the treatment led to a higher incidence of major, but non-fatal bleeding (23).

Administered as thromboprophylaxis to acutely ill in-hospital medical patients with a high risk of venous thrombosis, rivaroxaban was non-inferior to enoxaparin, but led to significantly more haemorrhages (26).

Apixaban

A total of 11 000 patients were included in trials to investigate post-operative thromboprophylaxis with apixaban following total hip and knee replacement (6–8). Apixaban was non-inferior to enoxaparin 40 mg × 1 (7, 8), but *was* inferior to enoxaparin 30 mg × 2 daily (6). No differences were found in bleeding risk in these trials.

In patients with non-valvular atrial fibrillation, apixaban treatment resulted in significantly fewer cases of stroke or systemic embolism and lower total mortality than treatment with warfarin, and there were significantly fewer severe haemorrhages (27) (Table 2). In another trial, apixaban was significantly superior to acetylsalicylic acid as prophylaxis against stroke or systemic embolism in patients who were unsuitable for warfarin treatment. There were no differences in the incidence of major bleeding (16).

Apixaban treatment of patients with acute deep vein thrombosis and/or pulmonary embolism was non-inferior to conventional treatment (28). In long-term prophylaxis following initial anti-coagulation treatment, apixaban led to a significant reduction in the risk of recurrence of venous thrombosis compared with a placebo, without a significant increase in bleeding risk (21). At present, apixaban is not approved for treatment of venous thrombosis.

Apixaban was also tested as thromboprophylaxis for acutely ill in-hospital medical patients with a high risk of venous thrombosis (25) and in combination with antiplatelet therapy in cases of acute coronary syndrome (24). Apixaban was not superior to enoxaparin or a placebo in these two trials; on the contrary, there was an increased incidence of haemorrhages.

Interpretation of the phase 3 trials

The trials have shown that the new anticoagulants are either non-inferior to or superior to conventional therapy for the indications thromboprophylaxis after total hip or knee replacement surgery, prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation, treatment of acute venous thrombosis, even though only rivaroxaban has been approved for this indication as yet. In these trials, the incidence of serious bleeding was the same as or lower than that experienced with conventional anticoagulation therapy. In cases of atrial fibrillation, all three drugs showed a significantly lower incidence of intracranial haemorrhages than warfarin (14, 15, 27).

After the completion of anticoagulation treatment for acute venous thrombosis, there is a considerable risk of recurrence, but because warfarin also entails a significant risk of haemorrhage, the duration of the therapy, particularly after the first episode, is often limited. Secondary prophylaxis with new anti-coagulants can reduce the risk of recurrence by about 70–80 % compared with a placebo, without a significant increase in the number of severe haemorrhages (19–21).

Trials conducted with standard dose dabigatran, standard dose apixaban and low dose rivaroxaban with acute coronary disease showed inconsistent results as regards clinical efficacy and bleeding risk (22–24). Only low dose rivaroxaban resulted in lower mortality without a significant increase in the number of severe haemorrhages (23). Extended thromboprophylaxis with apixaban or rivaroxaban for acutely ill in-hospital medical patients resulted in significantly higher bleeding rates and hence no benefit compared with ten-day treatment with enoxaparin (25, 26).

All clinical trials on these drugs were conducted without adjusting the dose with respect to anticoagulation effect. This means that treatment with dabigatran, rivaroxaban and apixaban can be carried out without monitoring the anticoagulation effect. However, all three have a relatively short half-life. Lack of patient compliance is therefore a potential problem when these drugs are to be used in practice. As a rule, patients taking part in clinical trials are motivated and are closely monitored, which probably leads to greater compliance. It also contributes to more rapid identification and treatment of intercurrent conditions that may arise during treatment.

One such example is deterioration in kidney function/development of kidney failure, which in turn can cause a greater concentration of the drug and risk of bleeding. Expected poor patient compliance was one of the exclusion criteria in most trials, in addition

Table 5 Important practical advice for use of new oral anticoagulants. The advice is based on own experience in the use of these drugs and review and interpretation of the literature

Must be used for approved indication	The drugs must be used only for approved indications. These vary for the different products Recommended dose varies depending on indication, kidney function and the patient's age
Contraindications and precautionary rules	The drugs must not be administered in cases of: – mechanical heart valve – valvular atrial fibrillation – pregnancy/nursing – active bleeding – serious renal failure – impaired liver function with coagulopathy Be on the watch for comorbid conditions that increase the risk of bleeding such as impaired kidney and liver function, thrombocytopaenia and alcoholism Avoid the drugs where there is suspicion of poor compliance Check levels of haemoglobin, thrombocytes, ALT, bilirubin, creatinine and INR before starting
Drug interactions	Check interactions with the patient's other medication at http://interaksjoner.no/ Avoid using new anticoagulants if the patient uses drugs that inhibit or induce P-gp or CYP3A4. – Examples of inhibitors of P-gp and/or CYP3A4 which result in increased haemorrhage risk: amiodarone, verapamil[1], quinidine[1], ketoconazole/voriconazole[1], clarithromycin/erythromycin and HIVdrugs[1] – Examples of drugs that induce P-pg and/or CYP3A4 and result in reduced efficacy: rifampicin[1], St John's Wort[1], carbamazepine[1], phenytoin[1]. New oral anticoagulants must not be combined with platelet inhibitors (unless the combination is indicated), non-steroid anti-inflammatories or other anticoagulants
Patient information/follow-up	Patients must be equipped with a patient card and must be informed of the importance of – good compliance – how to handle a missed dose – possible interactions – the fact that all the drugs are contraindicated in pregnancy. Ask at check-ups about: compliance and any bleeding. Annual check-ups of Hb, creatinine/GFR – every 3–6 months in cases of impaired kidney function
Handling major bleeding	Discontinue the drugs and ensure local haemostasis Medical reversal in cases of life-threatening haemorrhaging
Transition from other anti-coagulants/brief treatment stop	Recommendations regarding INR level in connection with a switch from warfarin to the new anticoagulants vary from drug to drug. See the Felleskatalogen [Norwegian Pharmaceutical Product Compendium] for exact INR level New oral anticoagulants can be started 12–24 hours after the last dose of low-molecular heparin In the event of planned surgery it is sufficient to neutralise new oral anticoagulants 24–48 hours before the planned operation, depending on the patient's kidney function
Reporting	Treatment failure, side effects and interactions must be reported to RELIS – regional centres for pharmaceuticals information in Norway

[1] Indicates moderate to strong interaction

to slight or moderately elevated liver transaminases and bilirubin and uncontrolled hypertension. We therefore know little about patients who belong to one of these groups. The same applies to patients with cancer. A high age was not an exclusion criterion, but there are limited clinical data on patients aged over 75.

Practical advice

This advice is based on summaries of product characteristics (SPC), which can be obtained from the Norwegian Medicines Agency's website for the different formulations for each product (our download date 3 July 2013) (29), and the authors' experience and other sources of information (2). Table 4 summarises the indications for the different drugs, and Table 5 summarises practical advice regarding start-up and follow-up.

The drugs must be used only for approved indications

It is important that doctors familiarise themselves thoroughly with the summary of product characteristics with respect to information on indications, dosage and precautionary rules before using the drugs. The three drugs all have thromboprophylaxis following knee and hip surgery as an approved indication. All three also have non-valvular atrial fibrillation as an approved indication (2). At present only rivaroxaban is approved for acute treatment of deep vein thrombosis and/or pulmonary embolism and for secondary prophylaxis after venous thrombosis.

Contraindications and precautionary rules

The drugs must not be given to patients with a mechanical heart valve and valvular atrial fibrillation (serious post-rheumatic heart valve defect) or to pregnant women or nursing mothers. They have not been tested for treatment of children, nor for acute venous thrombosis in cancer patients. Patients with a glomerular filtration rate of < 30 ml/min must not take dabigatran, while rivaroxaban and apixaban must not be given to patients with a GFR < 15 ml/min. For these patients (with the exception of pregnant women) we rather recommend conventional anticoagulation treatment with warfarin.

Nor must the new oral anticoagulants be given to patients with seriously impaired liver function and signs of coagulopathy. Kidney function and liver status must therefore be checked before start-up. Caution should be exhibited in prescribing the drugs to patients with anticipated poor compliance. We recommend a dose reduction for elderly patients (aged > 80), because of impaired kidney function and generally higher risk of bleeding.

Drug interactions

Dabigatran, rivaroxaban and apixaban should preferably not be used where there is a significant risk of interaction with other drugs (Table 5). Nor should they normally be combined with other anticoagulants, platelet inhibitors or non-steroid anti-inflammatory drugs (NSAIDs).

Patient information and follow-up

It is important that patients have thorough information. They must be equipped with patient cards with information about dosage and indication. Patients must be regularly reminded of the importance of compliance, and that they are not protected if they fail to take 1–2 doses. It is important to stress that the medicine must be taken regularly at the same time of day.

Although laboratory monitoring of coagulation effect is not necessary, it is still important that patients be followed up regularly to evaluate bleeding risk, kidney function (especially in the case of dabigatran use by elderly patients) and compliance.

Handling serious bleeding

There may be a need to reverse the anticoagulation effect in the case of major bleeding, particularly cerebral bleeding, life-threatening bleeding and in the event that acute surgery is needed. At present there are no specific antidotes that can reverse the effect of the drugs. In the event of bleeding, the drugs must be discontinued and general measures implemented, such as local haemostasis and blood transfusion. Because of the short half-life, the effect will have dissipated in the course of 12–24 hours (30). If bleeding occurs after one half-life, the effect of the drug will normally be so low that there is no need for an antidote (30).

Carbon is particularly effective with dabigatran and must be administered in the event of overdose or bleeding if the dose has been taken within the last two hours (31). Since dabigatran is not protein-bound, most can be removed by dialysis (31). In the event of major bleeding, medical reversal of the effect may be necessary. Prothrombin complex concentrate should be administered: recommended dose 30–50 E/kg body weight (29). Activated prothrombin complex concentrate of 50–80 E/kg and recombinant FVIIa (rFVIIa) are probably the most effective treatment, and must be considered in the event of major bleeding (2). We recommend that all hospitals have activated prothrombin complex concentrate and recombinant FVIIa in readiness.

Transition from other anticoagulants after brief break in treatment

If there is an indication to switch from warfarin, the transition to the new anticoagulants can take place when the INR level is within a defined range depending on the patient's condition and the product (29). When making the transition from low-molecular heparin, treatment with new oral anticoagulants can start 12–24 hours after the last dose (29).

In the event of planned surgery it is normally possible to neutralise the new oral anticoagulants in the period 24–48 hours before the planned operation, depending on the patient's kidney function, the magnitude of the intervention and the anticipated bleeding risk. After the operation, drug therapy can begin again when haemostasis is assured and the risk of bleeding is over (2).

Measurement of anticoagulation effect

There may be a need to measure the anticoagulation effect in some situations – in the event of therapy failure, acute surgery or bleeding (32). The usual coagulation tests such as INR and activated partial thromboplastin time (APTT) may be affected by these drugs. However, none of these tests have a linear relationship with the drug concentration, and so they cannot be used to measure the anticoagulation efficacy. The APTT is extended by dabigatran, and values of > 90 seconds may indicate overdosing, while values between 70 and 90 seconds indicate optimal anticoagulation effect.

Specific tests for precise determination of the coagulation effect, such as «ecarin clotting time» for dabigatran, or anti-FXa which is calibrated for measuring rivaroxaban and apixaban (not for low-molecular heparin) are not available in Norway at present.

Reporting of adverse events

It is important to monitor and report unexpected effects of treatment and of drug interactions.

Conclusion

Marketing authorisations for Norway have recently been awarded for three new anticoagulants. Both efficacy and safety have been well documented in clinical trials for the most usual indications. It is important to restrict the use of these drugs to approved indications and to patients with good compliance. Even though there is no need to monitor the coagulation effect, patients should still be followed up regularly in order to deect conditions that may lead to changes in expected efficacy or safety.

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