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Original Article

A comparative analysis of DOACs vs warfarin for venous thromboembolism treatment in renal insufficiency

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Abstract

Aim: Annually, millions of people die from kidney diseases making it a serious public health concern. Patients with renal insufficiency have hemostatic defects that enhance their risk of thrombosis and bleeding. Evaluating the advantages and hazards of anticoagulant thromboprophylaxis is challenging.

Material and Methods: By using the fuzzy preference ranking organization method for enrichment evaluation (fuzzy PROMETHEE) and fuzzy multi-criteria optimization and compromise solution (fuzzy VIKOR), which are analytical multi-criteria decision-making (MCDM) techniques, this study aims to analyze diverse types of anticoagulants; specifically, Vitamin K-Antagonist (warfarin) and direct oral anticoagulants namely; Dabigatran, Rivaroxaban, Apixaban, and Edoxaban, by considering various criteria.

Results: Direct oral anticoagulants outperformed warfarin in terms of safety and effectiveness. Among all the analyzed anticoagulants, Apixaban was found to be the best-ranked anticoagulant with both fuzzy PROMETHEE and fuzzy VIKOR, with a net flow of 0.0064 and the lowest Qj value of 0.0000, respectively, compared with other alternatives depending on the selected criteria while warfarin was found to be the least ranked anticoagulant with a net flow of -0.0043 and the highest number of Qj being 1, respectively.

Conclusion: The MCDM techniques used were effective, highly accurate, and sensitive in the comparison of anticoagulant therapy for venous thrombosis in renal insufficiency based on the chosen criteria. The proper use of a safe and effective anticoagulant will boost better performance not only in patients' survival and well-being but also in the health care center.

Keywords: Direct oral anticoagulants, fuzzy logic, PROMETHEE, renal insufficiency, VIKOR

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INTRODUCTION

Renal insufficiency is a condition in which one or two kidneys are malfunctioning or incapable of performing their activities with high efficiency on their own. This type of disease is a serious public health concern. Its impact reaches over 10% of the world's inhabitants and causes 5 to 10 million deaths each year, mostly because of the elevated prevalence of obesity, diabetes, hypertension, and cardiovascular disease. Kidney problems have historically been divided into two distinct dysfunctions, acute kidney injury (AKI) and chronic kidney disease (CKD), despite recent research highlighting a strict interconnection in terms of causation [1]. CKD has topped the list of illnesses accountable for the global population's burden of fatality over the previous three decades. This condition was the 13th leading cause of mortality in 2016, and by 2040, it is expected to be the fifth leading cause of death [2]. Additionally, patients with renal insufficiency (RI) frequently have hemorrhagic and thrombolytic consequences whereas venous thromboembolism (VTE) affects roughly people with stage 5 CKD or end-stage kidney disease (ESKD) [3]. The increasing prevalence of RI raises serious concerns about human health around the globe. The restricted availability of medicines puts a lot of demand on researchers to come up with innovative ways to avert, slow, or stop the growth of kidney disease. Over two centuries ago, scientists began a long journey to learn how the kidney works and how to preserve and treat it; since then, enormous progress has been made [1]. Hemorrhage and thromboembolic consequences are more common in patients with CKD. Clotting, platelet activation, and platelet–vessel wall connection are all affected by uremic toxins, anemia, and hemodialysis (HD). In mild renal dysfunction, the incidence of thromboembolic illness is 2.5 times higher, whereas, in chronic kidney damage, the risk is 5.5 times higher. Concomitant morbidities such as arterial thrombosis, malignant tumors, surgical operations, or thrombophilia enhance the risk of thromboembolic illness in individuals with CKD [4].

Relationship Between VTE and CKD

Patients with the most advanced type of CKD are highly susceptible to cardiovascular events [5]. Most commonly both arterial and VTE, and also bleeding, are seen in people with CKD. Renal function deteriorations enhance the likelihood of VTE and bleeding. As a result, individuals with a glomerular filtration rate of less than 30 mL/min have the highest risk of fatal pulmonary embolism (PE) and bleeding events. When adjusted for population, the observed age and sex-standardized PE mortality rate is 12 or more times greater among dialysis patients [6]. Additionally, most individuals with RI have high homocysteine levels, which increase VTE risk. Furthermore, the coagulation and platelet activation that occurs within the extracorporeal hemodialysis device increases the risk of thrombosis in individuals with ESKD [6].

The management of key risk factors is responsible for the bidirectional link between VTE and CKD. CKD includes factors that are commonly associated with uremia, such as systemic inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system, malnutrition, anemia, microalbuminuria, hyper-homocysteinemia, hyperparathyroidism, malformations in bone and mineral metabolism; this causes a hypercoagulable condition, which can lead to VTE conditions, and also RI progression [7]. Studies have shown that due to the high frequency of atrial fibrillation (AF), individuals with an indication for anticoagulation are often seen in everyday clinical practice [8]. AF affects about one out of every five people with CKD, which is two to three times higher than the general population. Peritoneal dialysis patients have a prevalence of up to 7%, whereas hemodialysis patients have a prevalence of up to 13%. It has been observed that with age, the percentage of patients with AF and CKD increases [8].

Anticoagulants

Anticoagulants are also known as blood thinners; these are drugs that assist in preventing blood clotting or hardening. Therefore, the human body requires the ability to clot to assist in wound healing within and around the injured body part [9]. Anticoagulant agents are effective medications to prevent as well as treat cardiovascular diseases. These medications are divided into two essential categories; Vitamin K Antagonists, and direct oral anticoagulants, they all act in a distinct way to prevent clotting [9]. Vitamin K Antagonists (VKAs): Warfarin is known to be the preferable anticoagulant agent utilized in the past 70 years. Nevertheless, novel compounds, also known as direct oral anticoagulants (DOACs) having anticoagulant effects have recently been found to outperform older anticoagulants, namely Warfarin [10]. Anticoagulation treatment is prescribed to patients to avoid thromboembolic events. A moderately diminished glomerular filtration rate (GFR) estimates mortality as well as anticoagulant-related bleeding events [4]. This is because these compounds can interact with an altered hemostatic mechanism. Anticoagulation medication in CKD patients might exacerbate postpartum hemorrhage. DOACs such as Rivaroxaban, Edoxaban, Apixaban, or Dabigatran can all be deposited in individuals with kidney insufficiency [4]. In order to examine the risks and the benefits of DOACs over warfarin, Shin et al. [11] focused on the prevalence of DOACs utilization in individuals with AF by eGFR category. In a clinical practice context, they reported that DOACs had a higher risk of bleeding versus warfarin.

Considering the presence of hemostatic deficits that are likely to enhance the risk of thrombosis and bleeding in patients with RI, analyzing the benefits and drawbacks of anticoagulant thromboprophylaxis in RI circumstances is critical. Therefore, this study aims at analyzing the safety of DOACs and Warfarin which are used to treat VTE in RI by weighing several criteria

using multi-criteria decision-making (MCDM) models; fuzzy preference ranking organization method for enrichment evaluation (fuzzy PROMETHEE), and fuzzy multi-criteria optimization and compromise solution (fuzzy VIKOR).

This study contains four sections in which the first section introduces the study by explaining the study topic, the second section contains the materials and methods applied; the anticoagulant alternatives are explained in detail, as well as the model application on how the study has been conducted, the third section explains the study outcomes and discussion, and finally, the fourth section includes the conclusion.

MATERIAL AND METHODS

This section discusses the specific anticoagulants which were chosen for assessment and the methodology used for comparing and ranking these drugs. Ethics permission was not applicable because no patients were involved in this study but the center of excellence approved the contribution of this work to the scientific world.

Vitamin K Antagonists

These Antagonists aid in clotting. They come from foods with green leaves and microorganisms found in the stomach. Vitamin K Antagonists (VKAs), such as oral medication known as warfarin, prevent the liver from converting vitamin K into an active coagulation cascade by competitively inhibiting subunit 1 of the multi-unit vitamin K epoxide reductase complex 1 (VKOR1) [12], which allows the blood to clot correctly, thus limiting the coagulation [9]. Additionally, it prevents the hepatic synthesis of the proteins C and S as well as the vitamin K-dependent clotting factors II, VII, IX, and X [12]. To determine how well blood gets thin, the physician will most likely perform an international ratio test (INR) [9]. If a person is taking VKAs, it is critical to keep vitamin K intake consistent so that the doctor can figure out the proper dose to prescribe. Blood tests will be administered to easily monitor the effects of the drugs and food [9].

Though it is simpler to reverse this type of medication than others in the event of unexpected bleeding due to trauma or emergency surgery [9], during pregnancy, it should not be used or the powder from the pills should not be inhaled because it can be acquired via the skin and the airways of the unborn baby. Significant congenital abnormalities, deadly fetal bleeding, a high chance of pregnancy complications, and fetal death are all linked to exposure during pregnancy [12]. Warfarin can induce life-threatening hemorrhage; when the patient takes this type of drug or takes it excessively in a high amount, this is more likely to happen. Some foods may alter the way warfarin functions in the body, therefore, affecting therapy and dosage [12]. Some of the side effects that may arise from consuming this drug are allergic reactions, lethargy, numbness of joints, dizziness, anemia, cholesterol embolus syndrome, hypersensitivity reaction, and blood dyscrasias [12].

In advanced CKD or dialysis patients, therapy with VKA is more problematic since the INR is frequently outside the therapeutic range, which might be associated with an underlying vitamin K deficiency and adherence issues. Additionally, an argument against using VKA to treat CKD patients is the link between VKA and vascular calcification, including calciphylaxis. In several trials [12,13], individuals with significant RI with VKA treatment for AF had an elevated risk of strokes and hemorrhage. In a retrospective study [14], warfarin medication was linked to an increased risk of strokes in dialysis patients with AF. This, however, was contingent on INR monitoring [4].

Direct Oral Anticoagulants

This group of anticoagulants has become the gold standard for preventing and treating VTE. Warfarin was the sole oral anticoagulant accessible from 1954 to 2010 when DOACs were introduced. The most effective use of DOACs necessitates a full grasp of their pharmacology as well as the patient characteristics that influence their usage. There are four FDA-approved types of this novel group namely; Dabigatran, Apixaban, Edoxaban, and Rivaroxaban. They come in a variety of dosages and dose reduction criteria to fit several purposes. One of the most difficult aspects of anticoagulant therapy individualization is determining the optimum dosage. Because these chemicals are excreted via the kidneys, people with renal impairment should exercise caution [4]. People with acute VTE must have their kidney function evaluated before starting anticoagulant therapy. As kidney function deteriorates, the benefits of DOACs appear to diminish in comparison to VKAs. The burden is compounded by the fact that VTE is linked to several comorbid diseases [5]. DOACs could be worth exploring as a treatment alternative since they have been non-inferior in regards to effectiveness and improved safety profile than conventional therapy in patients with VTE.

Dabigatran

In individuals with a significant cardiac rhythm condition termed nonvalvular atrial fibrillation, it is utilized to reduce the likelihood of coagulation of blood and other arising health risks [15]. It can also be utilized to treat and prevent the coagulation of blood in individuals treated with different medications. Dabigatran is as well used following hip replacement surgery to avoid thromboembolic events by avoiding the formation of dangerous coagulation in the blood arteries [15].

The mechanism of this medication in blood clot prevention is by inhibiting both free and clot-bound thrombin directly and competitively, as well as platelet aggregation produced by thrombin. Even though this drug aids in the smooth circulation of blood throughout the body, it should not be used to prevent blood clots after artificial heart valve replacement [16]. The presence of inactive compounds in this drug may cause diverse

negative effects on the health of the patient some of which are severe cough, bloody vomits, headaches, dizziness, tiredness, blood stool, angioedema, thrombocytopenia, and many more depending on the patient [16].

When contrasted to Warfarin, Cohen et al. [17] found that Dabigatran was linked with a statistically significant lower incidence of major bleeding. According to the findings of Schulman et al. [18], Dabigatran is non-inferior to Warfarin in preventing VTE recurrent episodes since it has caused fewer nonmajor hemorrhage events than Warfarin. Since Dabigatran has no recognized interactions with foods and very minor interactions with other medicines, it is significantly more convenient than Warfarin and does not necessitate routine blood-coagulation monitoring.

Rivaroxaban

Rivaroxaban is a blood thinner medication in the category of direct factor Xa inhibitors that are employed to cure and avoid VTE [19]. PE occurs when blood clots move to the lungs and become lodged in the blood vessels of the lungs. Rivaroxaban enhances blood flow, making it less prone to the formation of potentially deadly coagulation [19]. It might be used to prevent stroke in people who have heart problems such as non-valvular AF. Furthermore, it can be prescribed with aspirin to reduce the likelihood of severe cardiac difficulties including heart attacks in those who have coronary artery disease or those who have recently had surgery and are having problems with blood flow [19]. Diverse effects may arise from consuming this medication some of which are: anemia causing fatigue, breathing difficulty, heart palpitations, pale complexion, dizziness, nausea, vomiting, anaphylaxis, thrombocytopenia, agranulocytosis, retroperitoneal hemorrhage, jaundice, hepatitis, and hypersensitivity [19].

Bauersachs et al. [20] found that Rivaroxaban is non-inferior when contrasted with Enoxaparin/VKA in terms of preventing recurrent VTE. In their study, they found that the two major hemorrhage types occurred in 8.7% of normal, 10.7% of mild, 11.6% of moderate, and 22.2% of severe kidney impairment patients who took Rivaroxaban. Therefore, they concluded that renal impairment at any phase increases the risk of severe hemorrhage in individuals administered with these anticoagulants, while RI did not increase the risk of severe bleeding in individuals on Rivaroxaban at any stage. According to their research, the risk of recurrent VTE and bleeding increases as renal function declines.

Apixaban

Apixaban is an anticoagulant and a factor Xa inhibitor. It lowers the coagulation of blood and inhibits the probability of occurrence in arteries. It is utilized to reduce stroke risks in AF patients and used in deep vein thrombosis (DVT) or PE therapy as well as to reduce the chance of recurrent ones [21]. Apixaban is the only DOAC that has been investigated for effectiveness in patients with ESKD and has been authorized by the FDA. When compared to other DOACs, Apixaban is eliminated by the kidneys at a lower rate. In the U. S., it is the most widely prescribed medicine for DOAC-treated individuals with RI [21].

Moreover, disorders of the circulatory and lymphatic systems, including thrombocytopenia, hypotension, epistaxis, hematochezia, hematuria, and many other wound complications are likely to occur when individuals are taking this medicine [21].

Chokesuwattanaskul et al. [22] found that Apixaban has lower risks of hemorrhage when contrasted to Warfarin, therefore, they concluded by suggesting that Apixaban is better than Warfarin in hemorrhage patterns in individuals with advanced CKD or ESKD since it is advantageous in patients who are on dialysis. On the other hand, Reed et al. [23] found that Apixaban consumers showed a reduced rate of VTE relapse than Warfarin patients 4.4% vs 28.6%, respectively, and the risk of recurrent stroke seen among Apixaban and Warfarin classes was found to be the same in their research.

Edoxaban

Edoxaban is an anticoagulant in the category of factor Xa inhibitors. It lowers the coagulation of blood and inhibits the probability of occurrence in veins and arteries. It is utilized to avert strokes as well as the coagulation of blood in people with cardiac rhythm disorder, and DVT [24]. The most frequent Edoxaban adverse effect is excessive bleeding, which can include nosebleeds, heavier periods, bleeding gums, bruises, dizziness, nausea, and vomiting. In addition, anemia, fatigue, and breathing difficulty may also result as side effects from the consumption of this medication [24].

Studies have continuously investigated the use and efficacy of Edoxaban for VTE in RI. Fazio et al. [25] claimed how safe and efficient edoxaban is in individuals with severe CKD, despite the observed minor hemorrhage, since no major bleeding, as well as thrombotic events, were found [26]. In the study of Shimada et al. [26], a 39-year-old male with renal dysfunction was hospitalized. Renal VTE and segmental PE were diagnosed using contrast-enhanced CT hence anticoagulation therapy was initiated. The PE returned a month after Warfarin therapy, and then the patient was switched from Warfarin to Edoxaban, which resulted in the absence of renal VTE thereby proving the effectiveness of Edoxaban in treating thromboembolism conditions in patients with RI.

Methodology

Fuzzy-Based MCDM Models

MCDM is a field of study that entails analyzing the pros and cons of many options in a given condition or area of research, which can include sciences, engineering sectors, health-related sectors, and a variety of other fields. One of the key issues in practical situations is gathering clear data to examine systems. Zadeh,

(1965) [27] created the groundwork for the idea of constructing a rule that works and then passing it to a computer using real-life experiences and diverse types of information.

In its most basic form, fuzzy logic is a soft computing approach that investigates logical models. Linear and nonlinear programming, geometric, dynamic, and integer programming are some of the modeling methodologies used with fuzzy logic [28]. These techniques are paired with fuzzy logic to establish an optimal solution under vague settings, giving the decision-maker more flexible solutions under a fuzzy environment. Because of its effectiveness and efficacy in analyzing options with several conflicting criteria, fuzzy-MCDM has been used in medicine and is being applied in diverse fields. It is well suited to the development of knowledge-based algorithms in healthcare, as well as applications such as medical diagnostics, therapy decisions, and real-time surveillance of patient records [29].

Fuzzy PROMETHEE

The PROMETHEE technique is one of the MCDM models that enables a researcher to examine and rank various alternatives considering multiple criteria [30]. It is a valuable and sensitive method that can address both qualitative and quantitative criteria simultaneously. It allows the user to have complete control over alternatives based on the chosen criteria [30].

When using PROMETHEE, the decision-maker requires two types of data: the relevance weights of the defined criteria and the preference function, which compares the contribution of the criteria to the alternatives to be ranked [31]. In PROMETHEE diverse preference functions are accessible to define diverse criteria. The preference function assigns values to each pair of the alternatives regarding certain criteria in particular and a preference degree that ranges between 0 and 1. Brans et al. [32] provided a thorough description of the preference functions, and how to choose the optimum function for a given case, for each parameter, the outranking test compares pairs of alternatives. The decision-maker can choose between normalization and equality of weights depending on the application [30].

Fuzzy logic and PROMETHEE are integrated into the fuzzy PROMETHEE approach. This enables a variety of decision-making scenarios feasible for implementation. Wang, et al. [33] used the same approach to compare non-numeric options. It is challenging to gather the data needed to identify a case effectively and come to the best choice. However, using fuzzy sets, the person making the decision can study the system in a usefully fuzzy state. This permits the decision-maker to define the matter under imprecise circumstances, which is more realistic. The fuzzy PROMETHEE model's key purpose is to suggest a comparison between two fuzzy sets. To evaluate the fuzzy numbers, Yager discovered an index that is based on the center of weight of the surface of the membership function. For assessing the fuzzy numbers in this study, the Yager index was used [34].

Fuzzy VIKOR

The VIKOR is a strategy for rating and evaluating alternatives and generating suitable approaches to problems based on criteria that assist decision-makers in reaching an effective option in their decision-making operations [35]. Since a consensus approach maximizes group utility while minimizing individual regret, decision-makers are more likely to accept it.

S. Opricovic [35] presented the VIKOR approach in his Ph.D. dissertation in 1979, and it offers a consensus option depending on the proximity to an optimal solution. It ranks options based on criteria and the preferences of the decision-maker. The major steps in the VIKOR method are [31]:

1. Establishment of a decision matrix (a matrix of criteria and various alternatives)
2. Calculating the positive and negative solutions
3. Calculating the weighted normalized decision matrix
4. Determining the utility; S_j and regret; R_j values
5. Calculating the preference index; Q_j
6. Ranking the preference order by the obtained values of Q_j.

Within the collection of a better option, the alternative with the minimal Q_j value is designated as the best and, as a result, a preference ranking can be computed [35].

Application of Proposed Methods

The proposed MCDM models, namely Fuzzy PROMETHEE and fuzzy VIKOR, have been applied in various sectors of life, starting from education, logistics, the environmental sector, engineering, the medical field [36-38], and many more. They are being used in solving many daily problems faced by the community worldwide. Diverse weights are attributed to every criterion following considerable collaboration with doctors, relatives of the patient, and other health practitioners.

In this study anticoagulants used in the treatment of VTE in RI were analyzed; namely, VKA; Warfarin, and DOACs; Dabigatran, Rivaroxaban, Apixaban, and Edoxaban. These alternatives were ranked using MCDM techniques; fuzzy PROMETHEE and fuzzy VIKOR, depending on the weights assigned to different chosen criteria: dose, bioavailability, peak time, half-life, renal elimination, neutralization, plasma protein, binding drug-drug interaction, monitoring, major and minor bleeding, pregnancy, thrombocyte function, food interaction, GIS bleeding, intracranial bleeding, elevated liver function test, onset-offset, cost, the usage in end-stage kidney disease, allergic reactions, numbness of joints, back pain effect, prodrug, the requirement of dose adjustment, whether the therapy requires bridging or not,

whether it is dialyzable or not. The criteria of interest were scaled according to the linguistic fuzzy scale as shown in Table 1 with the corresponding importance weight.

Table 1. The used criteria with their corresponding weights with a linguistic fuzzy scale

Linguistic scale for evaluation	Triangular fuzzy scale	Criteria
Very High	(0.75,1,1)	Major bleeding, minor bleeding, end-stage kidney disease, dialyzable
High	(0.50, 0.75,1)	Dose adjustment, bioavailability, peak time, half-life, drug-drug interaction, monitoring, thrombocyte function, GI bleeding, intracranial bleeding, elevated liver test function, onset-offset action, cost, numbness of joints, allergic reactions, back pain effect
Moderate	(0.25, 0.50, 0.75)	Renal elimination, plasma protein, neutralization, food interaction, bridging, prodrug.
Low	(0, 0.25, 0.50)	
Very Low	(0, 0, 0.25)	

VH: Very High, H: High, M: Moderate, L: Low, VL: Very Low

RESULTS

Table 2 shows the ranking of the selected alternatives from the application of the fuzzy PROMETHEE method, while the positive and negative sides of each of the anticoagulants and their corresponding criteria have been illustrated in Figure 1. By the preference ranking shown in Table 3, Apixaban outranked other alternatives, being the first preferable anticoagulant with the lowest Qj value of 0.0000 as a result of applying the fuzzy VIKOR method. Dabigatran, Edoxaban, and Rivaroxaban followed with Qj of 0.6043, 0.6222, and 0.8985; respectively. VKA; Warfarin, came out as the 5th ranked anticoagulant making it to be the less preferable anticoagulant with the highest number of Qj being 1.0000. The utility; Sj, and regret; Rj, values were calculated, as shown in Table 3 thereby leading to the computation of the preference index; Qj, which aided in ranking the alternatives as seen in Table 4.

Table 2. Complete ranking of anticoagulant alternatives with fuzzy PROMETHEE

Ranks	Alternatives	Phi	Phi+	Phi-
1	Apixaban	0.0064	0.0093	0.0030
2	Dabigatran	0.0018	0.0085	0.0067
3	Edoxaban	-0.0015	0.0047	0.0062
4	Rivaroxaban	-0.0024	0.0055	0.0079
5	VKA	-0.0043	0.0079	0.0122

Phi: Net flow, Phi+: Positive outranking flow, Phi-: Negative outranking flow

Table 3. S_j and R_j indexes of the anticoagulant options

Anticoagulants	S_i	R_i
VKA	0.6621	0.0616
Dabigatran	0.4636	0.0616
Rivaroxaban	0.6112	0.0616
Apixaban	0.4113	0.0502
Edoxaban	0.4726	0.0616

S_j: Utility index, R_j: Regret index

Table 4. Ranking result of the anticoagulant alternatives using the fuzzy VIKOR method

Ranking	Anticoagulants	Q_i
1	Apixaban	0.0000
2	Dabigatran	0.6043
3	Edoxaban	0.6222
4	Rivaroxaban	0.8985
5	VKA	1.0000

Q_i: Preference index

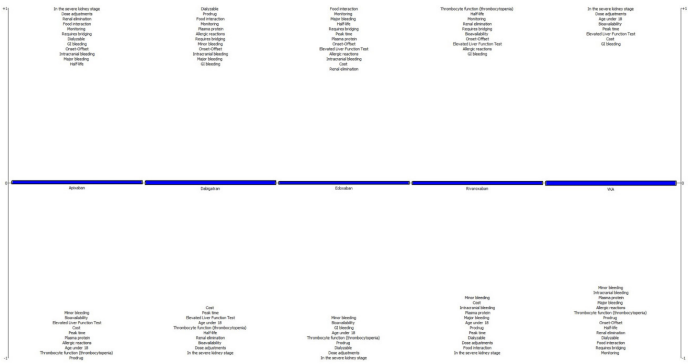

Figure 1. The benefits and drawbacks of each anticoagulant alternative

DISCUSSION

Clinically, DOACs were found to have a similar thromboembolic and equivalent to decreased major bleeding risks to Warfarin [39]. In this study, various anticoagulant alternatives were compared using two major MCDM approaches; fuzzy PROMETHEE and fuzzy VIKOR. Anticoagulants are globally applied in treating cardiovascular diseases that include VTE as well as PE. Despite their advantages, various negative side effects may arise from anticoagulant therapy such as major bleeding which puts a patient at high risk of death.

DOACs provide several benefits against Warfarin, including a uniform dose, unnecessity for routine lab monitoring, and fewer medication interactions. This is the first study to compare the two most essential anticoagulant classes used in the treatment of VTE (DOACs; Dabigatran, Rivaroxaban, Apixaban, Edoxaban, and

VKA; Warfarin) in RI, and it is also the first to employ MCDM models to help in the analysis and the preference ranking of two anticoagulant categories.

According to society guidelines, Warfarin is the recommended anticoagulant for people with CKD; nevertheless, it has been linked to an increased risk of bleeding, which is not directly related to creatinine clearance (CrCl). ESKD patients possess an elevated risk of bleeding owing to platelet dysfunction caused by uremia. In this study, DOACs performed better than Warfarin in terms of safety and effect for VTE treatment in RI, except for individuals with severe RI, Apixaban and Warfarin were found to be more in use than other anticoagulants. This information might aid in the selection of oral anticoagulants for patients at various stages of RI and with different risks for bleeding. DOACs have significantly higher pharmaceutical prices than Warfarin due to their newness on the market and brand-only availability.

This study was able to weight and analyze diverse criteria and from these, the alternatives were ranked from the best to the least preferable anticoagulant with a safe and high-efficiency profile. Apixaban was found to be the safest, and most effective anticoagulant to use as a treatment option in patients with severe kidney conditions when compared to other DOACs as well as VKA. Low risk is connected with this alternative since there is a lower chance of bleeding when compared to the often-prescribed Warfarin.

Dabigatran was found to be the second-best option, it showed low side effects; rare allergic reactions, and back pain effects, and no unwanted interactions (either food or drug) were found that may inhibit its action. However, as observed in this study, it is not advisable to use this anticoagulant in severe CKD cases because of severe bleeding. In their comparative study, Chan et al. [40] compared the effects of Dabigatran and Rivaroxaban in treating AF in patients on hemodialysis. In their findings, an 88% increase in the fatal bleeding risk of Dabigatran in comparison to warfarin was found. In addition, they also found a 58% increase in the Rivaroxaban risk of fatal bleeding in comparison to warfarin in treating AF in hemodialysis patients. These results correspond to the outcomes of this study regarding the bleeding effects that comes with Dabigatran when used in treating venous thromboembolism in renal insufficiency.

Edoxaban was the third-best method with its lowest cost, rare allergic reactions, as well as fewer back-pain effects, and no food or drug interactions that may interfere with its action. Rivaroxaban followed as the fourth-ranked alternative. It is not used in patients with the fifth phase of CKD. Severe bleeding close to that of Warfarin is linked to this alternative which lessens its preference in being chosen as one of the best oral anticoagulants to be used in treating VTE.

VKAs; Warfarin, was found to be the least preferable anticoagulant. It leads to severe bleeding which is very risky for RI patients with VTE. This might trigger a stroke or heart failure which may even result in the loss of a patient's life. Its need for monitoring, food interaction, severe allergic reactions, and back pain effects, as well as the lack of dialysis action and many negative effects rendered this alternative a low preference. However, depending on its lowest cost compared to all alternatives, it is still used in some regions, especially in low-income countries. Apart from Apixaban, Warfarin is one of the approved anticoagulants used in the treatment of patients with ESKD. A bridge with a parenteral anticoagulant is required when warfarin is used to treat VTE mainly due to its long peak time as well as its slow onset-offset of action, this diminishes its usage in the medical field when compared to the rapid onset-offset of action in DOACs.

Although the use of DOACs in VTE therapy is advancing, the choice of oral anticoagulant to use in RI patients remains a personal decision based on the effects of the drug and patient preferences, patient health concerns, and financial status. Additional research is needed to assess the long-term economic impact of DOACs due to their higher drug costs. Fuzzy PROMETHEE and Fuzzy VIKOR may evaluate a high number of inputs; therefore, this research can be expanded by considering different types of anticoagulants as well as diverse criteria or adding to the examined alternatives. Additionally, weights assigned to each criterion might change depending on the researcher's goal and due to the high sensitivity of the used MCDM models, this may hinder the results; hence, further research considering more variant criteria is recommended.

In this study, various types of anticoagulants used in the reduction/inhibition of severe bleeding for VTE treatment in RI were analyzed. The use of anticoagulants can be harmful; therefore, physicians should be familiar with these agents and know how to use them safely. The inability to acknowledge the pharmacology and pharmacokinetics of these drugs causes severe kidney failure, which can even lead to serious life-threatening hemorrhage. Using MCDM Models, namely Fuzzy PROMETHEE and Fuzzy VIKOR, different anticoagulant alternatives (Warfarin, Apixaban, Edoxaban, Dabigatran, and Rivaroxaban) were analyzed. As a result, Apixaban was ranked in the 1st place, whereas warfarin was found to be the least preferable option with 5th place in the ranking system. Results from this study will guide decision-makers when it comes to selecting the best anticoagulant to use which will not only enhance the patient's treatment but also benefit health care professionals in providing effective therapy.

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