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Review Article

Usage and Safety of Direct Oral Anticoagulants at Patients with Atrial Fibrillation and Planned Diagnostic Procedures, Interventions, and Surgery

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Abstract

Atrial fibrillation (AF) affects about 2% of the population, with the increasing prevalence with age. It is associated with poorer quality of life, effort intolerance, frequent hospitalizations, heart failure, and increased risk of systemic embolization, stroke, and mortality. Warfarin has been the only choice of chronic anticoagulant therapy for over 50 years. Its disadvantages are reflected by interaction with various foods, drugs, and alcohol, while its action is highly dependent on liver function, age, and genetic background. Administration of direct oral anticoagulants (DOACs) to patients with AF and acceptable bleeding risk reduces the risk of systemic thromboembolic complications and stroke; these drugs are superior or at least as effective as warfarin. Their use is safer than warfarin in terms of reduced risk of major bleeding. This is a group of drugs with wide clinical use, except in patients with severely impaired renal and hepatic function. Proper use is a guarantee of the safety of DOACs, which in the future will be even more pronounced with the advent of new antidotes, such as Praxbind.

Keywords: Atrial fibrillation, direct oral anticoagulant, risk reduction, safety, stroke, thromboembolism, warfarin

Introduction

Atrial fibrillation (AF) affects about 2% of the population. Its prevalence increases with age and about 15% of the population aged 80 years has this arrhythmia. It is associated with poorer quality of life, effort intolerance, frequent hospitalizations, heart failure, and increased risk of systemic embolization, stroke, and mortality.[1-3] In developed countries, the majority of patients have nonvalvular AF, while the less have valvular AF due to moderate/severe mitral stenosis and/or mechanical valves.[1-3] It is classified as follows:

a. Paroxysmal AF – Self-terminating, in most cases within 48 h. Some AF paroxysms may continue up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal
b. Persistent AF – Lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more
c. Long-standing persistent AF – Continuous AF lasting for at least 1 year when it is decided to adopt a rhythm control strategy and
d. Permanent AF – It is accepted by the patient and physician. Hence, rhythm control interventions are not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be reclassified as a long-standing persistent AF.

Warfarin, a Vitamin K antagonist, has been the only choice of chronic anticoagulant therapy for over 50 years. Its disadvantages are reflected by interaction with various foods, drugs, and alcohol, while its action is highly dependent on liver function, age, and genetic background (polymorphism of the

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cytochrome P-2C9 enzyme). Warfarin efficacy is evaluated periodically by monitoring prothrombin time (PT) and international normalized ratio (INR). Despite the widespread availability of the drug and a clear indication of its use, a number of patients do not take it or have no INR values in the therapeutic range. In the past few years, several drugs from the direct oral anticoagulants (DOACs) have appeared on the market that are equally (or more) effective, safer, and more suitable than warfarin, and include dabigatran, apixaban, and rivaroxaban.[1-9]

According to the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines, indications for the use of anticoagulant therapy at patients with AF are based on an assessment of the risk of thromboembolic events and bleeding by using the:[1-3]

a. CHADS-VASc (heart failure [1 point], hypertension [1 point], age ≥ 75 years [2 points], diabetes [1 point], stroke/transient ischemic attack/thromboembolism [2 points], vascular disease [1 point], age 65–74 years [1 point], female gender [1 point]) and
b. HAS-BLED scoring systems (hypertension [1 point], liver and kidney failure [2 points, 1 point for each one], stroke [1 point], bleeding [1 point], labile INR value [1 point], age [>65 years] [1 point], drugs and alcohol [2 points, 1 point for each one]), respectively.

Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHADS-VASc score of 2 or more and all females with AF with CHADS-VASc score of 3 or more (Class I, Level A). Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHADS-VASc score of 1 and in female AF patients with a CHADS-VASc score of 2 (Class IIa, Level B). Vitamin K antagonist therapy (INR 2–3 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves (Class I, Level B). When oral anticoagulation is initiated in a patient with AF who is eligible for a DOAC, a DOAC is recommended in a preference to a Vitamin K antagonist (Class I, Level A). AF patients already on treatment with a Vitamin K antagonist may be considered for DOAC treatment if time in therapeutic range is not well controlled despite good adherence, or if patient preference without contraindications to DOAC (e.g., prosthetic valve) (Class IIb, Level A). Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk (Class III, Level A). Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent (Class I, Level II). In patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF (Class I, Level C).

A high HAS-BLED score (values ≥3) is not a contraindication to the use of anticoagulant therapy, but with increased caution and recommendation of correction of corrective factors (hypertension, withdrawal/replacement of certain drugs that do not interact with anticoagulants).[1-3]

Direct Oral Anticoagulant Drugs

Dabigatran

Dabigatran-etexilate is the first drug approved by the regulatory bodies after results of Randomized Evaluation of the Long-term Anticoagulant Therapy (RE-LY) study.[10] It is approved for the prevention of stroke and systemic embolization in adult patients with nonvalvular AF, and in the primary prevention, acute treatment, and secondary prevention of venous thromboembolism (VTE). It is a small synthetic molecule (analog in hirudin), a direct inhibitor of thrombin (Factor IIa of coagulation cascade), which prevents the conversion of fibrinogen to fibrin and thus clot formation.[10]

Pharmacological properties

Inactive prodrug dabigatran-etexilate is converted into active dabigatran by digestive, plasma, and hepatic esterases. Dabigatran-etexilate is not metabolized with P450 liver enzymes, thus avoiding drug–drug interactions with cytochrome P450 substrates. However, about 20% of the created dabigatran is conjugated with glucuronic acid and such conjugates may have an active role and interact with other drugs. Finally, drugs that reduce the activity of the P-glycoprotein (P-gp) enzyme in the intestinal epithelium (amiodarone, quinidine, verapamil, and antifungals) increases the absorption of dabigatran-etexilate and the concentration of the active drug in the plasma. The primary route of elimination is renal (80%–85%) and less via the biliary tract.[1-10]

Efficiency and safety profile

Dabigatran is more effective than warfarin in stroke prevention and systemic embolism in patients with nonvalvular AF (RE-LY study). The risk of stroke or systemic embolism was reduced by 35%. The safety profile is reflected in the risk of bleeding. Usage of dabigatran in a daily dose (150 mg twice daily) results with equal risk of major bleeding in comparison with warfarin. However, it reduces the risk of intracranial and minor bleeding.[1-10]

Dosage and route of administration

Dabigatran-etexilate is administered orally, not related with food. The daily dose depends on renal and hepatic function. Renal function is assessed by creatinine clearance (CrCl) calculated by the Cockroft–Gault formula. People with CrCl >50 mL/min are taking the drug at full dose. In the elderly (>80 years), high risk of bleeding (HAS-BLED ≥3), interaction with other drugs (i.e., verapamil), or CrCl 30–49 mL/min, the dose is reduced to 110 mg ×2 daily. The administration of the drug is contraindicated at CrCl <30 mL/min, although according to the Food and Drug Administration recommendations, it can be applied at CrCl 15–30 mL/min, at a dose of 75 mg ×2 daily with special caution, and preferably discontinuation of therapy. Renal function is monitored once a year (CrCl ≥60 mL/min), every 6 months (CrCl 30–60 mL/min), and every 3 months (CrCl 15–30 mL/min).[1-10]

Patients with mild-to-moderate liver damage (Child-Pugh Classes A and B) can take dabigatran-etexilate, while in more severe cases (Child-Pugh C), its usage is contraindicated. Its usage in pregnancy and during lactation is contraindicated. The forgotten dose can still be taken up to 6 h before the next scheduled dose according to the dosing schedule. If these 6 h elapse, the missed dose is skipped. Dabigatran has a predictable effect and does not require routine coagulation monitoring but can be done by determining activated partial thromboplastin time (APTT) and thrombin time (TT).[1-10]

Interaction with other drugs

The concomitant administration of dabigatran-etexilate with a group of potent P-gp inhibitors (systemic ketoconazole, cyclosporine, itraconazole, dronedarone, and tacrolimus) is contraindicated. Caution should be exercised with mild-to-moderate P-gp inhibitors (amiodarone, posaconazole, quinidine, verapamil, and ticagrelor), with dose reduction to 110 mg ×2 daily. Antacids and proton-pump inhibitors may reduce the concentration of dabigatran, so it should be taken 2 h before the above medicines. Concomitant administration of P-gp inducers (rifampicin, St. John's wort, carbamazepine, and phenytoin) may decrease the concentration of dabigatran and should be avoided.[1-10]

Diagnostic procedures, interventions, and surgery

Minor bleeding risk (cataracts, glaucoma, extraction of 1–3 teeth, periodontal procedures, abscess incision, implant placement, endoscopy without surgery, and small surgical procedures on the skin) do not necessarily require discontinuation of therapy; it is enough a minimum of 12 h from the last dose to the beginning of surgery. The drug is reintroduced at least 6 h after the procedure.[1-10]

Low bleeding risk (endoscopy with biopsies, electrophysiology with catheter ablation of right-sided supraventricular tachycardia, noncoronary angiography, pacemaker, or cardioverter-defibrillator placement) requires the cessation of the drug, depending on renal function for at least 24 h (CrCl ≥80 mL/min), 36 h (CrCl 50–80 mL/min), and 48 h (CrCl 30–50 mL/min) before the procedure.[1-10]

High bleeding risk (catheter ablation of left-sided supraventricular tachycardia, spinal/epidural anesthesia, lumbar puncture, thoracic surgery, abdominal surgery, major orthopedic surgery, liver biopsy, transurethral resection of the prostate, kidney biopsy, and lithotripsy kidney stones) requires the cessation of the drug, depending on renal function at a minimum of 48 h (CrCl ≥80 mL/min), 72 h (CrCl 50–80 mL/min), and 96 h (CrCl 30–50 mL/min) before the procedure.[1-10]

After a procedure with immediate and complete hemostasis, dabigatran can be generally resumed 6–8 h after the end of the intervention. After other surgical interventions, treatment continues after 48–72 h; the initiation of thromboembolism prophylaxis (enoxaparin) should be performed 6–8 h after reaching complete hemostasis.[1-10]

Rivaroxaban

Rivaroxaban is the second approved drug and the first direct oral inhibitor of clotting Factor Xa.[11] It was approved for the prevention of stroke and systemic embolization in adult patients with nonvalvular AF, and in primary prevention, acute treatment, and secondary prevention of VTE, based on the results of rivaroxaban versus warfarin and nonvalvular AF (ROCKET-AF) study. Rivaroxaban is an unusually important factor that links the internal and external pathways of blood clotting and thus determines thrombin formation.[11]

Pharmacological properties

It is rapidly absorbed after oral administration in an active form; about two-third of the dose is metabolized by the liver cytochrome P-450, half of which is excreted in feces and the other half in the urine. A third of the remaining dose is eliminated unchanged via the kidney. Thus, about 60% of the drug is eliminated via the urinary tract. It has a predictable effect, so routine coagulation monitoring is not required but can be done by determining anti-Xa activity.[1-9,11]

Efficiency and safety profile

Rivaroxaban is noninferior (equally effective) to warfarin in stroke prevention and systemic embolization in patients with nonvalvular AF (ROCKET-AF study). Administration of rivaroxaban at a daily dose (20 mg once daily) results in a reduced risk of major and intracranial bleeding in comparison with warfarin.[1-9,11]

Dosage and route of administration

It is administered orally, at a daily dose of 20 mg once daily, with food, or within 2 h after a meal. People with CrCl >50 mL/min are taking the drug at full dose. In patients with CrCl 15–49/min, or high bleeding risk (HAS-BLED ≥3), the dose should be reduced to 15 mg once daily, while for worse renal function, the use of rivaroxaban is contraindicated. Renal function is monitored once a year (CrCl ≥60 mL/min), every 6 months (CrCl 30–60 mL/min), and every 3 months (CrCl 15–30 mL/min).[1-7,9] Patients with mild hepatic impairment (Child-Pugh Class A) may take rivaroxaban with increased caution, whereas in more severe impairment (Child-Pugh Class B and C), its usage is contraindicated. Its usage in pregnancy and during lactation is contraindicated. Missed dose should be taken immediately, with emphasize that two doses may not be taken on the same day.[1-9,11]

Interaction with other drugs

The concomitant use of rivaroxaban with potent inhibitors of P-4503A4 and P-gp enzymes (ketoconazole, itraconazole, voriconazole, posaconazole, and ritonavir) is contraindicated.[1-9,11]

Diagnostic procedures, interventions, and surgery

Minor bleeding risk (cataracts, glaucoma, extraction of 1–3 teeth, periodontal procedures, abscess incision, implant placement, endoscopy without surgery, and small surgical procedures on the skin) do not necessarily require discontinuation of the drug; it is enough a minimum of 24 h

from the last dose to the beginning of surgery. The drug is reintroduced at least 6 h after the procedure.[1-9,11]

Low bleeding risk (endoscopy with biopsies, electrophysiology with catheter ablation of right-sided supraventricular tachycardia, noncoronary angiography, pacemaker, or cardioverter-defibrillator placement) requires the cessation of the drug, depending on renal function for at least 24 h (CrCl ≥30 mL/min) and 36 h (CrCl 15–30 mL/min) before the procedure.[1-9,11]

High bleeding risk (catheter ablation of left-sided supraventricular tachycardia, spinal/epidural anesthesia, lumbar puncture, thoracic surgery, abdominal surgery, major orthopedic surgery, liver biopsy, transurethral resection of the prostate, kidney biopsy, and lithotripsy kidney stones) requires the cessation of the drug for at least 48 h before the procedure and not dependent about renal function.[1-9,11]

For procedures with rapid and complete hemostasis, rivaroxaban administration may be continued for 6–8 h after the intervention. After other surgical interventions, treatment continues after 48–72 h; the initiation of thromboembolism prophylaxis (enoxaparin) should be performed 6–8 h after reaching complete hemostasis.[1-9,11]

Apixaban

Apixaban also belongs to the group of direct inhibitors of clotting Factor Xa. It was approved according to the results of apixaban versus warfarin in patients with AF (ARISTOTLE) study, for the prevention of stroke and systemic embolization in adult patients with nonvalvular AF, and in primary prevention, acute treatment, and secondary prevention of VTE.[1-9,12]

Pharmacological properties

The drug is administered in the active form. It is rapidly absorbed after oral administration and (like rivaroxaban) metabolized by the liver cytochrome P-450 and P-4503A4 isoenzymes. The drug has a dual-elimination pathway: 27% is excreted by the kidney and the rest by stool. It has a predictable effect, so routine coagulation monitoring is not required but can be done by determining anti-Xa activity.[1-9,12]

Efficiency and safety profile

Apixaban is more effective than warfarin in the prevention of stroke and systemic embolization in patients with nonvalvular AF (ARISTOTLE study). The safety profile is reflected in the risk of bleeding. The use of apixaban at a daily dose (5 mg twice daily) reduces the risk of major and minor bleedings in comparison with warfarin.[1-9,12]

Dosage and route of administration

It is administered orally, at a dose of 5 mg twice daily, with food or within 2 h after a meal. The daily dose depends on renal and hepatic function. People with CrCl ≥30 mL/min take the drug depending on age (≥80 years), body weight (≤60 kg), and serum creatinine (≥133 mmol/L). If there are more than one of the mentioned features, apixaban is taken in a reduced dosage (2.5 mg twice daily).[1-9,12] In the case of patients with CrCl 15–29 mL/min, the dose should be reduced to 2.5 mg twice daily, while in more severe renal dysfunction administration is contraindicated. Renal function is monitored once a year (CrCl ≥60 mL/min), every 6 months (CrCl 30–60 mL/min) and every 3 months (CrCl 15–30 mL/min).[1-9,12] Patients with mild or moderate hepatic impairment (Child-Pugh Class A and B) may take apixaban, whereas in severe (Child-Pugh Class C) cases, administration is contraindicated. Its usage in pregnancy and during lactation is contraindicated. If the case of forgotten dose, patient must take the medicine immediately and then continue to take twice a day as before.[1-9,12]

Interaction with other drugs

It is contraindicated to use of apixaban with potent inhibitors of P-4503A4 and P-gp enzymes (ketoconazole, itraconazole, voriconazole, posaconazole, and ritonavir).[1-9,12]

Diagnostic procedures, interventions, and surgery

Minor bleeding risk (cataracts, glaucoma, extraction of 1–3 teeth, periodontal procedures, abscess incision, implant placement, endoscopy without surgery, and small surgical procedures on the skin) do not necessarily require discontinuation of the drug, it is enough a minimum of 12 h from the last dose to the beginning of surgery. The drug is reintroduced at least 6 h after the procedure.[1-9,12]

Low bleeding risk (endoscopy with biopsies, electrophysiology with catheter ablation of right-sided supraventricular tachycardia, noncoronary angiography, pacemaker, or cardioverter defibrillator placement) requires discontinuation of the drug depending on renal function for at least 24 h (CrCl ≥30 mL/min) and 36 h (CrCl 15–30 mL/min) before the procedure.[1-9,12]

High bleeding risk (catheter ablation of left-sided supraventricular tachycardia, spinal/epidural anesthesia, lumbar puncture, thoracic surgery, abdominal surgery, major orthopedic surgery, liver biopsy, transurethral resection of the prostate, kidney biopsy, and lithotripsy kidney stones) requires the cessation of the drug for at least 48 h before the procedure and not dependent about renal function.[1-9,12]

For procedures with rapid and complete hemostasis, rivaroxaban administration may be continued for 6–8 h after the intervention. After other surgical interventions, treatment continues after 48–72 h; the initiation of thromboembolism prophylaxis (enoxaparin) should be performed 6–8 h after reaching complete hemostasis.[1-9,12]

Other considerations

Preoperative bridging with low molecular weight heparin or heparin is not recommended at patients treated with DOAC since the predictable waning of the anticoagulation effect allows properly timed short-term cessation of DOAC therapy before surgery.

If an emergency intervention is required, the DOAC should be discontinued immediately. Immediate procedures (e.g., organ or life-saving traumatic, cardiac, vascular, neurosurgical)

need to be performed within minutes of the decision to operate and cannot be delayed. In these cases, reversal with idarucizumab (for dabigatran) and andexanet alfa (for rivaroxaban and apixaban) or with prothrombin complex concentrates (PCCs) if reversal agents are not available should be considered, especially in moderate-to-high hemorrhagic risk procedures.[13-17] If no specific reversal agent is available, it may be advisable to perform immediate (and urgent) procedures under general rather than spinal anesthesia due the risk of epidural hematoma.

Urgent procedures (e.g., intervention for acute onset or clinical deterioration of potentially life-threatening conditions, conditions that may threaten the survival of limb or organ, fixation of fractures, relief of pain, or other distressing symptoms) need to be performed within hours of the decision to operate. In these situations, surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Furthermore, coagulation test results can be awaited in this situation to gauge the necessity for reversal or application of PCCs. Expedite procedures (patients requiring early treatment where the condition is not an immediate threat to life, limb, or organ survival) should be performed within days of decision to operate. In these situations, interruption of DOAC should follow the proposed rules for elective surgery.

In all such situations, a full panel of coagulation assays (PT, APTT, anti-FXa for rivaroxaban/apixaban, diluted TT/ecarin chromogenic assay for dabigatran) should be obtained in order to assess the coagulation status of the patient. Even if in the emergency situation application of pro-hemostatic agents will not be postponed, results of these initial tests may have implications for further treatment during the ensuing hours.

Direct oral anticoagulant in renal impairment and the elderly

With varying degrees of renal impairment, dabigatran-etexilate is the most potent in reducing the risk of adverse thromboembolic events in comparison to well-controlled warfarin. With respect to significant bleeding, apixaban has the best safety profile. In the elderly (≥75 years), dabigatran-etexilate again has a better efficacy and safety profile compared to well-controlled warfarin.[1-12,18]

Bleeding Complications

If bleeding occurs, the drug should be discontinued immediately. In these cases, determination of APTT and TT (dabigatran) and Factor Xa activity (apixaban, rivaroxaban) may help. General measures include hemostasis, hydration, maintenance of diuresis, blood transfusion, and waiting for the drug to be metabolized and excreted. The use of activated carbon can help to reduce the absorption of dabigatran and rivaroxaban. Dabigatran is dialysable, while the remaining two drugs cannot be removed by dialysis. In more severe bleeding cases, the prothrombin complex (25 U/kg) may be used. The administration of recombinant Factor VIIa is also considered. Dabigatran antidote (idarucizumab), a defragmented monoclonal antibody with a high affinity for dabigatran, is available on the market. Other drugs are andexanet alfa (recombinant Factor Xa, an antidote for rivaroxaban and apixaban) and aripazine, a small synthetic molecule that eliminates the effect of all DOACs and heparin.[1-18]

Safety of Direct Oral Anticoagulant Application in Certain Clinical Situations

In everyday clinical practice, there are certain situations, in which the use of one DOAK in patients with AF is more effective/safer than another, as follows: moderate renal failure (CrCl 30–50 mL/min) – recommended rivaroxaban or apixaban; increased risk of gastrointestinal bleeding-recommended apixaban; increased risk of bleeding from mucous membranes (upper respiratory system, genitourinary) – recommended dabigatran; recent ischemic stroke on warfarin-dabigatran – recommended; recent acute coronary syndrome – recommended rivaroxaban; moderate/severe heart failure – recommended dabigatran; a parallel treatment of thromboembolism/deep vein thrombosis or the prevention of recurrence-rivaroxaban or apixaban; poor patient compliance – recommended single-dose rivaroxaban; and enteral administration-recommended rivaroxaban or apixaban.[1-18]

Conclusion

Administration of DOACs to patients with AF and acceptable bleeding risk reduces the risk of systemic thromboembolic complications and stroke; these drugs are superior or at least as effective as warfarin. Their use is safer than warfarin in terms of reduced risk of major bleeding. This is a group of drugs with wide clinical use, except in patients with severely impaired renal and hepatic function. Proper use is a guarantee of the safety of DOACs, which in the future will be even more pronounced with the advent of new antidotes, such as Praxbind.

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Conflicts of interest

There are no conflicts of interest.

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