AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Review on Apixaban use and its Associated Outcomes in Dialysis-dependent Patients with End Stage Renal Disease and Atrial Fibrillation

Ayyanki Anisha*, Mekhala Nandini, Kuragayala Vamshi, Tula Meena Amrutha Sai, Saba Ruksaar

Pulla Reddy Institute of Pharmacy

ABSTRACT

End-stage renal disease patients have a higher prevalence of diabetes mellitus, hypertension, congestive heart failure and advanced age, along with an increased incidence of non-valvular atrial fibrillation, thereby increasing the risk for cerebrovascular accidents. The most frequent arrhythmia treated is atrial fibrillation, which necessitates the use of novel oral anticoagulants that have been approved to reduce the risk of thromboembolism and stroke. So, compared to traditional anticoagulants, apixaban was associated with a significantly lower risk of stroke or systemic embolism (2).Patients with chronic kidney disease are more likely to develop AF, with a 10% frequency among those on chronic dialysis. Warfarin is the most widely prescribed OAC for individuals with end-stage kidney disease. On the other hand, DOACs are generally safer than warfarin, with fewer fatal bleeding events and a fixed dose that does not require close international normalized ratio monitoring (1). Several studies have investigated the safety and efficacy of apixaban in patients with ESRD and NVAF. The goal of this study is to determine the patterns of apixaban use and its associated outcomes in dialysis-dependent patients with ESKD and AF (3). This article gives an overview of clinical presentations, diagnostic procedures, complications and management of end stage renal disease.

Keywords: Chronic kidney disease, End stage renal disease, Novel oral anticoagulants, Atrial fibrillation, Dialysis, Traditional anti-coagulants.

*Corresponding Author Email: ayyankianisha@gmail.com

Received 29 June 2023, Accepted 29 July 2023

Please cite this article as: Anisha A *et al*., A Review on Apixaban use and its Associated Outcomes in Dialysis-dependent Patients with End Stage Renal Disease and Atrial Fibrillation. American Journal of PharmTech Research 2023.

INTRODUCTION

Most of the elderly people in the world with diabetes and hypertension are at increased risk of developing ESRD (End Stage Renal Disease). ESRD is the final stage of chronic kidney disease (CKD). ESRD can lead to many complications that include; cardiovascular diseases (high BP, thrombotic events), anemia, bone diseases and infections. Anti-coagulants are the drugs used for prevention of thrombotic events in CKD patients with elder age. Previously traditional anti-coagulants like heparin and warfarin were used for thrombotic complications in ESRD patients but due to increased risk of bleeding and need for regular monitoring made to look for alternative drugs like NOACs Novel Oral Anti-Coagulants (Apixaban, Rivaroxaban, Edoxaban, Betrixaban and Dabigatran) which doesn't need regular monitoring, has predictable pharmacokinetics and comparable efficacy to traditional anti-coagulants Among NOACs Apixaban has proved as safest drug to use in patients with chronic kidney disease (CKD). In 2012, Apixaban (Eliquis) was approved by FDA to reduce risk of stroke and systemic embolism in patients with NVAF (Non-Valvular Atrial Fibrillation). In 2014, Apixaban (Eliquis) was approved to reduce the risk of VTE (Venous Thrombo-Embolism) following hip or knee replacement surgery.

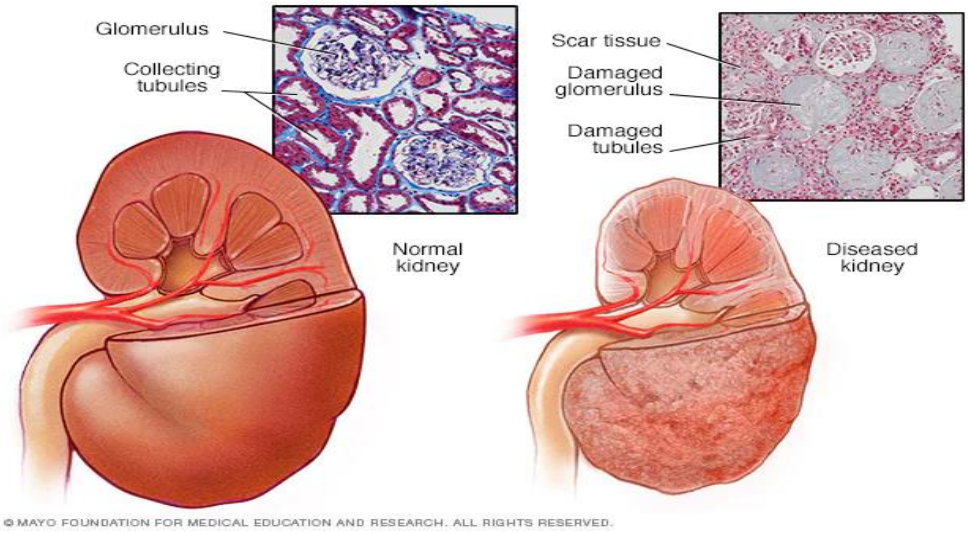

Figure 1: End stage renal disease

End-stage renal failure also known as end-stage renal disease (4) is a condition in which the final stage of kidney disease, i.e., under stage 5 of the National kidney foundation kidney disease outcomes quality initiative classification of CKD, where it refers to individuals with an estimated glomerular filtration rate less than 15 mL per minute per 1.73 m2 body surface area(5), or those requiring dialysis irrespective of glomerular filtration rate. Reduction in or absence of kidney function leads to a host of maladaptive changes including fluid retention (extracellular volume

overload), anemia, disturbances of bone and mineral metabolism, dyslipidemia, and protein energy malnutrition (6).

Where kidney function has declined to the point that the kidneys can no longer function on their own. A patient with end-stage renal failure must receive dialysis or kidney transplantation to survive for more than a few weeks.

THE CORRELATION BETWEEN ATRIAL FIBRILLATION AND END STAGE RENAL DISEASE:

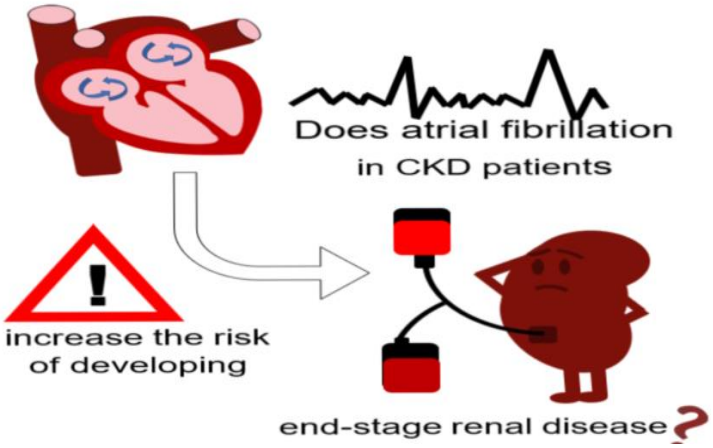

Figure 2: Correlation between AF and ESRD[7]

Atrial fibrillation (AF) is associated with increased risk of stroke and systemic thromboembolism. Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with Atrial Fibrillation and risk factors for Stroke or Thromboembolism. These include prevention and treatment of deep vein thrombosis and pulmonary embolism, and stroke prevention in AF. Patients with end-stage renal disease (ESRD) have increased risk of AF, but a definitive indication for anticoagulation treatment in ESRD patients with AF was never established, because the risk-benefit profile of anticoagulation in patients with ESRD is unclear. The population of patients with ESRD on hemodialysis (HD) treatment were not included in any trials on stroke prevention and treatment of venous thromboembolism and have therefore not profited from the introduction of direct oral anticoagulants (DOACs). These direct anticoagulation agents are small molecules and act via direct factor inhibition and are therefore classified as DOACs. The members of the DOAC drug class differ with respect to their pharmacokinetic properties. Differences between DOACs include renal elimination, oral bioavailability, protein binding and plasma half-life. Atrial fibrillation (AF) is estimated to occur in 7% to 20% among patients with end-stage renal disease (ESRD), which is 2- to 3-fold higher than reported in the general population.1

Studies have shown that the prevalence of AF is increasing among patients with ESRD and is associated with worse outcomes such as ischemic stroke and death(8,9).

Advantages of apixaban with end stage renal disease and atrial fibrillation:

Apixaban is an oral anticoagulant medication that has several advantages for patients with end-stage renal disease (ESRD) and atrial fibrillation (AF) compared to other anticoagulant medications.

1. Apixaban has a lower risk of bleeding compared to warfarin, which is another commonly used anticoagulant. This is particularly important in patients with ESRD, who are at a higher risk of bleeding due to their underlying kidney disease.
2. Apixaban does not require routine monitoring of blood levels or frequent dose adjustments, unlike warfarin which requires regular blood testing to ensure the appropriate dose is being administered.
3. Apixaban has a shorter half-life compared to other anticoagulants, meaning that it is cleared from the body more quickly. This can be an advantage in patients with ESRD, as these patients are more likely to experience drug accumulation and toxicity due to their impaired kidney function.

Finally, apixaban has been shown to be effective in reducing the risk of stroke and systemic embolism in patients with AF, including those with ESRD. This is an important benefit as AF is a significant risk factor for stroke, and ESRD patients are already at an increased risk for cardiovascular complications.

EPIDEMIOLOGY:

Chronic kidney disease affects 14.9% of the population overall; the sub-populations with the highest prevalence are females (16%), adults older than 65 years (38.6%),The leading causes of CKD are diabetes, hypertension, and glomerular disease; among patients older than 65 years, CKD is associated with a 2-fold greater prevalence of cardiovascular disease, most commonly in the form of atherosclerotic disease, which is present in 40% of CKD patients.

In 2018, the incidence of end stage kidney disease prevalence was per million; ESKD is most commonly a result of diabetes, followed by hypertension, glomerulonephritis, and cystic kidney disease. The incidence of ESKD has declined since 2006, partly due to improved recognition and care of CKD, resulting in decreased progression of CKD to ESKD. As with CKD, ESKD older patients are at the highest risk for developing ESKD. Adults older than 65 years comprise nearly three-fourths of all ESKD cases and are the largest growing segment of patients with ESKD. Adults older than 75 years had a 4-fold greater incidence of ESKD than the average adult and more

than double the incidence of adults in the 45- to 64-year-old age group. Among ESKD patients, 70.7% are treated with hemodialysis (HD) or peritoneal dialysis (PD) and 29.3% have a kidney transplantation (10).

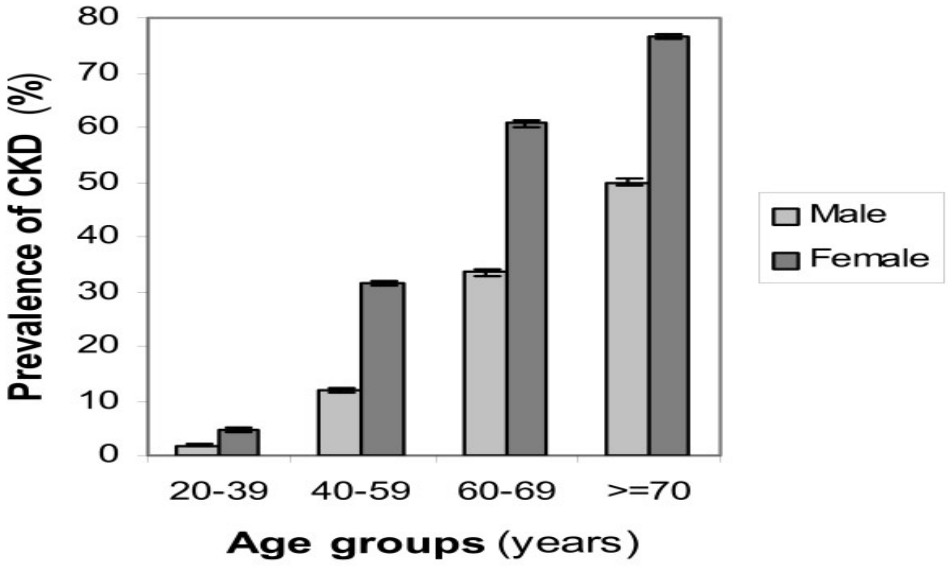

Figure 3: Age-specific prevalence of CKD

CLINICAL MANIFESTATIONS OF END STAGE RENAL DYSFUNCTION:

➢ The most common clinical manifestations of chronic kidney disease progress to end-stage renal disease, typical signs and symptoms of kidney failure include swelling of the feet and legs due to fluid retention, trouble sleeping, muscle cramps, numbness or tingling in the fingers or toes, loss of appetite, metallic taste in the mouth.

➢ By stage 5(ESRD), signs and symptoms may also include: headache, producing little or no urine, trouble breathing, nausea and vomiting, changes to skin color (11).

ETIOLOGY (12,13):

Causatives to ESRD (End Stage Renal Disease) are:

- High Blood pressure
- Diabetes
- Glomerulonephritis (an inflammation of the tiny filters in the kidneys).
- Cystic disease
- Autoimmune diseases
- Inherited Kidney disease

- Certain medications (NSAIDs, Antibiotics, Dyes, Chemotherapy, Illegal drugs...)

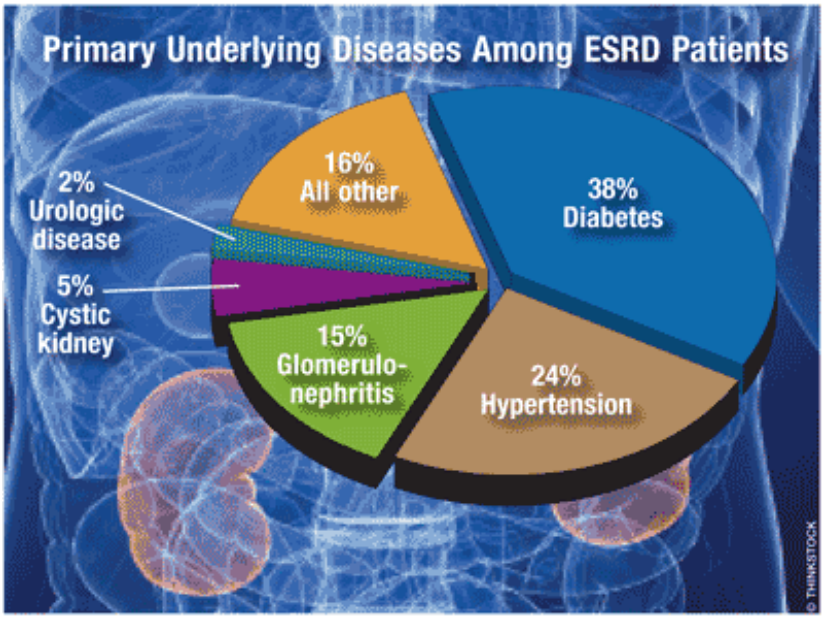

Figure 4: Primary Underlying diseases among ESRD Patients[14]

- Risk factors for developing ESRD include a history of chronic renal insufficiency, diabetes mellitus, heroin abuse, tobacco or analgesic use, non-white race or ethnicity, lower socioeconomic status, obesity, hyperuricemia, and a family history of kidney disease(15).
- Complications are Anemia, Bone disease, Brain damage, Edema (swelling), Fluid in and around the lungs, High levels of certain minerals (potassium or phosphorus), Infections, Nerve damage, Seizures, Stroke (16).

DIAGNOSIS (5):

ESRD stands for End-Stage Renal Disease, which is a medical condition in which the kidneys no longer function properly to filter waste and excess fluids from the blood. Diagnosis of ESRD typically involves a combination of medical history, physical examination, blood and urine tests, and imaging studies.

Some of the common diagnostic tests for ESRD include:

- **Medical history:** The healthcare provider will ask the patient about their medical history, including any past kidney problems, medications they are taking, and any symptoms they are experiencing.
- **Physical examination:** The healthcare provider will perform a physical examination to check for signs of kidney disease, such as swelling in the legs and feet, high blood pressure, and fluid buildup in the lungs.

- **Blood tests:** A blood test called creatinine blood test is used to measure the level of creatinine in the blood. Creatinine is a waste product that is normally removed from the body by the kidneys. When the kidneys are not functioning properly, the level of creatinine in the blood increases.
- **Urine tests:** Urine tests measure specific substances such as protein or blood. Damaged kidneys let more protein pass into urine than healthy kidneys. The amount of urine that is made. Little or no urine is made as the kidneys fail. Technicians will then analyze your urine sample at a lab.
- **Imaging tests:** Imaging tests such as ultrasound, CT scan, or MRI can be used to evaluate the size and structure of the kidneys and detect any abnormalities that may be causing or contributing to ESRD (End-Stage Renal Disease).
- **Ultrasound:** An ultrasound uses sound waves to create images of the kidneys. This non-invasive imaging test is often the first imaging test performed to evaluate the kidneys. It can provide information on the size, shape, and texture of the kidneys, as well as any signs of blockages or cysts.
- **CT scan:** A CT (computed tomography) scan uses X-rays and computer technology to create detailed images of the kidneys. This imaging test can provide more detailed information than an ultrasound, such as the precise location of any abnormalities and their size. A contrast dye may be injected into a vein to help highlight the kidneys during the CT scan.
- **MRI:** An MRI (magnetic resonance imaging) uses a strong magnetic field and radio waves to create detailed images of the kidneys. This imaging test can provide even more detailed information than a CT scan, such as the blood flow to the kidneys. A contrast dye may be injected into a vein to help highlight the kidneys during the MRI.
- Imaging tests can be useful in diagnosing ESRD and identifying any underlying conditions that may be contributing to kidney damage. The choice of imaging test will depend on the patient's individual circumstances and the healthcare provider's evaluation of their condition. Imaging tests are non-invasive and generally safe, but some patients may not be able to undergo certain imaging tests due to the presence of medical conditions or allergies to contrast dye.
- **Kidney biopsy:** Removing a sample of kidney tissue (biopsy), to examine under a microscope to learn what type of kidney disease you have and how much damage there is

Certain tests might be repeated over time to help your provider follow the progress of your kidney disease.

Here are some additional tests that may be used to diagnose ESRD:

- **Glomerular filtration rate (GFR):** GFR is a test that measures how well the kidneys are filtering waste from the blood. It is calculated based on the level of creatinine in the blood, age, sex, and race. A GFR of less than 15 ml/min/1.73m2 indicates ESRD.
- **Electrolyte levels:** Blood tests may be used to measure the levels of electrolytes such as potassium, sodium, and calcium. Abnormal levels can be an indication of kidney damage.
- **Blood urea nitrogen (BUN):** BUN is a blood test that measures the amount of nitrogen in the blood that comes from urea, a waste product made by the liver. Elevated BUN levels can indicate kidney damage.
- **Urinalysis:** Urinalysis can provide additional information on the presence of red and white blood cells, bacteria, and other substances that can indicate underlying kidney problems.
- **Kidney function tests:** These tests can be used to evaluate how well the kidneys are functioning. They may include urine output measurement, measurement of serum creatinine and urea nitrogen, and calculation of creatinine clearance.
- **Autoimmune testing:** In some cases, autoimmune testing may be used to diagnose underlying autoimmune conditions that may be contributing to kidney damage.

PATHOPHYSIOLOGY OF AF IN ESRD:

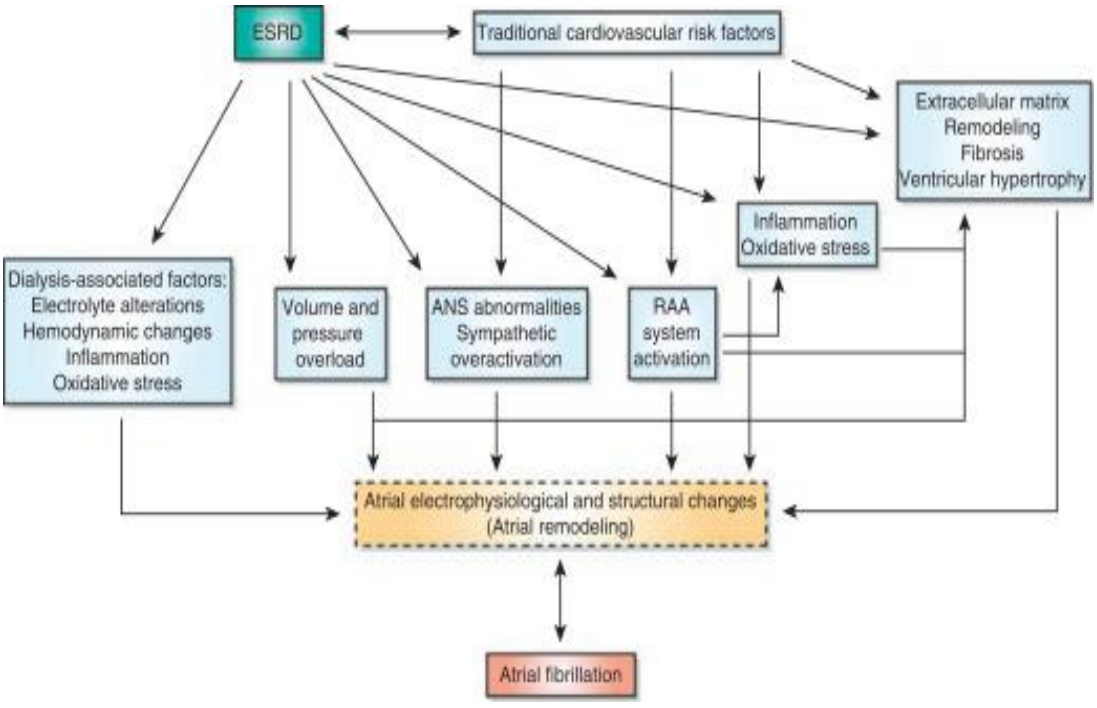

Figure 5: Pathophysiology of AF in ESRD

The pathophysiology of AF in ESRD is complex as such associated with volume overload and neurohormonal alterations (mainly activation of the sympathetic system and the renin–angiotensin–aldosterone system) that promote ventricular hypertrophy and dilation as well as increased left atrial size and pressure. Inevitably, these abnormalities contribute to the structural and electrical remodeling of the atria. In addition, inflammation and oxidative stress have been implicated in the pathophysiology of ESRD and represent major mechanisms of cardiovascular dysfunction (17).

MANAGEMENT:

APIXABAN USE AND ITS ASSOCIATED OUTCOMES:

Apixaban, inhibits the Xa factor and was introduced to the market in 2012, after the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, which showed clear superiority over traditional anticoagulants for thromboembolic events while having fewer bleeding events.

It is one of the most used DOACs in CKD and ESKD since it is only 25% excreted by the kidney and it is not affected by dialysis, as was published in 2016. Specifically, only 6.7% of the drug may be removed after 4 hours of dialysis. The FDA has approved the use of apixaban for patients with ESKD on dialysis at 5 mg twice daily, reduced to 2.5 mg twice daily for patients 80 years old or with a bodyweight <60 kg. Although this was written in 2014, resulting in further use of apixaban in ESKD patients, it was already used before the FDA approval, off-label in high percentages. There is no confirmed data on single- and

multiple dose apixaban in patients with AF and ESKD on dialysis, who have maintained their diuresis. In patients on chronic dialysis, apixaban exposure is affected not only by the medication dose but also by the timing of intake in relation to the hemodialysis process. And many studies suggested that the exposure and the concentration of apixaban were lower when the drug was administered 30 minutes before the hemodialysis session, which makes dialysis computable enough for the drug exposure.

In 2018, compared apixaban (5 mg vs 2.5 mg twice daily) and warfarin in patients with ESKD and AF. People taking standard-dose apixaban (5 mg) had a lower thromboembolic risk than those taking low-dose apixaban (2.5 mg) or warfarin illustrating a lower risk of death and major bleeding. Additionally, in 2020, showed that when ESKD on chronic dialysis patients received 5 mg of apixaban twice daily for 8 days, it resulted in a similar drug concentration to healthy controls, with the observation of potentially higher, probably harmful levels of the drug in this group. Apixaban was related to a greater risk of fatal or cerebral hemorrhage rather than a reduced

incidence of a new stroke, transient ischemic attack, or systemic thromboembolism. Nevertheless, this study had some limitations since it did not assess long-term clinical outcomes like bleeding. Although apixaban seems to have become a clear alternative to warfarin for ESKD on chronic dialysis and AF patients (18).

End-stage renal disease treatments include (11):

- **Kidney transplant**
- **Dialysis**
- **Supportive care**

Kidney transplant is a surgical procedure to place a healthy kidney from a live or deceased donor into a person whose kidneys no longer function properly. A kidney transplant is often the treatment of choice for end-stage renal disease, compared with a lifetime on dialysis.

The kidney transplant process takes time. It involves finding a donor, living or deceased, whose kidney best matches your own. You then have surgery to place the new kidney in your lower abdomen and attach the blood vessels and ureter the tube that links the kidney to the bladder that will allow the new kidney to function.

After a successful kidney transplant, your new kidney filters your blood, and you no longer need dialysis.

Dialysis: Dialysis does some of the work of your kidneys when your kidneys can't do it themselves. This includes removing extra fluids and waste products from your blood, restoring electrolyte levels, and helping control your blood pressure. Dialysis options include peritoneal dialysis and hemodialysis.

Peritoneal dialysis: During peritoneal dialysis, blood vessels in your abdominal lining (peritoneum) fill in for your kidneys with the help of a fluid that washes in and out of the peritoneal space.

Hemodialysis: During hemodialysis, a machine does some of the work of the kidneys by filtering harmful wastes, salts and fluid from your blood (13).

Lifestyle and home remedies:

As part of the treatment for kidney disease, health care providers might recommend that you follow a special diet to help support your kidneys and limit the work they must do. Ask for a referral from a registered dietitian with expertise in kidney disease to learn ways to make diet easier on kidneys.

Depending on situation, kidney function and overall health, dietitian might recommend:

Avoid products with added salt. Lower the amount of sodium you eat each day by avoiding products with added salt, including many convenience foods, such as frozen dinners, canned soups and fast foods. Other foods with added salt include salty snack foods, canned vegetables, and processed meats and cheeses.

Choose lower potassium foods. A dietitian might recommend choosing lower potassium foods at each meal. High-potassium foods include bananas, oranges, potatoes, spinach and tomatoes.

Examples of low-potassium foods include apples, cabbage, carrots, green beans, grapes and strawberries. Be aware that many salt substitutes contain potassium, so generally you should avoid them if you have kidney failure.

Limit protein. The dietitian will estimate the grams of protein needed each day and make recommendations based on that amount. High-protein foods include lean meats, eggs, milk, cheese and beans. Low-protein foods include vegetables, fruits, breads and cereals.

PREVENTIVE MEASURES:

- Exercise
- Maintaining healthy weight
- Avoid smoking
- Avoid/ minimize alcohol consumption
- Keeping diabetes and hypertension under control and
- Regular check-ups with your physicians help in detecting any renal problems early so that they can be alleviated or that they can be treated on time.

CONCLUSION:

Apixaban is a direct oral anticoagulant (DOAC) and appears to be safe and effective and reduce stroke & systemic embolism in patients with ESRD and NVAF. The dosage of apixaban needs to be adjusted in these patients, as their impaired renal function may lead to drug accumulation and an increased risk of bleeding. The recommended dosage of apixaban for patients with ESRD and NVAF is 5 mg twice daily, although lower doses may be required in some patients based on individual clinical factors. Apixaban showed clear superiority over traditional anticoagulants for thromboembolic events while having fewer bleeding events and does not require routine monitoring of blood levels or frequent dose adjustments, unlike warfarin which requires regular blood testing to ensure the appropriate dose is being administered. Apixaban has a shorter half-life compared to other anticoagulants, that it is cleared from the body more quickly. This can be an advantage in patients with ESRD, as these patients are more likely to experience drug accumulation and toxicity due to their impaired kidney function. The incidence of end stage

kidney disease (ESRD) is 50% higher in adult men than in women, even though there is a higher prevalence of chronic kidney disease (CKD) in women. Kidney disease can develop at any time, those over the age of 60 are more likely to develop than other age groups. With proper treatment and self-care, patients with ESRD and AF can lead fulfilling lives despite the challenges posed by this condition.

REFERENCES:

1. Nikolaos Ktenopoulos, Marios Sagris, Panagiotis Theofilis, Sophia Lionaki, Loukianos S. Rallidis. Direct Oral Anticoagulants in Patients on Chronic Dialysis and Concomitant Atrial Fibrillation: A Common Clinical Impasse. Front. Biosci. (Schol Ed) 2022, 14(3), 21. https://doi.org/10.31083/j.fbs1403021
2. Update on the Safety and Efficacy of Oral Anticoagulation in CKD and ESRD (uspharmacist.com)
3. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X, Noseworthy PA, Shah ND, Saran R, Nallamothu BK. Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States.Circulation.2018Oct9;138(15):1519-1529. oi: 10.1161/CIRCULATIONAHA.118.035418. Erratum in: Circulation. 2018 Oct 9;138(15):e425. PMID: 29954737; PMCID: PMC6202193.
4. End Stage Renal Disease (ESRD) | Johns Hopkins Medicine
5. End-Stage Renal Disease - StatPearls - NCBI Bookshelf (nih.gov)
6. Hall YN, Chertow GM. End stage renal disease. BMJ Clin Evid. 2007 Oct 17; 2007:2002. PMID: 19450356; PMCID: PMC2943808.
7. Suwanwongse K, Shabarek N (February 07, 2020) Does Atrial Fibrillation Increase the Risk of Developing End-stage renal disease in Patients with Chronic Kidney Disease?. Cureus 12(2): e6908. doi:10.7759/cureus.6908
8. Königsbrügge O, Ay C. Atrial fibrillation in patients with end-stage renal disease on hemodialysis: Magnitude of the problem and new approach to oral anticoagulation. Res Pract Thromb Haemost. 2019 Aug 18;3(4):578-588. doi: 10.1002/rth2.12250. PMID: 31624777; PMCID: PMC6781927.
9. Hsieh HL, Hsu SC, Cheng HS, Chen CY, Huang WC, Sue YM, Lin FY, Shih CM, Chen JW, Lin SJ, Huang PH, Liu CT. The influence of atrial fibrillation on the mortality of incident ESRD patients undergoing maintenance hemodialysis. PLoS One. 2020 Jan

30;15(1): e0228405. doi: 10.1371/journal.pone.0228405. PMID: 31999778; PMCID: PMC6992232.

10. Gupta R, Woo K, Yi JA. Epidemiology of end-stage kidney disease. Semin Vasc Surg. 2021 Mar;34(1):71-78. doi: 10.1053/j.semvascsurg.2021.02.010. Epub 2021 Feb 4. PMID: 33757639; PMCID: PMC8177747.
11. Medically reviewed by Elaine K. Luo, M.D. —on December 12, 2019, what you need to know about kidney failure
12. Kidney failure (ESRD) - Symptoms, causes and treatment options | American Kidney Fund
13. Kidney Failure: Causes, Symptoms & Treatment (clevelandclinic.org)
14. Trends in Chronic Kidney Disease (uspharmacist.com)
15. Kidney Int Suppl (2011). 2013 Dec; 3(4): 368–371. Published online 2013 Nov 27. doi: 10.1038/kisup.2013.79 PMCID: PMC4089662PMID: 25019021
16. End-Stage Renal (Kidney) Disease: What is it, Causes, Dialysis & More (clevelandclinic.org)
17. Panagiotis G. Korantzopoulos, John A. Goudevenos, Atrial fibrillation in end-stage renal disease: an emerging problem, Kidney International, Volume 76, Issue 3,2009, Pages 247-249, ISSN 0085-2538,https://doi.org/10.1038/ki.2009.144.
18. Apixaban for End-Stage Kidney Disease | Circulation (ahajournals.org)