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Clinical Pharmacology of Oral Anticoagulant in Patient with Kidney Disease

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ABSTRACT:
Thrombotic cardiovascular events, and sudden cardiac death are common in CKD and ESKD, this population is also at a disproportionately higher risk of nonvalvular atrial fibrillation (AF) compared with the general**.** Oral anticoagulants are commonly used drugs in patients with CKD and patients with ESKD to treat atrial fibrillation to reduce stroke and systemic embolism. Some of these drugs are used to treat or prevent deep venous thrombosis and pulmonary embolism in patients with CKD who undergo knee and hip replacement surgeries. Warfarin is the only anticoagulant that is approved for use by the Food and Drug Administration in individuals with mechanical heart valves. Each oral anticoagulant affects the coagulation profile in the laboratory uniquely. Warfarin and apixaban are the only anticoagulants that are Food and Drug Administration approved for use in patients with CKD and patients with ESKD. However, other oral anticoagulants are commonly used off label in this patient population. Given the acquired risk of bleeding from uremia, these drugs are known to cause increased bleeding events, hospitalization, and overall morbidity.

Keywords:
Anticoagulant,Apixaban,Dabigatran,Edoroxaban,Kidney Disease

I. INTRODUCTION:

The range of sufferers with CKD and patients with ESKD is growing in the United States on the premise of the country wide health and vitamins exam Survey information from 1999 to 2014 despite the fact that coronary heart failure, populace. occurrence of AF increases as kidney ailment worsens, and it's far close to 15% by the time that patients with CKD grow to be dialysis dependent, that's extra than 3 times that of age-matched controls. Use of oral anticoagulants is common, and those sellers are most of the pinnacle 15 tablets prescribed to sufferers with CKD and sufferers with ESKD enrolled in Medicare component D, Medicare benefit, or controlled Care prescription drug programs.[(1)] Warfarin is one of the most typically prescribed oral anticoagulants. within the general populace, more moderen oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) lessen danger of stroke or systemic embolism and bleeding as opposed to warfarin in patients with AF, and they are more and more prescribed in sufferers with CKD and patients with ESKD. Newer anticoagulants can be favoured over warfarin in patients with ESKD and calciphylaxis. [(2)] The reader can confer with preceding evaluation articles that have discussed considerably the scientific software of oral anticoagulants in CKD. This evaluate article will focus at the pharmacology of generally used oral anticoagulants which might be important in nephrology exercise. similarly, it will pick out know-how gaps concerning use of those drugs on this affected person population.

❖ RATIONALE & OBJECTIVE:

Health humans 2030 specializes in stopping diagnosing & education CDK human beings with CDK are much more likely to have coronary heart ailment and stroke- & to die early handling danger factors like diabetes and high blood strain can assist prevent or delay CDK. [(3)]

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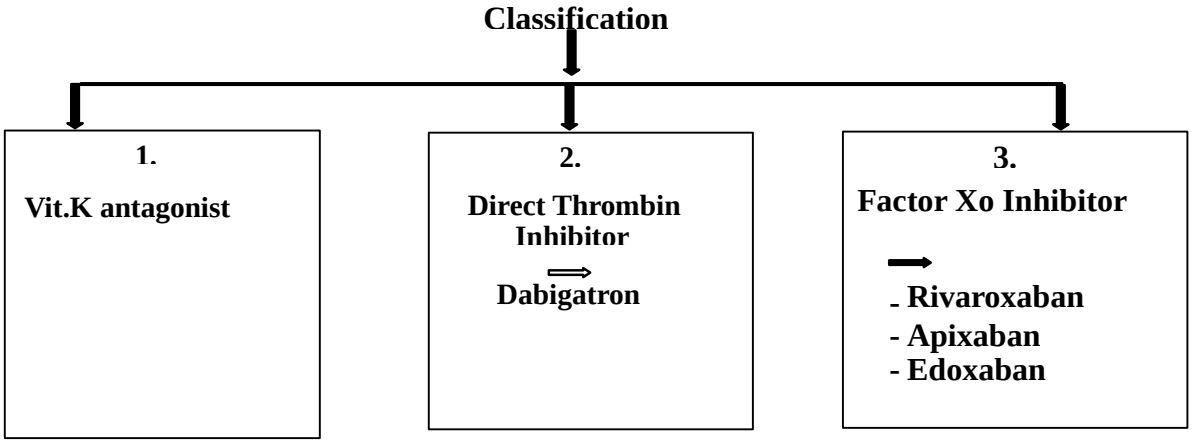
CLASSIFICATION:



❖ **WARFARIN:**

PHARMACOLOGY:

Warfarin is the oral anticoagulant with which doctors have the most experience. It is a racemic mixture of two optically active isomers (R and S) in the same ratio. Its pharmacokinetic and pharmacodynamic (PK/PD) properties are shown in Tables 1 and 2. Common drug interaction. Polymorphisms in the vitamin K epoxide reductase gene and cytochrome P450 type 2C9 (CYP2C9) are not race-specific and account for 25% and 10% interindividual variability in warfarin dosing. Vitamin K epoxide reductase genotype may be the best predictor of warfarin dose because it is responsible for the conversion of vitamin K epoxide to vitamin K. CYP2C9 alleles (eg, CYP2C9*2 and *3) are poor metabolizers, resulting in a prolonged t1/2 compared to the wild type (*1 allele). The observed frequencies of CYP2C9*2 are 8%–19% in Caucasians and <4% in Blacks. The corresponding frequencies for *3 alleles are 6%–10% and <2 %.[4]

TABLE NO.1

Summary of pharmacokinetic and pharmacodynamics properties of commonly used oral anticoagulants

OAC	Type	Prodrug	Pharmacokinetics			Pharmacodynamics: Binding to Effector
			Metabolism	Renal Dose Adjustment	Dialyzable	
Warfarin	Vitamin K–dependent factor inhibitor	No	Extensive metabolism by CYP2C	No	No	Irreversible
Dabigatran	Direct thrombin inhibit	Yes	Metabolized by esterase, 80% excreted by kidney	Yes	Yes	Reversible

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Apixaban	Free and clot-bound Xa inhibitor	No	Metabolized in liver by CYP3A4, then excreted in faces and kidney (25%), no active metabolite	No	Small	Reversible
Rivaroxaban	Free and clot-bound Xa inhibitor	No	66% Excreted by kidney, 36% unchanged, minimal in faces	Yes	No	Reversible
Edoxaban	Free Xa inhibitor	No	50% Excreted unchanged by the kidney, 10% hydrolysed by carboxyesterase 1	Yes	No	Reversible

OAC, oral anticoagulant; CYP2C9, cytochrome P450 type 2C9; Xa, factor Xa; CYP3A4, cytochrome P450 type 3A4.

TABLE NO.2

Common drug-drug interactions of oral anticoagulants.

Drug	Increase Anticoagulant Effects	Decrease Anticoagulant Effects
Warfarin	Amiodarone, fluconazole, tigecycline, voriconazole, fluoroquinolones, verapamil, diltiazem, other anticoagulants, antiplatelet drugs, NSAIDs, and SSRIs	Rifampin, phenobarbital, carbamazepine, cigarette smoking
Dabigatran	Amiodarone, verapamil, ketoconazole, dronaderone, clopidogrel, enoxaparin, other anticoagulants, antiplatelet drugs	Rifampin
Apixaban	Ketoconazole, other anticoagulants, antiplatelet drugs	Rifampin
Rivaroxaban	Other anticoagulants, antiplatelet drugs, fluconazole, ketoconazole, erythromycin, and clarithromycin	Rifampin, phenytoin, carbamazepine, St. John's Wort
Edoxaban	Other anticoagulants, antiplatelet drugs,	Rifampin

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NSAID, nonsteroidaldrug; SSRI, serotonin reuptake inhibitor. Carboxylation of nutrition ok–structured proteins requires the reduced shape of nutrition okay, γglutamyl carboxylase enzyme, molecular oxygen, and carbon dioxide. because body shops of nutrition k are low, the oxidized (inactive) shape of nutrition ok is recycled to the decreased (energetic) form by vitamin k epoxide reductase, that's inhibited through warfarin. Inhibition consequences in decreased hepatic synthesis of those clotting factors and reduction of their activities with the aid of forty%–50%. Oral anticoagulants act at extraordinary websites in the coagulation cascade for his or her anticoagulant results.

❖ LABORATORY SIZE OF ANTICOAGULANT EFFECT:

20 & 30 in comparison with internal normalized ratio (INR) is the maximum not unusual take a look at used to reveal warfarin reaction. drugs, nutritional modifications, and sickness procedures regulate warfarin outcomes. consequently, its use requires frequent tracking to maximise individual time spent inside the therapeutic range on the premise of an INR between individuals spending the least amount of man or woman time in the healing variety (<57%), those with the highest amount of individual time spent in the therapeutic range (>seventy three%) experienced lower charges of stroke or systemic embolism (2% as opposed to 1%), major bleeding (5% versus three%), and all-purpose mortality (7% versus 3%).[5]

❖ PHARMACOLOGY IN KIDNEY DISEASE:

The PK/PD of warfarin in CKD and ESKD isn't always properly established. medical practice guidelines do not recommend dosage discount for CKD or ESKD.Found that mean (95% confidence c program language period [95% CI]) dose discounts of 10% (95% CI, 4% to 14%) and 19% (95% CI, 11% to 26%) had been required in sufferers with eGFR=30–59 and <30 ml/min consistent with 1.73 m^2 in comparison with people with eGFR≥60 ml/min consistent with 1.73 m^2 to preserve healing warfarin dosing. This move-sectional evaluation additionally adjusted for other confounders in the multivariable statistical version, and as a result, interpretation of dose discounts entirely on the idea of eGFR can be an oversimplified method. But, it gives most important proof of elevated exposure of drugs cleared by way of the liver in patients with CKD. With a unmarried warfarin dose (0.75 mg/kg), people with GFR of 30–59 ml/min in step with 1.73 m^2 had a shorter t1/2 at 29.9±5.0 versus 44.8±6.0 hours in healthy controls. A boom in warfarin clearance was observed from 2.6 ml/kg in keeping with hour in healthy controls to a few.7 ml/kg consistent with hour in CKD [6]. It stays to be mounted whether or not the dialysis process (haemodialysis or peritoneal dialysis) results in modifications in warfarin kinetics and dynamics. Warfarin has widespread drug-drug interactions which can be specifically important given the polypharmacy that is so frequent in sufferers with CKD and patients with ESKD. [6]

❖ REVERSAL OF ANTITHROMBOTIC EFFECTS:

Warfarin's antithrombotic effects are reversed through low doses of diet okay. When pharmacologic doses of diet k (phytonadione 2.5–5 mg) are administered, decreased vitamin k is generated by means of a mechanism that bypasses epoxide reductase (through vitamin okay reductase) this is much less touchy to warfarin. huge nutrition ok doses (10 mg) can result in warfarin resistance for >1 week. TheAmerican college of Chest Physicians suggestions endorse, for INRs≥9 and no bleed, an unmarried oral 2.5- to 5-mg dose to convey the INR down in 1–2 days [7]. For serious bleeding, regardless of INR fee, 10 mg is administered parentally, and it's far supplemented by clean frozen plasma, prothrombin complicated listen, or recombinant component VIIa. Those measures are repeated every 12 hours if the INR stays expanded. Becausehaemorrhagic consequences can be extended in sufferers with CKD and patients with ESKD for a given INR value in comparison with in non-CKD individuals, clinicians need to bear in mind repeated remedy to ensure adequate reversal.[8]

❖ EFFICACY AND SAFETY:

In comparison with people with normal kidney characteristic, CKD, mainly GFR<30 ml/min in line with 1.73 m^2, or ESKD complicates warfarin remedy. [9] Specifically, lower doses are required to maintain therapeutic INR. More fluctuations in INR values with decrease man or woman time inside the healing variety and higher dangers of fundamental bleeding events for any given INR price are suggested [10]. In an observational examine of 1273 long-term warfarin

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customers, one 0.33 had a GFR of <60 ml/min per 1.73 m2 [11]. Compared with individuals with GFR of >60 ml/min per 1.73 m2, those with GFR of 30–44 ml/min consistent with 1.73 m^2 and those with GFR<30 ml/min consistent with 1.73 m2 had 2.2- and 5.8-fold better dangers, respectively, of essential bleeding occasions at an INR value ≥4. GFR did now not regulate threat of haemorrhage for INR values <4 [12].

Because higher stroke rates were reported in patients with ESKD with versus without AF (4.57 versus 0.48 per 100 person-years, respectively), previous cost utility analyses reported an increase in quality-adjusted life years with aspirin or warfarin treatment. However, warfarin increases bleeding risk, including intracranial haemorrhage, in patients with ESKD. [13]In a retrospective study of patients with ESKD and AF, warfarin doubled stroke risk, presumably haemorrhagic, compared with no treatment [14]. Another study evaluated patients with ESKD in the Fresenius Medical Care North America (FMCNA) database and reported 27% higher death risk with warfarin treatment [15]. Observational studies are fraught with selection bias, especially because patients with ESKD and AF may be more likely to die compared with individuals with ESKD without AF. Data are limited to confirm or refute these concerns. There is concern of increased vascular calcification and calciphylaxis with warfarin given that it reduces function of vitamin K–dependent vascular calcification inhibitors, such as matrix Gal proteins [14, 15]. Finally, there are concerns about the possibility of AKI secondary to glomerular haemorrhage due to thrombin depletion in patients on warfarin with INR>3 in whom there's no other identifiable ethology of AKI. It's also believed to result in accelerated development of CKD and worsen all-reason mortality in the quick and long-time. but actual mechanisms and medical presentation stay elusive so far. Regardless of a food and Drug administration (FDA) black box caution for warfarin use in sufferers with kidney dysfunction due to multiplied chance of major bleeding, it's far nonetheless generally used. Moreover, scientific exercise hints keep to advocate warfarin in treating AF amongst sufferers with CKD and patients with ESKD. The American coronary heart affiliation 2014 updated hints for anticoagulation management in AF endorse warfarin because the drug of desire in patients with advanced CKD (creatinine clearance <30 ml/min) and patients with ESKD [16]. The jury remains out regarding capacity blessings and risks. If this excessive-danger patient populace isn't always treated, its miles estimated that stroke price, along with intracranial haemorrhage, could be approximately 7% [17]. but, three wonderful observational research mentioned that warfarin did not reduce ischemic strokes among sufferers with ESKD. Further, these studies pronounced an alarmingly better intracranial haemorrhage rate as compared with within the popular population (3% as opposed to 1% in keeping with yr., respectively).

DIRECT THROMBIN INHIBITOR—DABIGATRAN:

PHARMACOLOGY:

Dabigatranetexilate, 150 mg two times every day, is FDA authorised to prevent stroke or systemic embolism in patients with AF. Nonspecific, ubiquitous esterase hastily convert this nonpeptideprodrug right into a potent, direct, and selective inhibitor of unfastened and fibrin-sure thrombin (table 1) [18]. PK/PD homes are shown in Tables 1 and 2. Not unusual drug-drug interactions are proven in table three. Its tablet (75 or 150 mg) includes dabigatran-lined pellets with a tartaric acid middle to augment bioavailability at low pH. The middle increases dyspepsia chance and gastrointestinal bleeding, especially with the a hundred and fifty-mg dose [19]. Patients must now not chunk, break, or open capsules, because bioavailability will increase dramatically [20]. Enormousinterindividual drug exposure variability exists [21]. Dabigatran is permitted at lower doses (75 mg twice each day), with a creatinine clearance of 15–30 ml/min [21].

LABORATORY SIZE OF ANTICOAGULANT EFFECT:

Activated partial thromboplastin time (APTT) is better than prothrombin time (PT) to come across dabigatran presence, however it cannot reliably distinguish among healing and sub therapeutic concentrations [22]. An everyday thrombin time has the high-quality poor predictive cost to exclude the presence of dabigatran. Ecarin, a metalloproteinase, cleaves prothrombin to meizothrombin. Dabigatran inhibits this step. Ecarin-based totally assays, together with the ecarin clotting time, are rather touchy and correlate strongly with drug concentrations. Studies showed that thrombin time and ecarin clotting time are linearly correlated with drug attention measured with the aid of liquid chromatography tandem mass spectrometry [23].

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PHARMACOLOGY IN KIDNEY DISEASE:

An open label, controlled study investigated PK/PD properties of a single 150-mg dabigatran dose in 23 patients with CKD and 50 mg in six patients with ESKD. Thecomparator group (six non-CKD controls) received two doses of 150 mg (standard dose) [24]. Versus controls, areas under the plasma concentration-time curve (AUCs) were 1.5-, 3.2-, and 6.3-fold higher in patients with CKD and creatinine clearances of 50–80, 30–50, and ≤30 ml/min, respectively. Time to maximal plasma concentration (Cmax) was similar in patients with CKD and controls. Elimination $t_{1/2}$ doubled in patients with CKD (creatinine clearance ≤30 ml/min) compared with non-CKD controls. Although six patients with ESKD received a reduced dose (50 mg), AUC was twofold higher than in non-CKD controls. A single haemodialysis session removed 62%–68% of the 50-mg dose. APTT and ecarin clotting time increased in correlation with changes in plasma drug concentration. Another PK/PD study was conducted in 15 patients with creatinine clearance of 15–30 ml/min. Participants received 75 mg twice daily, a dose resulting in mean steady-state drug exposure without drug accumulation [25]. These studies suggest that drug exposure correlates with kidney disease severity and prescribed dose, which can be measured by APTT or ecarin clotting time.

REVERSAL OF ANTITHROMBOTIC EFFECTS:

There are patient reports using fresh frozen plasma and prothrombin complex concentrate to reverse dabigitran's effects in patients with major bleeding [26]. A recent randomized, controlled trial (RCT) in subjects with normal kidney function raised questions about the efficacy of prothrombin complex concentrate as an effective reversal agent [27]. In another study in subjects with normal kidney function, nonspecific anti-inhibitor coagulant complex (e.g., factor VIII inhibitor bypass activity) but not recombinant factor VIIa reversed dabigatran's anticoagulant effects [28]. No studies have evaluated these agents in patients with CKD and patients with ESKD. A patient series of 11 life-threatening dabigatran-related major bleeding episodes reported use of haemodialysis and continuous venovenous hemofiltration [29]. A PK/PD study of dabigatran 150 mg twice daily for 3 days in seven patients on haemodialysis reported 49% and 59% drug removal with blood flow rates of 200 and 400 ml/min, respectively, over a 4-hour treatment [30]. Another study reported 62%– 68% dabigatran removal with a single dialysis session. Although studies are limited by lack of control groups, randomization, and small sample size, available data suggest a possible role for kidney replacement therapy in reversal of dabigatran's antithrombotic effects.

Recently, the FDA approved idarucizumab to reverse the antithrombotic effects of dabigatran[31]. As a humanized mAb fragment directed against dabigatran and its acylglucuronide metabolites, its binding affinity to dabigatran is higher than dabigatran to thrombin, thus neutralizing the anticoagulant effect immediately after a single 5-g intravenous dose [32]. Nearly one third (32%) of idarucizumab is excreted in urine, and the remainder undergoes metabolism primarily in kidney [32]. In 12 subjects with creatinine clearance ≥60 to <90 ml/min and six subjects with creatinine clearance ≥30 to <60 ml/min, total antidote clearance was reduced, resulting in higher drug exposure by 44% and 84%, respectively. The package insert recommends no dose reduction for kidney dysfunction. More studies are needed to assess its efficacy in patients with CKD and patients with ESKD.

EFFICACY AND SAFETY:

After FDA approval, patient reports of major bleeding were reported in frail elderly individuals, patients with CKD, and patients with ESKD. In the Randomized Evaluation of Long-Term Therapy Trial, 19% of patients had a baseline creatinine clearance <50 ml/min, and individuals with baseline creatinine clearance <30 ml/min were excluded [33]. A subgroup analysis reported lower rates of stroke or systemic embolism with dabigatran 150 mg twice daily versus warfarin across all creatinine clearance categories (≥80, 50 to <80, and <50 ml/min). Lower major bleeding rates were observed only in participants with creatinine clearance ≥80 ml/min. Summarizes four retrospective cohort studies and one meta-analysis reporting comparative effectiveness and safety data for dabigatran versus warfarin in CKD subgroups, and they concluded that dabigatran versus warfarin reduces risk of stroke or systemic embolism and intracranial haemorrhage, with an increased risk of gastrointestinal bleeding events. There is only one study in patients on haemodialysis using the FMCNA database; it reported a 1.5-fold higher risk

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of death or hospitalization from bleeding with dabigatran versus warfarin. [34]

FACTOR XA INHIBITORS:

RIVAROXABAN:

Rivaroxaban is FDA approved in patients with AF to prevent stroke or systemic embolism. It is also FDA approved for deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis after knee and hip replacement. Like dabigatran, it is not approved in patients with mechanical heart valves. Oral bioavailability varies with dosing strength: 80%–100% with a 10-mg dose and 66% with a 20-mg dose. Other PK/PD properties are shown inTables 1andand2. It is prescribed at a fixed oral dose with the evening meal: 20 mg/d for patients with a creatinine clearance of >50 ml/min and 15 mg/d for patients with a creatinine clearance of 30–50 ml/min. It should be avoided in patients with AF and a creatinine clearance of <15 ml/min. With a creatinine clearance of 15 to 50 ml/min the package insert recommends a reduced dose of 15 mg once daily with the evening meal in patients with nonvalvular atrial fibrillation. Rivaroxaban is not recommended for other indications with a creatinine clearance <30 ml/min. It does not interact with foods and interacts minimally with other drugs. [35]For DVT and PE prophylaxis, dosage is 10 mg/d. Rivaroxaban has a shorter $t_{1/2}$ and more rapid onset of action than warfarin. Timing of initiation after procedures and daily adherence are prerequisites for clinical success. It is typically started 6–10 hours after surgery for DVT/PE prophylaxis, and it is continued for 35 days after hip replacement and 12 days after knee replacement. To transition from heparin to rivaroxaban, infusion is stopped, and rivaroxaban is started simultaneously. When transitioning from low molecular weight heparin, rivaroxaban is initiated within 2 hours of the next scheduled administration. An open label, controlled take a look at investigated PK/PD properties of an unmarried 150-mg dabigatran dose in 23 patients with CKD and 50 mg in six patients with ESKD. The comparator organization (six non-CKD controls) obtained doses of a hundred and 50 mg (popular dose). versus controls, regions beneath the plasma awareness-time curve (AUCs) have been 1.5-, 3.2-, and 6.3-fold higher in sufferers with CKD and creatinine clearances of 50–80, 30–50, and ≤30 ml/min, respectively. Time to maximal plasma attention (Cmax) was similar in patients with CKD and controls. elimination t1/2 doubled in sufferers with CKD (creatinine clearance ≤30 ml/min) compared with non-CKD controls. although six patients with ESKD obtained a discounted dose (50 mg), AUC changed into twofold better than in non-CKD controls. An unmarried haemodialysis session removed 62%–68% of the 50-mg dose. APTT and ecarin clotting time extended in correlation with adjustments in plasma drug concentration. Every other PK/PD observe become carried out in 15 sufferers with creatinine clearance of 15–30 ml/min.(36) Contributors acquired 75 mg twice day by day, a dose ensuing in suggest regular-kingdom drug exposure without drug accumulation . These studies endorse that drug exposure correlates with kidney disorder severity and prescribed dose, which can be measured via APTT or ecarin clotting time.

❖ **REVERSAL OF ANTITHROMBOTIC EFFECTS:**

There are patient reports the usage of sparkling frozen plasma and prothrombin complex concentrate to reverse dabigitran's results in patients with fundamental bleeding. A latest randomized, managed trial (RCT) in topics with regular kidney feature raised questions on the efficacy of prothrombin complex pay attention as a powerful reversal agent. In every other look at in topics with ordinary kidney function, nonspecific anti-inhibitor coagulant complex (e.g., component VIII inhibitor pass pastime) however no longer recombinant factor VIIa reversed dabigatran's anticoagulant consequences. No research have evaluated these retailers in sufferers with CKD and sufferers with ESKD. An affected person collection of eleven life-threatening dabigatran-associated important bleeding episodes suggested use of haemodialysisand continuous venous hemofiltration. A PK/PD take a look at of dabigatran 150 mg twice each day for three days in seven patients on haemodialysis pronounced 49% and 59% drug removal with blood go with the flow rates of 200 and 400 ml/min, respectively, over a 4-hour remedy. Any other have a look at reported 62%– 68% dabigatran removal with an unmarried dialysis session. even though studies are limited via loss of control corporations, randomization, and small sample length, to be had facts suggest a likely role for kidney alternative therapy in reversal of dabigatran's antithrombotic results. Lately, the FDA permitted idarucizumab to opposite the antithrombotic outcomes of dabigatran[31]. As a humanized mAb fragment directed against

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❖ EFFICACY AND PROTECTION:

After FDA approval, patient reviews of main bleeding had been stated in frail aged individuals, sufferers with CKD, and patients with ESKD. Inside the Randomized assessment of lengthy-time period therapy Trial, 19% of patients had a baseline creatinine clearance <50 ml/min, and individuals with baseline creatinine clearance <30 ml/min were excluded [33]. A subgroup evaluation said decrease prices of stroke or systemic embolism with dabigatran 150 mg two times daily versus warfarin across all creatinine clearance classes (≥80, 50 to <80, and <50 ml/min). decrease principal bleeding fees had been found simplest in members with creatinine clearance ≥80 ml/min. [35,36]Summarizes 4 retrospective cohort research and one meta-analysis reporting comparative effectiveness and protection records for dabigatran versus warfarin in CKD subgroups, and that they concluded that dabigatran versus warfarin reduces risk of stroke or systemic embolism and intracranial haemorrhage, with an multiplied hazard of gastrointestinal bleeding activities.[37]There may be most effective one examine in patients on haemodialysis the usage of the FMCNA database; it reported a 1.5-fold higher danger of loss of life or hospitalization from bleeding with dabigatran versus warfarin [38].

❖ PHARMACOLOGY IN KIDNEY DISEASE:

A subgroup analysis of the Rivaroxaban once each day Oral Direct issue Xa Inhibition in comparison with vitamin k Antagonism for Prevention of Stroke and Embolism Trial in Atrial fibrillation (ROCKET AF) with impaired creatinine clearance (<80 ml/min) said no impact of kidney ailment on rivaroxaban's effectiveness and protection. A PK/PD have a look at prolonged this finding by means of reporting similar AUCs (plasma concentration-time curve) in sufferers with ESKD and a 10-mg dose and healthful controls with a 20-mg dose. But, different controlled PK/PD research challenged those findings and said a 56% increase in AUC in patients with ESKD after a fifteen-mg dose administered post dialysis. Predialysis administration re-sulted in decreased drug exposure through handiest 5%. Eventually, a PK/PD have a look at of an unmarried 10-mg dose become conducted in 24 sufferers with CKD (creatinine clearance <80 ml/min) and 8 healthful controls (creatinine clearance ≥80 ml/min). in comparison with controls, the AUCs were 1.4-, 1.5-, and 1.6-fold better with creatinine clearances of 50– 80, 30–50, and <30 ml/min, respectively. The AUCs (factor Xa inhibition-time curve) were 1.5 - 1.9, and a couple of. Zero-fold, respectively. This looks at indicates that decreased rivaroxaban clearance with worsening creatinine clearance led to extended drug exposure. Rivaroxaban is possibly to accumulate in sufferers with CKD and patients with ESKD even at lower doses (10 or 15 mg/d), and it's far poorly cleared by means of haemodialysis. [39]

❖ APIXABAN:

Apixaban is FDA accredited for discount of stroke or systemic embolism in patients with AF at 5 mg two times day by day. With serum creatinine ≥1.5 mg/dl, age ≥80 years old, or frame weight ≤60 kg, a discounted dose of 2.5 mg two times every day is suggested. It's also accepted for DVT/PE prophylaxis after hip and knee alternative at 2.5 mg two times every day and remedy of DVT/PE at 10 mg two times day by day for per week followed by means of 5 mg twice day by day. It isn't accredited to be used with mechanical coronary heart valves. PK/PD properties are proven in Tables 1 and and2. Drug-drug interactions are minimal. [40]

❖ PHARMACOLOGY IN KIDNEY DISEASE:

No massive kinetic changes have been located in top plasma drug awareness (Cmax) or AUC amongst patients with CKD (creatinine clearance of 15–29 ml/min) and patients with ESKD. An open label, parallel organization, unmarried five-mg dose PK/PD look at was performed in eight patients with ESKD and eight wholesome controls (49). After 2 hours of drug

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management, a 4-hour haemodialysis session changed into performed with dialysate glide price of 500 ml/min and blood drift rate of 350–500 ml/min. The AUC in patients with ESKD became 36% better as opposed to controls. because of its excessive diploma of protein binding, dialysis clearance is low (18 ml/min), ensuing in a 14% lower in drug publicity.(40) In a latest retrospective evaluation of sufferers on haemodialysis, cumulative days of apixaban use in an outpatient putting, better overall day by day apixaban doses, and total haemodialysis periods had been impartial chance factors for bleeding events (adjusted odds ratio, 13.07; 95% CI, 1.54 to 110.54; adjusted odds ratio, 1.72; 95% CI, 1.20 to 2.48; and changed odds ratio, 2.04; 95% CI, 1.06 to a 92, respectively). Any other PK/PD look at prescribed a single 10-mg dose to 24 patients with CKD and diverse classes of creatinine clearance and eight healthy controls. compared with controls, geometric suggest AUCs extended by means of 16%, 29%, and 38% in patients with CKD and creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. ordinary, removal t1/2 became slightly improved in all topics with CKD (17 hours) as opposed to controls (15 hours). a direct linear relationship turned into determined among apixaban plasma concentration and antifactorXa pastime. those research advise that apixaban accumulates in patients with CKD and sufferers with ESKD and that it is poorly dialyzable. In another PD/PK take a look at seven haemodialysis patients were given apixaban at 2.5 mg twice every day for eight days. The AUC, Cmax, and Cmin all elevated when measured at day 8 in comparison to day 1 suggesting accumulation of the drug. At day 8 drug tiers were nonetheless inside the regular reference variety. Drug tiers comparing day five as opposed to day 8 counseled that a regular nation were reached. Regardless of that it nonetheless might be of interest to observe levels with an extended period of exposure [41].

❖ EDOXABAN:

Edoxaban turned into FDA authorised after an ordeal that hooked up noninferiority as compared with warfarin in sufferers with AF. It's also accredited for remedy of DVT/PE most effective after a preliminary 5- to 10-day treatment with parenteral anticoagulation [19]. It's far endorsed at 60 mg once daily for sufferers with creatinine clearance of 50–95 ml/min and 30 mg once daily for sufferers with creatinine clearance of 15–50 ml/min. PK/PD houses are shown in Tables 1 and and2. not unusual drug-drug interactions are shown in desk three.

❖ PHARMACOLOGY IN KIDNEY AILMENT:

Drug exposure increases through 32%, 74%, and 72% with creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. even though its molecular weight is 738 g/mol and it is most effective 55% protein certain, it is poorly cleared by way of dialysis (9% with a blood glide charge of 350 ml/min, a dialysate glide price of 500 ml/min, and an F180NR dialyzer), likely because of the massive extent of distribution (107±20 L).[42]

❖ LABORATORY DIMENSION OF ANTICOAGULANT CONSEQUENCES:

PT prolongation occurs to an extra degree than APTT prolongation with thing Xa inhibitors. A prolonged PT on warfarin does no longer equate to a comparable anticoagulant effect on aspect Xa inhibitors with the exact identical PT cost. Compared with PT and APTT assays, chromogenic anti-Xa activity assay (e.g., Rotachrom) may be greater reliable and accurate. There is strong correlation between antifactorXa pastime and aspect Xa inhibitor attention (r2=0.95–1.00). There aren't any FDA-permitted kits that may be used for usual standardization of the anti-Xa activity assay. [43]

❖ REVERSAL OF ANTITHROMBOTIC effects:

Prothrombin pay attention complex, recombinant component VIIa, and factor VIII inhibitor skip activity can opposite their anticoagulant effects. There are not any specific antidotes. Andexanetalfa, a changed recombinant human factor Xa molecule that acts as a decoy molecule, is below research. [44]

❖ EFFICACY AND SAFETY:

The RCT (the ROCKET-AF) that brought about FDA approval of rivaroxaban for AF blanketed members with CKD and excluded individuals with a creatinine clearance <30 ml/min. On the idea of research inside the popular populace, more modern oral anticoagulants (dabigatran, rivaroxaban, or apixaban) compared with warfarin have been extra effective in decreasing stroke or systemic embolism without an accelerated risk of intracranial haemorrhage and gastrointestinal bleeding. As a result, off-label use

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is increasing in patients with a creatinine clearance of <30 ml/min and ESKD. A study of the FMCNA database of patients with AF on chronic haemodialysis reported a 1.7-fold higher risk of death or hospitalization from bleeding with rivaroxaban versus warfarin (adjusted rate ratio, 1.71; 95% CI, 0.94 to 3.12). With apixaban, there is one published patient report of a major bleeding event noted in a patient on haemodialysis. Apixaban was superior to warfarin in reducing stroke or systemic embolism rates and major bleeding among participants with kidney dysfunction in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial. A meta-analysis of RCTs comparing newer oral anticoagulants (dabigatran, rivaroxaban, and apixaban) with warfarin reported no difference in stroke, systemic embolism risk, or major bleeding in the CKD subgroup (relative risk, 0.64; 95% CI, 0.39 to 1.04 and relative risk, 0.89; 95% CI, 0.68 to 1.16, respectively). Another metaanalysis reported reduced bleeding risk in the CKD subgroup (risk ratio, 0.80; 95% CI, 0.66 to 0.96). In addition, bleeding rates were similar between individuals with creatinine clearance of 50–80 versus 30–50 ml/min on apixaban.[45]

Compared with participants with creatinine clearance >50 ml/min, individuals with creatinine clearance of 30–50 ml/min within the powerful Anticoagulation with element Xa next technology in Atrial fibrillation-Thrombolysis in Myocardial Infarction look at 48 said comparable stroke or systemic embolism chance on edoxaban. Any other subgroup evaluation suggested comparable findings and a 24% discount in bleeding danger (adjusted danger ratio, 0.76; 95% CI, 0.58 to 0.98). Finally, no difference in bleeding became mentioned among 15- and 30- to 60-mg/d doses in sufferers with GFR 15–30 ml/min per 1.seventy three m^2. [46]

A recent Cochrane evaluate mentioned decreased hazard of stroke or systemic embolism and comparable chance of fundamental bleeding amongst patients with AF and CKD treated with thing Xa inhibitors as opposed to warfarin (hazard ratio, 0.81; 95% CI, 0.65 to 1.00 and chance ratio, 0.79; 95% CI, 0.59 to 1.04, respectively). For both rivaroxaban and apixaban fundamental clinical trials excluded sufferers on haemodialysis. With both pills, at reduced dosages in haemodialysis patients, drug concentrations approximate the ones found in sufferers without kidney ailment. However, the quantity of patients studied is very small and no conclusions may be drawn concerning their protection or efficacy, and caution should be exercised with their use in this patient population. [47]

❖ GAP WITHIN THE LITERATURE:

Despite the fact that patients with CKD and patients with ESKD account for almost 10% of the general Medicare paid claims costs and even though oral anticoagulant tablets are one of the pinnacle ten prescribed drugs of Medicare prescription drug expenditure,[48] comparative efficacy and protection statistics continue to be restricted to aid use of 1 oral anticoagulant over another in patients with CKD degrees 4–5 or ESKD. due to the fact these patients suffer from expanded fees of hospitalization, negative results, and high health care–related fees, RCTs to analyze efficacy and safety of oral anticoagulants to enhance difficult medical results are seriously critical. sooner or later, there is lack of a standardized approach to evaluate kidney feature in studies, because debate keeps regarding the preferred technique for adjusting drug dosage. as an instance, the change of weight-reduction plan in Renal diseases eGFR calculation and the Cockcroft Gault creatinine clearance calculation were pronounced to over- or underestimate kidney function in various clinical settings.[49,50]

II. SUMMARY:

Oral anticoagulants are commonly prescribed in sufferers with kidney sickness. know-how their scientific pharmacology and adjustments that arise as GFR declines is prime to their effective use. risks and blessings of oral anticoagulants are different in patients with CKD and patients with ESKD. All of those factors need to be considered irrespective of whether or not oral anticoagulants are prescribed for FDA-accredited warning signs or used off label. sufferers with GFR<30 ml/min in keeping with 1.73 m2, inclusive of those on dialysis, have been systematically excluded from landmark trials. Extrapolation of comparative efficacy and protection in this affected person population is hard. Warfarin stays the most widely used oral anticoagulant. In our opinion, INR need to be carefully monitored in patients with ESKD. In our clinical practice, we test INR as soon as every week in sufferers with ESKD. In our opinion, if the individual time in healing INR variety is <50% or if patients experience complications, which includes calciphylaxis, we recollect switching them to apixaban. in the end, till extra facts come to be to be had, we presently

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do now not use dabigatran, rivaroxaban, and edoxaban in sufferers with CKD stage five and ESKD. destiny research are needed to establish whether or not use of oral anticoagulants result in internet clinical benefit for people with CKD levels 4–5 and people with ESK.

III. CONCLUSION:

Decision on whether or not and which type of oral anticoagulant to apply in affected person with CDKand AF are strongly affected by the CDK stage. In CDK level 3, there's some, albeit not steady, proof that NOAC showcase extra efficacy and better protection compared eighth warfarin. patient receiving NOAC need everyday test of their renal feature to avoid over dosing of NOAC, in particular state of affairs vulnerable to acute on chronic kidney injury VKA need to be used instead of NOAC in ckd degree four and 5 patient till more medical statistics are available in our opinion, dialysis dependent CDK with AF is an exception to this recommendation, given the conflicting information at the efficacy and principal situation approximately safety of vitamin k antagonism in dialysis patient.

IV. FUTURE SCOPES:

The future holds lots pleasure: scientific studies are underway to extend the warning signs for DOACs and revel in keeps to grow out of doors the pains setting. For decades, the only oral anticoagulants (DOACs) available global were the diet okay antagonists (VKAs) (Johnson et al, 2016), of which warfarin is the maximum usually prescribed in the United Kingdom (Protty& Hayes, 2017). The direct oral anticoagulants (DOACs) offer an appealing opportunity to VKAs and feature some of advantages, together with:

1) no requirement for ordinary tracking,
2) fixed dosing,
3) greater predictable dose responses,
four) no food interactions and
5) Fewer drug interactions (Baglin 2013).

There are four DOACs available inside the united kingdom, with differing traits, and figuring out which DOACs and at what does is the quality preference for an man or woman affected person with multiple comorbidities can be hard, in particular in complicated ‘real world’ sufferers who're underrepresented in scientific trials. obtrusive-primarily based used for added indications is increasing (e.g. rivaroxaban for acute coronary syndrome (ACS)), in conjunction with experience of DOACs outdoor the scientific trial setting. The software of acting DOACs drug ranges stays controversial however the lack of habitual monitoring means that mechanisms to promote premier adherence and persistent need consideration. Once termed ‘new’ or ‘novel’, DOACs use is now sizable and diagnosed as a value-powerful opportunity to VKAs, e.g. in outpatient venous thromboembolism (VTE) remedy pathways (Coleman et al, 2017).

REFERENCES:

[1]. US Renal Data System: 2013 Annual Data Report. Available at:https://www.usrds.org/atlas13.aspx. Accessed December 11, 2017 [PubMed]
[2]. Olsen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C: Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 367: 625–635, 2012 [PubMed][Google Scholar]
[3]. King BJ, El-Azhary RA, McEvoy MT, Shields RC, McBane RD, McCarthy JT, Davis MDP: Direct oral anticoagulant medications in calciphylaxis. Int J Dermatol 56: 1065–1070, 2017 [PubMed][Google Scholar]
[4]. Bansal N: Use of oral anticoagulation for patients with ESRD on hemodialysis with atrial fibrillation: Verdict 1. Clin J Am SocNephrol 11: 2093–2094, 2016 [PMC freearticle][PubMed][Google Scholar]
[5]. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians EvidenceBased Clinical Practice Guidelines (8th Edition). Chest 133[6 Suppl]: 160S–198S, 2008 [PubMed][Google Scholar]
[6]. Owen RP, Gong L, Sagreiya H, Klein TE, Altman RB: VKORC1 pharmacogenomics summary. Pharmacogenet Genomics 20: 642–644, 2010 [PMC freearticle][PubMed][Google Scholar]
[7]. Harder S: Renal profiles of anticoagulants. J ClinPharmacol 52: 964–975, 2012 [PubMed][Google Scholar]
[8]. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG,

Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am CollCardiol 64: e1–e76, 2014 [PubMed][Google Scholar]

[9]. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, Acton RT, Allon M: Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am SocNephrol 20: 912–921, 2009 [PMC free article][PubMed][GoogleScholar]

[10]. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, Allon M, Beasley TM: Warfarin dosing in patients with impaired kidney function. Am J Kidney Dis 56: 823–831, 2010 [PMC free article][PubMed][Google Scholar]

[11]. Limdi NA, Nolin TD, Booth SL, Centi A, Marques MB, Crowley MR, Allon M, Beasley TM: Influence of kidney function on risk of supratherapeutic international normalized ratiorelatedhemorrhage in warfarin users: A prospective cohort study. Am J Kidney Dis 65: 701– 709, 2015 [PMC free article][PubMed][Google Scholar]

[12]. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, Castellano P, Garcia-Cortes MJ,

[13]. Liebana A, Lozano C: Atrial fibrillation in incident dialysis patients. Kidney Int 76: 324–330, 2009 [PubMed][Google Scholar]

[14]. Quinn RR, Naimark DM, Oliver MJ, Bayoumi AM: Should haemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. Am J Kidney Dis 50: 421–432, 2007 [PubMed][Google Scholar]

[15]. Yalamanchili V, Reilly RF: Does the risk exceed the benefit for anticoagulation in endstage renal disease patients with nonrheumatic atrial fibrillation? Seminar Dial 24: 387–388, 2011 [PubMed][Google Scholar]

[16]. Chan KE, Lazarus JM, Thadhani R, Hakim RM: Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. J Am SocNephrol 20: 872–881, 2009 [PMC free article][PubMed][Google Scholar]

[17]. Eiser AR: Warfarin, calciphylaxis, atrial fibrillation, and patients on dialysis: Outlier subsets and practice guidelines. Am J Med 127: 253–254, 2014 [PubMed][Google Scholar]

[18]. Wheeler DS, Giugliano RP, Rangaswami J: Anticoagulation-related nephropathy. J ThrombHaemost 14: 461–467, 2016 [PubMed][Google Scholar]

[19]. Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ: Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol 29[Suppl]: S71–S78, 2013 [PubMed][Google Scholar]

[20]. Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, Perkovic V, Maddux FW, Piccini JP: Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am CollCardiol 67: 2888–2899, 2016 [PubMed][Google Scholar]

[21]. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA: Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: A systematic review. Chest 151: 127– 138, 2017 [PMC free article][PubMed][Google Scholar]

[22]. Pradaxa drug label. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf. Accessed December 18, 2017

[23]. Cuker A, Siegal DM, Crowther MA, Garcia DA: Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am CollCardiol 64: 1128– 1139, 2014 [PMC free article][PubMed][Google Scholar]

[24]. Adcock DM, Gosselin R: Direct Oral Anticoagulants (DOACs) in the laboratory: 2015 Review. Thromb Res 136: 7–12, 2015 [PubMed][Google Scholar]

[25]. Stangier J, Rathgen K, Stähle H, Mazur D: Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatranetexilate: An open-label,

parallel-group, single-centre study. ClinPharmacokinet 49: 259–268, 2010 [PubMed][Google Scholar]

[26]. Kooiman J, van der Hulle T, Maas H, Wiebe S, Formella S, Clemens A, van Buren M, Janssen M, Rabelink TJ, Huisman MV: Pharmacokinetics and pharmacodynamics of dabigatran 75 mg b.i.d. in patients with severe chronic kidney disease. J Am CollCardiol 67: 2442–2444, 2016 [PubMed][Google Scholar]

[27]. Dumkow LE, Voss JR, Peters M, Jennings DL: Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. Am J Health Syst Pharm 69: 1646–1650, 2012 [PubMed][Google Scholar]

[28]. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebocontrolled, crossover study in healthy subjects. Circulation 124: 1573–1579, 2011 [PubMed][Google Scholar]

[29]. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Pernod G: Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover ex vivo study in healthy volunteers. ThrombHaemost 108: 217–224, 2012 [PubMed][Google Scholar]

[30]. Ross B, Miller MA, Ditch K, Tran M: Clinical experience of life-threatening dabigatranrelated bleeding at a large, tertiary care, academic medical center: A case series. J Med Toxicol 10: 223–228, 2014 [PMC free article][PubMed][Google Scholar]

[31]. Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Lewinsky T, Neumayer HH, Liesenfeld KH, Lehr T, Härtter S, Friedman J, Peters H, Clemens A: Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. ThrombHaemost 109: 596–605, 2013 [PubMed][Google Scholar]

[32]. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI: Idarucizumab for dabigatran reversal. N Engl J Med 373: 511–520, 2015 [PubMed][Google Scholar]

[33]. BoehringerIngelheim Pharmaceuticals Inc.: Praxbind package insert. Available at:http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf.Accessed October 26, 2015

[34]. Ribés-Cruz JJ, Torregrosa-Maicas I, Ramos-Tomás C, Solís-Salguero MA, PuchadesMontesa MJ, González-Rico MA, Juan-García I, Tomás-Simó P, Tejedor-Alonso S, Zambrano-Esteves P, Miguel-Carrasco A: Dabigatran-induced upper intestinal bleeding in a patient with chronic kidney disease. Nefrologia 33: 864–866, 2013 [PubMed][GoogleScholar]

[35]. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361: 1139–1151, 2009 [PubMed][Google Scholar]

[36]. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L: Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation 129: 961–970, 2014 [PubMed][Google Scholar]

[37]. Romanelli RJ, Nolting L, Dolginsky M, Kym E, Orrico KB: Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice: A systematic review and metaanalysis. CircCardiovascQual Outcomes 9: 126–134, 2016 [PubMed][Google Scholar]

[38]. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G: Effectiveness and safety of dabigatran and warfarin in real-world US patients with nonvalvular atrial fibrillation: A retrospective cohort study. J Am Heart

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 392-405 www.ijprajournal.com ISSN: 2456-4494

Assoc 4: 1–12, 2015 [PMC free article][PubMed][Google Scholar]

[39]. Hernandez I, Baik SH, Piñera A, Zhang Y: Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med 175: 18–24, 2015 [PMC free article][PubMed][GoogleScholar]

[40]. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S: Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation 128: 2325–2332, 2013 [PubMed][Google Scholar]

[41]. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman JA: Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 131: 157–164, 2015 [PubMed][Google Scholar]

[42]. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW: Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation 131: 972–979, 2015 [PMC free article][PubMed][Google Scholar]

[43]. Xarelto drug label. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf. Accessed December 18, 2017

[44]. Hylek EM: Therapeutic potential of oral factor Xa inhibitors. N Engl J Med 363: 2559– 2561, 2010 [PubMed][Google Scholar]

[45]. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M; J-ROCKET AF study investigators: Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the JROCKET AF study –. Circ J 76: 2104–2111, 2012 [PubMed][Google Scholar]

[46]. De Vriese AS, Caluwé R, Bailleul E, De Bacquer D, Borrey D, Van Vlem B, Vandecasteele SJ, Emmerechts J: Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis 66: 91–98, 2015 [PubMed][Google Scholar]

[47]. Dias C, Moore KT, Murphy J, Ariyawansa J, Smith W, Mills RM, Weir MR: Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. Am J Nephrol 43: 229–236, 2016 [PubMed][Google Scholar]

[48]. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, Lufft V, Wand DD, Philipp T, Bruck H: Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J ClinPharmacol 70: 703–712, 2010 [PMC free article][PubMed][Google Scholar]

[49]. Apixaban drug label. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s006lbl.pdf. Accessed December 22, 2017

[50]. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, Song Y, Pursley J, Boyd RA, Frost C: Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J ClinPharmacol 56: 628– 636, 2016 [PubMed][Google Scholar]

[51]. Steuber TD, Shiltz DL, Cairns AC, Ding Q, Binger KJ, Courtney JR: A multicenter analysis of factors associated with apixaban-related bleeding in hospitalized patients with end-stage renal disease on hemodialysis. Ann Pharmacother 51: 954–960, 2017 [PubMed][Google Scholar]