IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 8 Ser.6 (August. 2020), PP 13-20
www.iosrjournals.org

Antidotes for Reversal of Direct oral Anticoagulants

HarichandanaPunukula, Puligari Praveen Reddy.
Corresponding Author: HarichandanaPunukula

Abstract:*The primary benefit from direct oral anticoagulants is a decreased rate of significant bleeding, particularly intracranial hemorrhaging, against vitamin K antagonists. The absence of preclinical and clinical evidence is concerned because numerous supplements to the clotting factor have been used in patients who have been administered with direct oral anticoagulants caused by severe bleeding. Idarucizumab is a certain 350 fold antibody that has a larger affinity to dabigatran than its pharmacological target thrombin. Andexanet is a modified factor Xa molecule, which connects Xa inhibitors directly and indirectly without enzyme activity. The ability of Ciraparantag is to reverse the behavior of several anticoagulants.*
Keywords: *DOACs, idarucizumab, andexanetalfa, ciraparantag.*
Methods: *Existing literature has been examined and updating information about DOACs and their agents is collected.*

Date of Submission: 30-07-2020 Date of Acceptance: 15-08-2020

I. Introduction:

Anticoagulant Therapy:

Anticoagulation therapy refers to an "anticoagulant" drug prescribed to avoid blood coagulation of the patient. Anticoagulants have an effect on the patient's plasma coagulation, on the plasma coagulation causes, and on reducing / inhibiting activity for coagulation. Present and emerging anticoagulants:

- vitamin K antagonists
- indirect anticoagulants
- direct anticoagulants

Vitamin K Antagonists

These anticoagulants are in the coumarin group. The synthesis of coagulation factors based on vitamin K is reduced and the plasma-coagulation is thus inhibitory. A daily tablet intake is the dosage form. The dosage is determined by daily blood samples and INR values.

Indirect Anticoagulants

Heparins are administered parenterally only (glycosaminoglycans). Their action mechanism is based on increased endogenous antithrombin activity. Therefore, the anticoagulant effect depends on the antithrombin of the patient. Heparins are classified between low molecular heparin (LMWH) and non-fractional heparin, depending on the molar mass. For other cases, LMWH calculation can be beneficial, such as kidney failure, underweight/overweight/obesity, thrombosis of blood complications for spite of proper treatment, elderly, babies, and neonates.

Direct Anticoagulants

These interfere directly with the coagulation cascade and directly inhibit certain coagulation factors, such as Xa and IIa (thrombin) which are discussed below.

Factor Xa inhibitors

- Apixaban
- Rivaroxaban
- Edoxaban
- Betrixaban

Factor IIa inhibitors

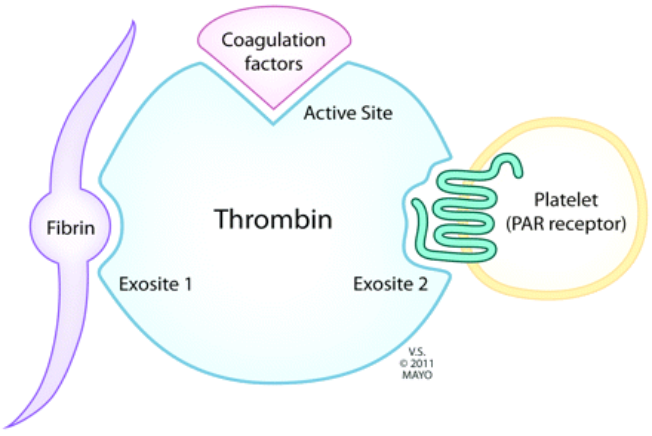
- Dabigatran

For decades, the only oral agent available for long-term anticoagulation was vitamin K antagonists, such as warfarin. The variable bioavailability of Warfarin and the drug-medicine interaction make therapeutic anticoagulation complicated and require regular monitoring. The continuing and growing clinical use of non-vitamin K or direct OACs changes the status quo. Active Factor Xa (apixaban and rivaroxaban) inhibitors and active thrombin (dabigatran) are approved for atrial fibrillation stroke prevention, prevention, and therapy of the thromboembolism of the vein (VTE). Direct oral anticoagulants (DOACs) in patients with non-valvular atrial fibrillation (NAF) are approved for the use of acute treatment, long term venous thromboembolism, and stroke prevention. Direct thrombin inhibitors like dabigatran. factorXa, Rivaroxaban, Apixaban, and edoxaban are included in DOACs.By direct inhibition of coagulation factors, DOAC demonstrates its effects. DOACs do not usually need regular coagulation monitoring because they are stable with lower drug-reactions and a shorter half-life, which enables quick removal of the body. Fresh frozen plasma and prothrombin complex concentrate (PCC) can be reversed immediately. Contrary to VKAs, the key drawback of DOACs in the absence of special reversals. So in emergency operations or life-threatening bleeding situations, unique DOAC reversal agents are urgently needed. PCC, recombinant activated factor VII (RFVIIa), aPCC, hemodialysis for dabigatran overdose are considered as nonspecific reversal agents. Ciraparantag, idarucizumab, andexanetalfa are the antidotes for the reversal of DOACs. This brief analysis concentrates on DOAC reversal data, including non-specific and specific agents that are currently available.

DOACs: The DOACs is both fast and quick-acting agents with fairly low bleeding risks as well as good safety profiles in general. Both medications do not require routine blood testing, unlike warfarin. Such drugs specifically prevent the blood from forming blood clots. Dabigatran (factor IIa), direct inhibitor of thrombin and rivaroxaban, apixaban, factor Xa inhibitor) produce an anticoagulant effect that is more reliable and less labile; warfarin has been shown to be at least as safe and effective in the prevention of strokes in AF.

Dabigatran(factorIIa inhibitor): Direct thrombin inhibitor dabigatran which was FDA's first direct oral anticoagulant to be used as an alternative to vitamin K antagonist and approved for non-valvular atrial fibrillation in 2010. Dabigatran is currently recommended for nonvalvular AF, Deep venous (DVT) therapy and pulmonary embolism (PE) in patients previously treated with a parenteral anticoagulant for 5-10 days as well as for minimizing risk and avoiding a recurrence of DVT and PE in previously treating patients and as prophylaxis of DVT and PE who underwent hip replacement surgery, approved by FDA in 2014.

Dabigatran (Pradaxa) connects to the active site of the thrombin molecule reversibly, avoiding coagulation factors through thrombin activation. The results of thrombin-mediated platelet aggregation may be less antagonistic. Moreover, even when thrombin is fastened, Dabigatran may inactivate thrombin; it can reduce fibrinolysis induced by thrombin and thus increases fibrinolysis.

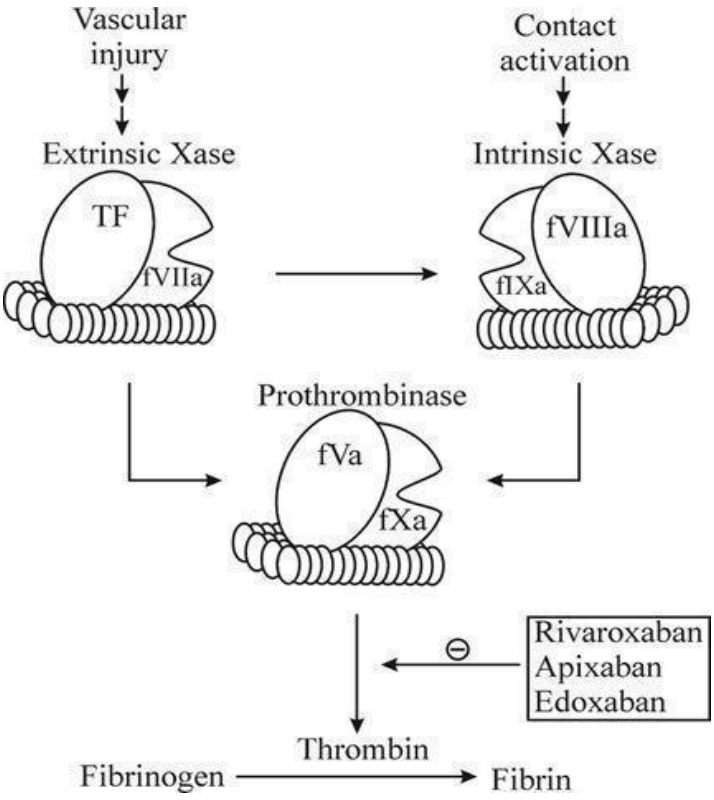


Warfarin (Coumadin, an "indirect" thrombin inhibitor) has its effect by reducing Vitamin K – a reliance on the thrombin synthesis and coagulation factors that accelerate the cascade, relative to the direct thrombin inhibitors. It leads to a late start of an anti-thrombotic effect (already known coagulant factors are up to 3 days a half) and to an initially prothrombotic effect, which is typically coadministered beforehand with heparins (Lipo-

Heping, and Liquaemin), which also inhibits the development of endogenous anticoagulants with slightly shorter half-lives.

Factor Xa inhibitors: Apixaban, Rivaroxaban, Betrixaban:

Compared to the VKA traditionally used for anticoagulants, FXa inhibitors possess a single mechanism of action. FXa is specific to the intrinsic and external pathways of the coagulation cascade, making it a good anticoagulation therapy target. In the production of prothrombin thrombin, it plays a significant role. A single Xa molecule produces 1000 thrombin molecules. Xa inhibition leads to a major reduction in thrombin production, and ultimately coagulation production. Similar warnings are provided to all FXa inhibitors mainly aimed at increasing the risk of bleeding.



MEASUREMENT OF ANTICOAGULATION WITH THE DOACS:

For patients diagnosed with any approved DOACs, regular anticoagulation testing is typically not required or necessary. An on-demand evaluation of the current anticoagulant levels is important for patients who need emergency surgical or intrusive treatment. In these patients, the timing of the final dose of the appropriate anticoagulant and the renal function of the patient should be kept in mind that key information to guiding the interpretation of the results of individual coagulation tests. A number of general considerations and the appropriate coagulation test should be used for evaluating the anticoagulation effects of individual DOACs, including the individual drug in question. The International Standardized Ratio (INR) has been developed to monitor VKAs-related anticoagulation and is not as effective as the anticoagulant test for certain Xa-Factor (FXa) or apixaban inhibitors.

The FXa inhibitor results may be demonstrated by the prothrombin period (PT), but the check is rather insensitive. In the treatment range, for example, Pt is not sufficiently sensitive to reliably measure apixaban levels. The PT test was used to assess rivaroxaban anticoagulation with PT results in poor correlation with the rivaroxaban concentrations. It has been noted that similar results occurred. In addition, the outcomes of this test can depend on the batch of individual sample treatment reagents. The latest specialist anti-FXa studies were developed and approved for quantitative rivaroxaban, apixaban, and edoxaban measures, distinguishing them from those for small molecular heparin weights (LMWH). However, for optimal efficacy and precision, each medication must be manually adjusted. The PT test is not generally sufficiently sensitive for reliable clinical measurement of dabigatran concentrations, but the response may increase with high dabigatran.

A standardized activated partial thromboplastin time test can be used to evaluate a possible dabigatran anticoagulation effect, but this is not the most sensitive test available. The thrombin time for dabigatrananticoagulation is a responsive assessment, but the assay may overestimate high dabigatran concentration rates. The diluted thrombin times (DTT) correspond best with dabigatran concentrations and hence are a stronger predictor of the anticoagulant activity of dabigatran, as measured in the HEMOCLOT test (HYPHEN BioMed, Neuville-sur-Oise, France).

However, this test is currently not licensed in the U.S. The measurement of DTT in the EU is recommended as a tool of choice in assessing the impact of dabigatran on anticoagulation with a calibrated HEMOCLOT thrombin inhibitor test. The ecarin coagulation time test is most commonly used in the EU to determine dabigatran impact on anticoagulants in a manner similar to DTT.

REVERSAL OF DIRECT ORAL COAGULANTS:

NON SPECIFIC REVERSALS	SPECIFIC REVERSALS
• aPCC • RFVIIa • PCC • Hemodialysis	• Idarucizumab • Andexanetalfa • Ciraparantag

Non-specific reversals: Data for non-specific reversal agents in DOAC related bleeding are inadequate for reverse efficacy. However, in the case of life-threatening or major bleeding associated with DOAC, the use of non-specific reversal agents is appropriate because of the lack of specific reversal agents for dabigatran other than idarucizumab.

Dabigatran overdose hemodialysis: Hemodialysis was used to overcome dabigatran-related life-threatening bleeding. Dabigatran has a large fraction, not connected to protein, and a lipophilic structure, which promotes dialysis. Dabigatran is extracted up to 68 percent by hemodialysis. Apixaban and rivaroxaban are not dialysable since they are highly protein-bound. Edoxaban is roughly 50 percent protein-bound. However, in a randomized Phase I open-label trial for the evaluation of edoxaban in ten patients with edoxaban-pharmacokinetics, the patients received edoxaban 15 mg 2 hours before or between dialysis sessions. For both classes, the mean plasma maximum concentrations were comparable. This study showed that hemodialysis is not an effective way of eliminating edoxaban.

PCC comes from plasma; is used to reverse VKAs if the coagulopathy associated with DOAC administration is desperately required for correction. The PCC is made up of vitamin K coagulation factor: the 3-factor formulation is comprised of factors II, IX, X, and the 4-factor preparation is composed of factors II, VII, and IX and X along with varying amounts of protein C and S.

In three small randomized, placebo-controlled trials PCC reversed the anticoagulation effects of rivaroxaban and Edoxaban, but the effects in dabigatran-treated patients did not reverse. Six have been administered in 12 healthy volunteers with 20 mg rivaroxaban twice a day and another six healthy volunteers twice a day, or 150mg dabigatran 2 times a day for 2.5 days. Long prothrombin time (PT), caused by rivaroxaban, was adjusted by a PCC infusion (50 U / kg) whereas extended partly activated thromboplastin time (aPTT), thrombin time (TT) and ECT were not corrected. 35 healthy volunteers were administered twice daily for 4 days with the use of 20 mg of rivaroxaban accompanied by 50U/kg of three and four-factor PCC infusions in an open-label, parallel-group study comparing three-factor PCC with four-factor PCC formulation in PT reverse. The mean prothrombin time was reduced to three-factor PCC by 0.6 to 1 second, with the average prothrombin time reduced to 2.5–3.5 sec by four-factor PCC.

Based on these studies, a dose of 50U/kg of PCC may be used for reversing the effects of DOAC in patients with intense or life-threatening bleeding. Two 2.5 days with apixaban 5 mg, and 4-factor PCC (25 U/kg), 3 hours after the last apixaban dose, were given to 12 healthy volunteers in a random crossover trial. Thrombin production increased by 76 percent in 30 minutes after PCC infusion. In the anti-Xa or partial thromboplastin time (PTT) values, no significant differences were found between 4-factor PCC and placebo.

aPCCis an anti-inhibitor coagulant complex that acts as a bypassing VIII inhibitor for the activity factor (FEIBA). The agent also is extracted from plasma and is active ingredient VII along with inactive ingredients II, IX, and X. It was first introduced to treat bleeding in patients with VIII or IX inhibitors of

hemophilia. Recent studies have shown that this drug is an off label drug that can be used to reverse anticoagulant effects in severely bleeding patients. Studies have shown that aPCC-related DOACs can also reverse bleeding.

In a number of 127 patients, six patients developed secondary intracranial hemorrhage (ICH) and were treated at 50 U / kg with a PCC, neither of whom developed ICH expansion or thrombotic or hemorrhagic complicates.

Marlu et al examined 10 stable volunteers who were randomly receiving dabigatran or rivaroxaban. APCC has a dose-dependent correlation with the coagulation parameters of thrombin production (endogens and thrombin pitch). However, such tests were inconclusive, since the efficacy of the agent in reversing DOAC was not measured in quantitative studies.

RFVIIa: The first factor for bleeding treatment in patients with hemophilia who have inhibitors has been identified. A 90mg/kg dose was suggested to reverse major bleeding from DOAC. However, the DOAC reversal with RFVIIa was not tested in clinical trials. Increased risk of thromboembolic arterial events compared to placebo was associated with the offset use of RFVIIa.

The lack of effective antibodies has been the key drawback against the use of DOACs that makes VKAs more suitable for medical practitioners and patients. The above information concerning unspecific DOAC reversal is not sufficient to justify the use of the bleeding associated with DOAC. Therefore, several new different reversal agents have been recently created, such as idarucizumabandexanet-alfa, and ciraparantag (PER-977).

SPECIFIC ANTIDOTES FOR REVERSAL OF DOACs:

Idarucizumab comes from monoclonal, humanized antibody segments. It links the heavy- and light-chain variable domains via the salt bridge to the benzamide movement in the area.

hydrophobic and hydrogen bonds. This results in a more than 350 times greater irreversible affinity than the one that dabigatran has with thrombin and thus quickly neutralizes the effects of anticoagulants produced.

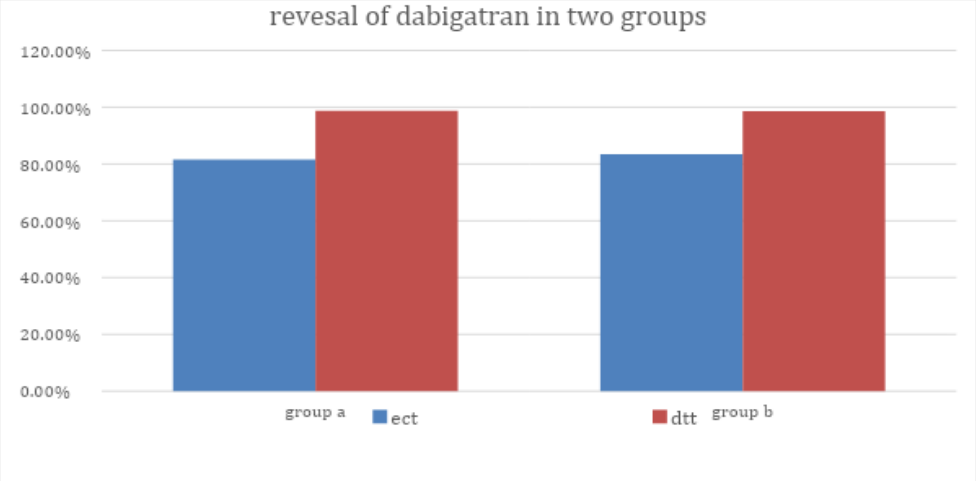
For patients with normal renal function, idarucizumab has a half-life of 45 minutes. This drug has been studied and proved extremely successful in reversing dabigatran-related bleeding in phase I and II clinical trials. In healthy volunteers and patients with renal impairment, Idarucizumab may alter the dose-dependent APTT, TT, diluted TT (DTT), and ECT.

The administration by healthy men of idarucizumab has no effect on the coagulation profile, which suggests that idarucizumab may be a non-prothrombotic agent. The REVERSE is an ongoing phase III study of two groups of patients treated with dabigatran: patients in group A required reversal due to extreme bleeding: and patients in group B revised due to vital procedure.

Idarucizumab was administered at a dose of 5g split over 5-10 minutes by two 25g intravenous boluses. The primary outcomes of the dabigatran impact anticoagulant reversal are based on central DTT and ECT laboratory tests, in the four hours following intravenous idarucizumab boluses. The second consequence is the time of bleeding in group A and the time of homeostasis in group B intraoperatively.

The initial sample of 51 patients in group A and 39 patients in group B comprised the first 90 patients surveyed in RE-VERSE AD. The median absolute reversal in both groups was 100%. Idarucizumab reversed damage to coagulation in 88 percent -98 percent of patients with high ECT and DTT. In 35 group A patients the median bleeding time was 11.4 hours. Intraoperative hemostasis in 33 of group B patients was considered normal and in 3 other patients, it was moderate to mildly abnormal. Within 72 hours of the administration of idarucizumab, one thrombotic incident took place and four events later.

RE-VERSE AD is analyzed on a follow-up basis on 494 patients, 298 in group A (serious bleeding patients), and 196 in group B (urgent intervention patients). The average reversal for both classes was 100% for ECT and DTT within 4 hours. Idarucizumab has reversed sustained ECT within 4 hours in 81.5% of patients in group A and 83.5% in group B. DTT normalization occurring in 98.7% of patients in Group A within 4 hours and in 98.6% of patients in Group B. The median blood cessation time of an investigator in Group A was 3.5 hours in 97 patients with GI bleeding and 4.5 hours in 61 patients who were not gastrointestinal or non-intra-cranial bleeding. In October of 2015 idarucizumab gained approval for use in patients with dabigatran-associated bleeding in emergency, life-suspected or uncontrolled bleeding procedures from the Food and Drug Management, US Administration (FDA). In 31 out of 494 (6.3%) patients at 90 days 35 thrombotic incidences occurring.



Andexantalfa: It is a specified antidote for direct and indirect factor Xa (low molecular heparin and fondaparinux) metabolites (rivaroxaban, apixaban, and edoxaban).The effects of anticoagulants specifically aiming at an activated factor X may be altered because they are a modified human recombinant factor X. This drug binds inhibitors of factor X with the same affinity as the activated native factor X. Andexanet reversed the anticoagulation effects in animal bleeding models, and decreased blood loss

In phase II trials, the researchers found that a dose-dependent factor Xa (rivaroxaban, apixaban, and edoxaban) was reversed by an IV andexanet bolus. A two-part randomized placebo-controlled study was conducted with healthy participants on the basis of these findings ANNEXA (Andexanet Alfa, a potential alternative to FXA inhibitors' effects on anticoagulation).

A total of 145 participants in both andexanet and placebo-treated with apixaban or rivaroxaban were assigned. Each trial was in two parts.A dose of 400 mg (30 mg/min) in part 1 or a 400 mg IV bolus was given in ANNEXA-A followed by 120 minutes continuous infusion at 4 mg/min dose, part. The intravenous andexanet bolus was administered in ANNEXA-R at 800 mg in Part 1 dose or 800 mg intravenous bolus followed by continuous infusion 120 minutes at a dose of 8 mg/min. Higherandexanet doses comparing with apixaban doses, higher plasma levels, and higher volume distribution of rivaroxaban were used to reverse rivaroxaban. The primary outcome was a percent improvement from baseline to nadir in the factor Xa inhibitor operation. The andexanet bolus decreased Xa anti-factor levels by > 90 percent in both trials within 2–5 minutes compared with ~20 percent with placebo ($P < 0.001$). After 2 hours, the levels of anti-factor Xa were returned to the levels seen in the placebo group; however, when andexanet was administered as a bolus and accompanied by infusion, the reversal effect remained. No severe or thrombotic incidents were recorded. In an ongoing Phase, IIIb / IV study (ANNEXA-4) for patients with intense bleeding taking rivaroxaban, apixaban, or edoxaban the efficacy and safety of andexanetalfa is under evaluation.

The first ANNEXA-4 analysis includes a 400-mg bolus dose followed by an infusion of 480 mg over 2 hours, 31 patients who have obtained enoxaparin, rivaroxaban or edoxaban over 7 hours, or an unknown 800-mg bolus infusion, followed by a 960-mg infusion over 2 hours Depending on specified parameters, an unknown dose of 800 mg bolus, an infusion of 850 mg over 2 hours. A partial summary of the ANNNEXA-4 research, of the 47 effectiveness cases, 37 have demonstrated either outstanding or strong no stasis (79%; 95 % CI, 64%-89%). Of those 67 health cases, 12 were thrombotic (18 percent) events within 30 days of andexanetalfa administration. The thromboses involved one myocardial infarction, five strokes, seven thromboses of the deep vein, and one embolism of the heart.

Ciraparantag: Ciraparantag is a water-solubly synthetic, formed molecule forming strong non-covalent links with large complex molecules that bind heparin, Xa factor direct inhibitors and inhibitors of thrombin. A decrease in blood loss has been observed in animal bleeding models to counteract the impact of anticoagulants. Ciraparantag reversed the dose-dependent effect of the direct factor Xa inhibitor in ex vivo human blood, without a procoagulant effect observed. Ciraparantag was given in one single intravenous dose (100 – 300 mg) in a Phase I trial on 80 healthy volunteers after a dose of edoxaban. A blood clotting time reduced to ~10 percent of baseline in 10 minutes with a sustained effect of 24 hours was assessed for the reversal of the anticoagulation. In the Phase II clinical trial, Ciraparantag is tested to explore reanticoagulation with edoxaban with cyraparantag for a second reversal. As the next universal reversing agent, Ciraparantag offers many possible benefits. It is not probable to induce immunogenic responses, can be given as single bolus

injection, and has quick onset with prolonged effects.Ciraparantag is less complex in comparison to Andexanet which is going to probably make it cheaper.

A significant drawback is the adaptation and validation of WBCT studies to other DOACs and Heparins in clinical practice.

PERIPROCEDURAL MANAGEMENT: In a new research RE-LY (Dabigatran vs. VKA) trials in "true world" communities with elevated risks for thrombo-lime diseases, similar results for dabigatran and rivaroxaban have been documented in clinical practice. Comparable perioperative bleeding and thromboembolism in warfarin and dabigatran-treated patients. Medical decisions on treatment for DOAC-treated patients who require an invasive procedure should be based on the patient's renal function, length of time since last DOAC, concomitant medications, and the risk of surgery.

For example, in patients with mild renal failure (CrCl 30-50 mL/min), medicinal products such as dronedarone inhibitors and systemic ketoconazole can increase the risk of exposure to dabigatran and potentially contribute to hemostatic dysfunction. Related concerns concerning FXa and major double inhibitors of Cytochrome P450 3A4 and P-gp, such as (i.e., ketoconazole, itraconazole, ritonavir, and apixaban)6 and rivaroxabandiltiazem, verapamil, drone, and erythromycin, have been posed. Related questions have been raised.

For edoxaban-treated patients, the concomitant application of P-gp-inducer Rifampin is often contraindicated. Recommendations for DOAC care delay, in particular for surgical conditions, have been provided in the past.

The European Society of Anaesthesiology and the French Working Group on Perioperative Hemostasis (GIHP) recommend interruption of DOAC therapy w24 hours (2 or 3 half-lives) before a procedure that carries a low risk of bleeding but 5 days before a medium or high risk of bleeding depends on the DOAC and factors such as a renal function of the patient.

The European Heart Rhythm Association DOAC guide proposes an overall 24-hour stop rule for low-risk and 48-hour operations. But for patients undergoing dabigatran with a < 80 mL/min CrCl and for those with a 15-30 mL/min CrCl with FXa inhibitors, longer delays are advised. It should be remembered that more studies are ongoing to evaluate standardized protocols for the care of DOAC patients, and our knowledge of this therapeutic problem is anticipated to improve outcomes.

INTERRUPTION OF ORAL ANTICOAGULATION AND BRIDGING / SWITCHING BETWEEN ANTICOAGULANTS: Previous recommendations for oral blood therapy patients advocated discontinuation of warfarin anticoagulation, suggesting that patients and atrial fibrillation and elevated probability of thromboembolic accidents use LMWH or unfractionated heparin. In addition, the latest recommendations from the United States Academy of Neurology suggest that heparin bridging therapy is likely to result in an elevated likelihood of bleeding in contrast to warfarin stopping.Such findings are supported by a new BRIDGE Investigator study, which argues that warfarin cessation (without bridging LMWH) is not lower than bridging when warfarin therapy for elective or alternative invasive treatment has been stopped.

One such example can be seen in a recent sub-analysis of data from a RE-LY study in which more major bridging therapy bleeding incidents were reported to dabigatran patients who had an interruption of care for an election process than those who had no noticable effect on bloody artery thrombosis. After the procedure, dabigatran anticoagulation begins as soon as possible medically.Theapixaban manufacturer also provides similar recommendations and also does not recommend bridging therapy during DOAC interruptions. Therapy patients will be halted at least 24 hours before an intrusive or surgical operation, particularly for edoxaban or for rivaroxaban. An anticoagulant parenteral can be prescribed before oral anticoagulants are readministered.

The medical requirement for bridging heparin or other parenteral agent therapy during interruptions of DOAC therapy seems to be an issue. The aim is to include evidence-based, intrusive or surgical clinical guidance on DOAC care in recent randomised and regulated clinical trials such as BRUISE CONTROL-2

II. Discussion

DOACs have developed into a new class of therapeutical substances over the last 10 years, increasingly used for prophylaxis, venous thromboembolism treatment as well as for NVAF stroke prevention. Protection evidence on such agents is scarce, which contributes to more conservative usage by certain physicians. Studies showed that these agents can have less bleeding than warfarin, but their use is still mainly concerned with major bleeding. While vitamin K may easily stop warfarin-induced bleeding, there are limited data on reverse toxicity

of DOAC, even with new approved reverse agents.Warfarin is commonly employed, including the need to control INR, given its many shortcomings. DOACs give many benefits over traditional anticoagulants, as do injection materials. The predictability of its pharmacological impact and a consistent method of dosing without the need for supervision is the clinical virtues which have rendered DOACs more attractive for clinicians and patients. DOACs' dependence on CYP clearance provides additional advantage in contrast with warfarin, with a reduced chance with pharmaceutical, dietary, and herbal medication interactions. In addition, as a consequence of the expense, it is understood that DOACs are not capable of reversing the impact of reliability.Mild bleeding is less an issue, and no intervention is usually needed. Severe bleeding is caused by significant morbidity and even death unless treated instantly and effectively. The offsetting of the use of PCC was the pillar of the DOAC reversal in addition to supporting measures.

Fortunately, extensive work has led to the establishment of two new antidotes and recommendations for direct practitioners if bleeding occurs after DOACs is used. The reversal agent for dabigatran, idarucizumab, rivaroxaban, and apixaban, andexanet has been very enthusiastic in the medical community. The effectiveness and utility of these two agents have been demonstrated as the first single DOAC reversing drug, while data for post-marketing remain scarce.

References:

[1]. Wang X, Mondal S, Wang J, et al. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. Am J Cardiovasc Drugs.2014

[2]. Dentali F, Marchesi C, GiorgiPierfranceschi M, et al. Safety of pro-thrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. ThrombHaemost.

[3]. Levy, J. H. (2016). Discontinuation and management of direct-acting anticoagulants for emergency procedures. The American journal of medicine, 129(11), S47-S53.

[4]. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med.2017

[5]. Chan NC, Coppens M, Hirsh J, et al. Real-world variability in dabigatran levels in patients with atrial fibrillation. J Thromb Haemost.2015

[6]. Almegren, M. (2017). Reversal of direct oral anticoagulants. Vascular health and risk management, 13, 287.

[7]. Yogaratnam, D., Ditch, K., Medeiros, K., Doyno, C., & Fong, J. J. (2016). Idarucizumab for reversal of dabigatran-associated anticoagulation. Annals of Pharmacotherapy, 50(10), 847-854

[8]. "Idarucizumab for Reversal of Dabigatran- Associated Anticoagulation", Annals of Pharmacotherapy, 2016

[9]. Levy, Jerrold H.. "Discontinuation and Management of Direct-Acting Anticoagulants for emergency Procedures", The American Journal of Emergency Medicine, 2016

[10]. .Lippi, G., Favaloro, E. J., &Mattiuzzi, C. (2014, October). Combined administration of antibiotics and direct oral anticoagulants: a renewed indication for laboratory monitoring?. In Seminars in thrombosis and hemostasis (Vol. 40, No. 07, pp. 756-765). Thieme Medical Publishers

[11]. Antibiotics and Direct Oral Anticoagulants: A Renewed Indication for Laboratory Monitoring?", Seminars in Thrombosis and Hemostasis, 2014

[12]. Kustos, S. A., &Fasinu, P. S. (2019). Direct-Acting Oral Anticoagulants and Their Reversal Agents—An Update. Medicines, 6(4), 103.

[13]. Levy, J. H., Spyropoulos, A. C., Samama, C. M., &Douketis, J. (2014). Direct oral anticoagulants: new drugs and new concepts. JACC: Cardiovascular Interventions, 7(12), 1333-1351

[14]. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabiga- tran: functional and structural characterization. Blood. 2013;121(18): 3554–3562.

[15]. .Cuker A, Husseinzadeh H. Laboratory measurement of the anticoagulant activity of edoxaban: a systematic review. J Thromb Thrombolysis. 2015.

[16]. Barrett YC, Wang Z, Knabb RM. A novel prothrombin time assay for assessing the anticoagulant activity of oral factor Xa inhibitors. ClinAppl ThrombHemost. 2013;19(5):522-528. doi:10.1177/1076029612441859

[17]. Honickel M, Maron B, van Ryn J, et al. Therapy with activated pro-thrombin complex concentrate is effective in reducing dabigatran-associated blood loss in a porcine polytrauma model. Thromb Haemost.2016;115(2):271-284.

[18]. Bakhru S, Laulicht B, Jiang X, et al. PER977: a synthetic small molecule which reverses over-dosage and bleeding by the new oral anticoagulants [abstract]. Circulation. 2013;128(suppl 22). Abstract 18809.

[19]. Vanassche, T., Greinacher, A., &Verhamme, P. (2016). Reversal of dabigatran by idarucizumab: when and how?. Expert Review of Hematology, 9(6), 519-528.

[20]. Lochu, A., Romari, N., Beltram, J., Magdelaine, A., Hermit, M. B., &Ezban, M. Influence of FIX and FVIII PEGylation on FIX and FVIII Activity Based on APTT Assays, 2013; PB4. 54-1, Abstract at XXIV Congress of the International Society on Thrombosis and Haemostasis.