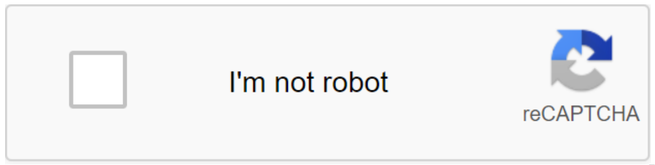

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Newer oral anticoagulants pdf

PDF Split View Article Content Figures and Tables Video Audio Additional data New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Unlike the VCA, these anticoagulants do not require regular INR monitoring and have favorable pharmacological properties. The lack of effective antidotes, their cost, or reservations in patients with kidney disease may explain their slow pace of expansion. The safe and effective use of these new drugs will depend on the clinical experience of the medical community. This review examines current NOAKs that provide practical and easy-to-use algorithms for clinical routine use. Atrial fibrillation, new oral anticoagulants, stroke vitamin K antagonists (VKAs) have been the main stone for antithrombotic prevention in atrial fibrillation (AF) for 60 years. Despite its undeniable effect to prevent strokes, the medical community must deal with significant limitations such as general medicinal or nutritional interactions, as well as the need for regular monitoring to adjust doses in particular. In the last 5 years, oral anticoagulant therapy has now witnessed a revolution after the completion of a large Phase III clinical trial on the commonly referred to as the new oral anticoagulants (NOACI). The benefits of these new agents, including the use of fixed dosing without the need for monitoring, multiple interactions, and a wider therapeutic window to counteract their current shortcomings. The lack of effective antidotes, their cost, or reservations in patients with kidney disease may explain their slow pace of expansion. After the inevitable enthusiasm, it is the responsibility of the medical community to ensure the current proper use of NOACs that very much depends on experience, and an exhaustive knowledge of their indications and features in specific clinical scenarios. This review discusses new anticoagulants such as dabigatran, edoxaban, rivaroxaban and apixaban, as well as practical and easy-to-use algorithms for use in a clinical routine specifically focused on AF prevention. New oral anticoagulants Two classes of NOACs are currently available, oral direct thrombin inhibitors (DTIs; e.g. dabigatran) and oral direct Xa factor inhibitors (e.g. rivaroxaban, apixaban, and edoxaban). Unlike VKAs, which block the formation of several active vitamins K-dependent coagulation factors (factors II, VII, IX and X), these drugs block the activity of one step in coagulation. Careful attention to patient characteristics will ensure the correct prescribing of antithrombotic for patients with AF (Figure 1). Open in the new tabDownload slideChoice anticoagulant treatment. Adapted from the ESC guidelines with permission.37 AF, atrial fibrillation; CrCl, creatinine clearance; VCA, vitamin K antagonists; PLA, PLA, oral anticoagulants. The latest data from seven European countries show much better adherence to evidence and recommendations for oral anticoagulation.1 Interestingly, NOAKis were given to young patients and only 6% of the study populations, reflecting the tendency to prescribe these new treatments reasonably at first and their inherent reimbursement limitations, respectively. Figures 2-4 show recommended practical algorithms to ensure correct readings, interactions and therapeutic dosing for each NOAC. At the time of publication of this review, rivaroxaban, dabigatran, and apixaban approved for antithrombotic prevention by the AF European Medicines Agency (EMA) and the Food and Drug Administration (FDA).2-4 Edoxaban was recently approved by the FDA but has not yet been EMA. All three PLAas may be a reasonable option for VKAs for elective cardioversion.5-7 Open in the new TabDownload slideStart-Up for dabigatran. active or recent gastrointestinal ulcers, the presence of malignancies with a high risk of bleeding, traumatic brain injury or recent brain surgery, cerebrospinal or ophthalmic, recent intracranial bleeding, known or suspected varicose varicose new formations, arteriovenous malformations, vascular aneurysis In, dose regimens for acute VTE: 150 mg BID; to prevent VTE after knee or hip replacement surgery (14 or 30 days, respectively): 110 mg (initial dose), then 220 mg per day. DVT, deep venous thrombosis; PE, pulmonary embolism; CrCl, creatinine clearance (preferably measured by Cockroft); VCA, vitamin K antagonists; INR, the international normalized ratio; VTE, venous thromboembolism; BID, twice a day. Open in the new Download slideStart-Up tab for rivaroxaban. active or recent gastrointestinal ulcers, the presence of malignancies with a high risk of bleeding, traumatic brain injury or recent brain surgery, cerebroscular or ophthalmic, recent intracranial bleeding, known or suspected varicose varicose new formations, arteriovenous malformations, vascular aneurysm Patients with CrCl 30 ml/min were excluded from ROCKET AF; In, accompanying procedures: quinidine, fvikonazole, cyclosporine, tacrolimus, claritromycin, erythromycin, rifampicin, carbamazepine, phenitoin and phenobarbital; In, dose regimens for acute VTE: 20 mg per day (15 mg twice a day for the first 21 days); to prevent VTE after knee or hip replacement surgery (14 or 30 days, respectively): 10 mg per day; CrCl, creatinine clearance (preferably measured by Cockroft); UKA, Vitamin K; INR, the international normalized ratio; VTE, venous thromboembolism. Open in the new slideStart-Up tab for apixaban. active or recent gastrointestinal ulcers, the presence of malignancies with a high risk of bleeding, traumatic brain injury or recent brain surgery, cerebrosal or ophthalmic, recent intracranial intracranial known or suspected varicose esophageal surgery, arteriovenous malformations, vascular aneurysms or intra-vascular abnormalities, or intracerebral above. In, dose regimens for acute VTE: 5 mg twice a day (10 mg twice a day for the first 7 days); to prevent VTE after knee or hip replacement surgery (14 or 30 days, respectively): 2.5 mg twice a day; Patients with serum creatinine levels of 2.5 mg per deciliter or calculated CrCl 25 ml per minute were excluded from ARISTOTLE; CrCl, creatinine clearance (preferably measured by Cockroft); VCA, vitamin K antagonists; INR, the international normalized ratio. Recently, rivaroxaban, dabigatran, and apixaban were approved for the treatment of venous thromboembolism (VTE), after showing no inferiority in terms of efficacy in Phase III clinical trials compared to the standard heparin/VKA regimen.8-15 Minor differences in dose regimen are recommended when NOCs are shown for prevention of AF or VTE treatment. Dabigatran Dabigatran etexilate was the first PLA studied and FDA approved, based on the results of RE-LY (a randomized assessment of the long-term anticoagulant therapy with dabigatran etexilate) trial.2 Dabigatran is a very specific and competitive direct thrombin inhibitor, which is orally administered as an inactive drug and after the complete conversion of esterase into an active form reaches peak plasma levels within 2-3 hours.16 It has a rapid onset of action (1-2 hours), a short period of semi-mile (12-17 h), and has 80% renal excretion. Unlike the ICA, dabigatran has no serious interactions between drugs and food and few interactions between drugs and drugs. However, simultaneous administration with P-glycoprotein inhibitors or P-glycoprotein inditions is contraindicated (Figure 2.17 Although concomitant administration of dabigatran and pantoprazole may reduce the effect of anticoagulant, Dose adjustment is not considered necessary.16.18Omic dose for dabigatran is 150 mg twice a day (BID), which has been approved by the FDA and EMA. A lower dose of 110 mg OF BID, only approved by EMA, is recommended for patients over 80 years of age or with a high risk of bleeding (Figure 2). The FDA, but not the EMA, approved 75 mg bid for patients with creatinine clearance (CrCl) 15-30 ml/min based on pharmacokinetic models, but this dose was not studied in a key Dabigatran study. RE-LY and RELY-ABLE RE-LY (Randomized assessment of long-term anticoagulant tetrapy with etexilate dabigatran) Phase III test was promising, randomized, open labels, phase III trials comparing two blinded doses of dabigatran etexilate (110 or 150 mg BID) with warfarin in 18,113 patients with AF and at least one additional risk factor (medium CHADS 2.1.2 Patients with severely impaired kidney function (CrCl 30 ml/min), active liver disease, stroke for 14 days, or with a high risk of bleeding were excluded. For The For The primary endpoint of stroke efficiency and systemic embolism, dabigatran 150 mg BID surpassed warfarin without significant differences in underlying bleeding. Gastrointestinal (GI) bleeding was more frequent with dabigatran 150 mg of BD. Dabigatran 110 mg of DB was not inferior to warfarin for the primary endpoint, with a reduction of 20% in large bleeding. In the warfarin group the international normalized ratio (INR) was within the therapeutic range of 64% of the study period after the first week. A post-special analysis of 1989 electrical cardioversions in 1,270 patients showed no significant differences in stroke rate within 30 days of the procedure between warfarin and dabigatran 110 or 150. About 25% of patients underwent transpophageal studies before cardioversion. There was no significant difference in the frequency of the left blood clot of the atrium (1.1% for warfarin, 1.2% for dabigatran 150 mg of DB, and 1.8% for 110 mg of BD.5 Follow-up Long-Term Multicenter Expansion Dabigatran Treatment in Patients with Atrial fibrillation (RELY-ABLE) study provided additional information on the long-term effects of two doses of dabigatran in patients completing RE-LY by extending follow-up to patients on dabigatran from an average of 2 years at the end of RE-LY another 2.19 years no patients were enrolled in this study. RELY-ABLE confirmed the results, as reported in RE-LY. In addition, there were no significant differences in stroke or mortality between dabigatran 110 and 150 mg of DB, but higher rates of large bleeding were observed with a higher dose of dabigatran. Recently, the safety profile of dabigatran (150 and 75 mg of BD) in real U.S. clinical practice was recorded in an elderly Medicare cohort with non-alvular AF.20 Compared to warfarin, dabigatran was associated with a reduced risk of stroke, intracranial bleeding and mortality, but with an increased risk of serious GI. These results were stronger in the subgroup treatment of dabigatran 150 mg of DB. About 16% of patients received 75 mg of DD and among them, none of the results of the study were statistically significantly different from warfarin, except for the lower risk of intracran bleeding with dabigatran. Unfortunately, known severe renal disorders were only present in up to 7% of the subgroup of dabigatran 75 mg of DB and the results should be interpreted carefully. Rivaroxaban Rivaroxaban is a competitive and dose-dependent direct inhibitor of the Xa factor and the second NOAC-approved FDA and EMA-based ROCKET AF (Rivaroxaban After daily oral direct factor Xa Inhibition compared to vitamin K antagonism for stroke prevention and embolism Trial in atrial fibrillation).3 It rapidly reaches the peak of plasma concentration within 24 hours. 9-13 hours with 35% renal renal (Table 1). Approximately two thirds of the intake of rivaroxaban is metaboilized by the liver using the enzymes cytochrome P450 (CYP3A4 and CYP2J2). Thus, the accompanying treatment of isoenzym's cytochrome and P-glycoprotein inhibitors, such as itrakonazole and voriconazole, are not contraindicated due to the increased risk of bleeding (Figure 3). Since one third of the drug is eliminated by the kidneys, rivaroxaban is not suitable for patients with severe renal failure. Table 1Pharmacological properties of new oral anticoagulants of the drug. Dabigatran. Rivaroxaban. Apixaban. Edoxabana. Mechanism Direct thrombin inhibitor Direct Factor Xa inhibitor Direct Factor Xa inhibitor Direct Factor Xa inhibitor Xa inhibitor Pro-drug Yes No Bioavailability, % 6% 66% without foodup to 100% with food 50% 62% Semi-ripe, h 12-17 h 5-9 hours (young)11-13 hours (elderly) 12 h 9-11 h Time maximum plasma concentration 0.5-2 2-4 h 1-4 h 1-2 h Kidney No problems of absorption with food No problem No problems absorption with food No effect No 39% no more effect 6-22% more Consumption with food? No mandatory No official Dosing recommendation twice a day twice a day Twice a day Twice a day Once a day It is administered 20 mg once a day with a large meal to increase bioavailability. A dose of 15 mg recommended for patients with mild renal disorders, high risk of bleeding, and/or potential drug-drug interactions (Figure 3) ROCKET ROCKET AF AF was a double-blind study in which 14,264 patients with non-valvular AF and CHADS2 scores No. 2 (average 3.5) were randomly assigned to rivaroxaban once a day or adjusted. patients with CrCl 30-49 ml/min received 15 mg of rivaroxaban. Excluded persons with CrCl in the amount of 30 ml/min, significant liver disease, any stroke within 14 days (or severe strokes within 3 months), HIV infection, associated treatments with non-steroidal anti-inflammatory drugs, cytochrome inhibitors P450 3A4, inductors of cytochrome P450 3A4 or with a high risk of bleeding. After an average subsequent 1.93 years, rivaroxaban was not inferior to warfarin for the prevention of stroke or systemic embolism; however, the rivaroxaban failed to show superiority over warfarin in the intention-to-treat analysis (P q 0.12). There was no difference in the risk of serious bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. With rivaroxaban, the requirements for gastrointestinal bleeding and blood transfusions were higher. The overall mortality rate between the groups did not differ significantly. Apixaban Apixaban is a direct, reversible, competitive and selective Xa factor inhibitor and the latest NOAC approved by the FDA and EMA for stroke prevention embolisms in non-valvular non-valvular It is well absorbed reaching peak plasma concentrations of 1-4 h.27-29 The current recommended dosage is 5 mg BID daily for patients with normal kidney function and 2.5 mg BID for patients with two of the following characteristics: weight of 80 years, weight of 60 kg, and serum creatinine's body 1.5 mg/dl (figure 4). It is predominantly metabolized by the liver and is similar to rivaroxaban, apixaban is contraindicated in concomitant use with drugs capable of inducing or inhibiting CYP3A4.4 ARISTOTLE and AVERROES Apixaban for contraction in STroke and other thromboembolic events in AF (ARISTOTLE) was randomized, double-blind, double dummy, phase III trial comparison apixaban (5 mg BID) with dose adjusted in 18,201 patients with non-valvular AF (average chadS2 score 2.1).4 Apixaban 2.5 mg BID was used among patients with two or more of the following conditions: 80 years, zlt;60 kg,or q a serum' creatinine After an average subsequent 1.8 years, apixaban was significantly better than warfarin, with fewer primary outcomes (common strokes- like ischametic and hemorrhagic- and systemic embolisms), but without significant differences in rates of ischameic strokes. Patients treated with apixaban had significantly less intracranial bleeding, but G.I. bleeding was similar between both groups. Mortality from all causes in the apixaban group was found to be much lower. Apixaban was also compared with aspirin only in the AVERROES study, a double-blind study of 5,599 patients who were not suitable candidates for VKA treatment (average CHADS2 score 2.30 After an average subsequent 1.1 years, the study was prematurely halted due to the apparent benefit of apixaban. The underlying result of a stroke or systemic embolism was significantly lower in the apixaban group compared to aspirin, while the risk of bleeding (major bleeding and intracranial bleeding) between the two groups was similar. The criteria were within the previous seven days, and concomitant treatment with aspirin at a dose of 165 mg per day or as aspirin so is clopidogrel. Edoxaban Edoxaban is another reversible Xa inhibitor, recently approved by the FDA but not yet an EMA. It is quickly absorbed and reaches peak plasma concentration within 1-2 hours up to 50% of edoxaban is eliminated by the kidneys. Since it is a substrate for P-glycoprotein, the accompanying administration with quinidadine, amiodarone, and verapamil will result in a significant increase in plasma levels edoxaban.31-34 Therefore, in patients with the associated use of powerful glycoprotein inhibitors (verapamil or quinidain), weight kg, or moderate–severe renal impairment (CrCl 50 mL/min), edoxaban dose should be reduced by 50%. ENGAGE kg,= or= moderate–severe= renal= impairment= (crcl= 50= ml/min),= edoxaban= dose= should= be= reduced= by= 50%.= engage=></60 kg, or moderate–severe renal impairment (CrCl 50 mL/min), edoxaban dose should be reduced by 50%. ENGAGE > тела</25> </60> </60> </60> Effective anticoagulation with the next-generation Xa factor in atrial fibrillation-thrombolysis in myocardial infarction 48 (ENGAGE AF-TIMI 48) was three-group, a randomized, double-blind, double dummy phase III trial that compared two doses of edoxaban circuits (30 and 60 mg once a day) with warfarin35 a total of 21,026 patients with non-valvular AF. For patients in any group of edoxaban, the dose was halved in any of the following characteristics: CrCl 30-50 ml/min, body weight 60 kg or less, or associated use of verapamil or quindine. After the next 2.8 years, both edoxaban regimes were no lower than warfarin for stroke prevention or systemic embolism; however, the lower dose is a tendency to be inferior, with a risk factor of 1.13 against warfarin, and inferior specifically to prevent ishamic stroke. Edoxaban was associated with lower dose-related bleeding rates, including heavy bleeding, intracranial bleeding and life-threatening bleeding. The exception was GI bleeding, which occurred more frequently with high doses of edoxaban, but less frequently with low doses of edoxaban compared to warfarin. Finally, the incidence of hemorrhagic stroke and the mortality rate from cardiovascular causes were significantly lower in both edoxaban schemes. Patients with severe kidney dysfunction (CrCl 30 ml/min), high risk of bleeding, use of double antithrombocyte, acute coronary syndromes or coronary revascularization and strokes within 30 days were excluded. Comparisons of new oral anticoagulants currently in randomized controlled trials do not make direct comparisons between NOACS, and extrapolation of primary trial data is the best available strategy for a medical prescription. However, differences in trial design, in the estimated risk of stroke in population studies, comparator uniformity, and determination of the effectiveness and safety of endpoints make complex direct comparisons. The choice of a noAC for a given patient depends on the individual characteristics of the patient, including the risk of stroke or VTE, the risk of bleeding and comorbidities, such as the presence of impaired kidney function. Figure 6 shows the comparative effectiveness of high doses of NOACs and warfarin.36 Comparative analysis of the four NOACAs confirmed that THE NOAKI significantly reduced the composition of stroke or systemic embolic events by 19% compared to warfarin, which largely depended on a significant reduction in hemorrhagic strokes. Data for all four NOACS showed they were associated with a 14% non-essential reduction in major bleeding.36 Open in the new Download slideStart-Up tab for edoxaban. , a history of intracranial, intraocular, spinal, retroperitoneal or bleeding; apparent gastrointestinal bleeding or active ulcer during the previous year; recent serious injury, major surgery, surgery, Deep organ biopsy within the previous 10 d; Active infectious endocarditis; uncontrolled hypertension (blood pressure N170/100 mmHg); or hemorrhagic disorder, including known or suspected hereditary or acquired bleeding or coagulation disorder. The question is, this population has been excluded in clinical trials; The issue is edoxaban is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) after 5 to 10 days of initial therapy with parenteral anticoagulant. Dose regimens for acute DVT and PE: 60 mg once a day or 30 mg once a day in patients with CrCL from 15 to 50 ml/min, patients who weigh less or equal to 60 kg, or patients who take certain accompanying drugs P-gp inhibitor. Patients with CrCL-30 ml/min were excluded from engage AF-TIMI 48; CrCL, creatinine clearance (preferably measured by Cockroft); VCA, vitamin K antagonists; INR, the international normalized ratio. Open in the new Download slide tab (A) Stroke or systemic embolic event. (B) Heavy bleeding. N/N data, unless otherwise stated. Heterogeneity: I2 and 47%; P 0'13. NOAC, the new oral anticoagulant; RR, risk factor. The question is, dabigatran 150 mg twice a day; The question is, rivaroxaban 20 mg once a day; The question, apixaban 5 mg twice a day; The question is, edoxaban 60 mg once a day. Reproduced from Ruff et al.36 with permission. While there is insufficient evidence to recommend one NOAC in relation to another, Table 2 summarizes general recommendations based on patient characteristics, drug compliance and tolerability. For example, dabigatran can produce dyspepsia, but this NOAC at 150 mg BID was the only agent to demonstrate a reduction in stroke. All NOACI, with the exception of apixaban, have been associated with greater GI bleeding than warfarin. Both rivaroxaban and apixaban are less reliant on renal elimination than dabigatran. Rivaroxaban and edoxaban have the advantage of once-a-day dosing, which may be attractive to those patients who are less compatible. Thus, patients with a history of these features can lead a doctor to prescribe one particular NOAC. However, it is important to emphasize that currently all NOAKs are clinically shown in non-valvular AF regardless of the perceived risk of stroke or bleeding. Table 2Suggested use of NOACs according to patient patient characteristics. NOAC . Dose mode. High Risk of Stroke (High Score CHADS-VASC) Dabigatran 150 mg BID Previous stroke Rivaroxaban 20 mg yD High risk of bleeding or previous life-threatening bleeding Dabigatran 110 mg BID Apixaban 5 mg BID Dyspepsia Rivaroxaban 20 mg qDpix Abanaban 5 mg BID GI bleeding Apixaban 5 mg BID Rivaroxaban 20 mg thD Elderly (80 years) and impaired kidney function Apixaban 2.5 mg BID Finally, VKAs remain the first line anticoagulant for patients with mechanical heart valves or rheumatic heart disease and for severe renal failure, in which NOAKi is not contraindicated. Although low doses of rivaroxaban and apixaban have been approved by the EMA and FDA (and 75 mg of dabigatran and 30 mg of edoxaban only by the FDA) for CrCl between 15 and 30 ml, in this vulnerable population there is no data on results, and current ESC guidelines do not recommend their use in such patients.37 According to patient preferences, VKAs remain a reasonable option for those who have good control. How to measure the effect of the clinical advantage of NOAC is their predictable anticoagulant effect, allowing the introduction of fixed doses without the need for regular monitoring. However, the lack of a reliable method or clear marker of anticoagulant activity makes compliance difficult. In addition, an assessment of the level of anticoagulation may be useful in specific scenarios, such as during acute bleeding, or stroke, or when patients need urgent surgery. Table 3 simplifies the expected coagulation results when receiving NOAC. When interpreting these results, it is necessary to take into account when the last dose of PLA was administered, as its maximum effect will be achieved at maximum plasma concentration. In addition, it is estimated that full life elimination will depend on the characteristics of the patient, and especially important on kidney function, especially for those PLA with high renal clearance. Table 3 Effect NOAC in coagulation test and possible measures in case of drug bleeding . Dabigatran. Xa factor inhibitors. Impact on coagulation tests: dTT, ECT, aPTT or unchanged: PT (not recommended): Anti-factor Xa or unchanged: PT, aPTTNo change: dTT, ECT U-turn in emergency bleeding Oral charcoalHaemodialysisPCC, aPCCDesmopressinAntifibrinolytic agents PCC, aPCCDesmopressinAntifibrinolytic agents Although quantitative tests for noac evaluation exist such as DTIs and FXa inhibitors, they are not usually available in most hospitals. However, other, more common tests can evaluate the qualitative performance of NOAC. For dabigatran may be useful diluted thrombin time (dTT), activated partial time of thromboplastin (aPTT) and clotting time of ekarin (EST); aPTT level (i.e. 12-24 hours after admission) of 2 upper limit normal or ECT 3 times higher may be associated with a higher risk of bleeding.38.39 A dTT with appropriate calibration for dabgatran also available (Gemoclot®) and that with hemoflot® 200 ng/ml after 12 h last dose is associated with a higher risk of bleeding as well. Each Xa inhibitor factor (rivaroxaban, apixaban, and edoxaban) affects PT and APTT to varying degrees, and any of these tests are ideal for evaluating anticoagulant effects. Activated partial time thromboplastin has a weak prolongation under these NOACs and suffers from variability of analyses, and low-level reaction On the other hand, PT is extended in a concentration-dependent manner for Xa factor inhibitors; however, its effect depends on the analysis and on the specific Xa inhibitor factor. This can be useful for rivaroxaban, although sensitivity largely depends on PT reagents. In particular, neoplastin plus has a close correlation with the concentration in plasma of rivaroxaban. Currently there is not much data for edoxaban and apixaban. Finally, plasma concentrations of Xa factor inhibitors can be estimated using commercially available Anti-FXa chromogenic analyses with good interlaboratory accuracy. Unfortunately, practical data to link the coagulation parameter or level to the risk of bleeding is not yet available. What to do if the scenarios of a patient bleeding complication are currently, specific antidotes for NALACs are missing and strategies to combat anticoagulant effects are limited. While this is considered a major drawback to their use, a recent meta-analysis presenting data on management and results of major bleeding events in the five phases of the III trial (Dabigatran v. AVK) showed the best result in those receiving dabigatran, reflected as a much shorter stay in the intensive care unit and a tendency to reduce adjusted mortality from all causes in 30 days.40 Time is the best benefit of NOACs, in their view of relatively short elimination. If there is a serious complication of bleeding, you need to start standard supporting measurements. These include mechanical compression, surgical hemostasis, fluid replacement and additional hemodynamic support. Hemodialysis can accelerate the removal of drugs in patients receiving dabigatran; however, its benefits from life-threatening bleeding have not been established. In contrast, dialysis is not effective for Xa factor inhibitors due to their high plasma binding and lower renal lumen. Administration of prothrombin integrated concentrate (PCC) or activated prothrombin complex (APC) concentrates can be considered for life-threatening bleeding, despite scant evidence. The PCC administration may start at a dose of 25 U/kg and can be repeated if clinically indicated. If available, the APCC can also be considered starting at 50 IE/kg (maximum 200 IE/kg/day). In addition, other procoagulants such as antifibrinolytics or desmopressin may also be considered, but again there is no clinical evidence of their effectiveness. Finally, the monoclonal antibodies of Fab molecules are directed against dabigatran and specific recombinant proteins (r-antidote) to reverse the anticoagulant effect of the Xa inhibitor factor currently being investigated and keep the promise in treating bleeding in life-threatening situations.41-43 A patient undergoing intervention Most appropriate management should be individualized in noAC is used, type of operation, operation, characteristics of patients, in particular, on their kidney function. For patients undergoing minor interventions, NOAC can be continued during the procedure, similar to patients undergoing VCA treatment. Some examples include skin cancer removal, joint injections, cataract removal, or tooth extraction, in which adequate local hemostasis is usually possible. Intervention should not be performed at peak concentrations, but 12 or 24 hours after the last intake, depending on their specific dosing regimen (once or twice a day). However, if significant bleeding is expected, the patient should skip 1-2 days of NOAC before the procedure and re-start NOAC the day after the procedure. Table 4 offers an up- and post-operative approach based on the type of surgery, noac type and kidney function. Treatment should be postponed for at least 24 hours after surgery, given the rapid onset of these drugs. Table 4Pre- and Postoperative Management of Patients Taking NOAKI. . Small surgery. The main surgeryb. NOAC Renal Function Preoperative Management Postoperative Management Postoperative Management Dabigatran Normal or with mild disorders (CrCl 50 ml/min) Stopping 2 days before surgery (skip 2 doses) Re-start 24 hours after surgery Stop 3 days before surgery (to miss 4 Doses) Re-start 48 hours after surgery Moderately abnormal (CrCl 30-50 ml/min) Stop 3 days before surgery (skip 4 doses) Stop 4-5 days before surgery (skip 6-8 doses) Rivaroxaban Normal, soft, or with moderate impairments (CrCl 30 ml/min) Stopping 2 days before surgery (skip 1 dose) Re-start 24 hours after surgery Stop 3 days before surgery (skip 2 doses) Re-start 48 hours after surgery Apixaban (CrCl 30 ml/ min) Normal, Mild, or moderately impaired Stop 2 days before surgery (skip 1 dose) Re-start 24 hours after surgery Stop 3 days before surgery (skip 4 doses) Re-start 48 hours after surgery Patient must switch between anticoagulant modes Table 5 summarizes how to move on from different anticoagulant regimes. Individual precautions should be kept in mind, especially in patients with kidney dysfunction. Table 5Recent on how to switch between different anticoagulant Switch modes. As?. VKA in NOAC After the INR is lower, than 2.0 intravenous non-fractional heparin (UFH) in NOAC After 2 hours of UHF stop (more in cases of renal disorders) Low-molecular-weight heparin (LMWH) in NOAC When the next dose of LMWH was prevised NOAC for VKA accompanying treatment up to INR 2-3 NOAC to parententral anticoagulant (UFH, LMWH) When the next dose of NOAC One was scheduled NOAC to another When the next dose of NOAC (longer in cases of renal disorders) Conclusion of New Oral Anticoagulants was planned that have a favorable balance between efficiency and safety compared to VKA, and three are now available for stroke in non-valvular AF. The benefits of NOACs include less interaction with drugs and lack of interaction with food, rapid onset, rapid clearance and lack of need for laboratory monitoring. Individual anticoagulant treatment should be based on the age of patients, kidney function and related procedures. The rate at which NOACS will replace VCA will depend on clinical experience, patient tolerance of these drugs, new data from further studies, reimbursement policies and other market forces. Further research is under way to develop reliable and accessible measures to monitor the anticoagulant effects of new agents, as well as antidotes that can effectively reverse the anticoagulant effect. Conflict of interest: no one has been declared. Links 1 . Management of atrial fibrillation in seven European countries following the publication in 2010 of the ESC Atrial Fibrillation Guidelines: the primary results of the PREvention OF-European Atrial fibrillation registry (PREFER in AF). ;;–.2 ; RE-LY steering committee and investigators. Dabigatran vs. warfarin in patients with atrial fibrillation. ;;–.4 ; COMMITTEES and investigators ar-ISTOL. 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