IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Comparative Review Of Clopidogrel And Aspirin For Cardiovascular Protection In Patients With Chronic Kidney Disease

[1]FARHANA N, [2]Dr.NITHIN MANOHAR R, [3]Dr.PRASOBH G R,

[1]SAFNA FAISAL, [1] SURYA S NAIR

1. Fifth Year Student, Doctor of Pharmacy, Sree Krishna College of Pharmacy and Research Centre, Parassala , Thiruvananthapuram, Kerala, India.
2. Professor and HOD, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre Parassala, Thiruvananthapuram, Kerala, India.
3. Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

ABSTRACT

A substantial percentage of deaths in individuals with chronic kidney disease (CKD) are attributable to cardiovascular disease (CVD), which is the primary cause of morbidity and mortality in this population. Endothelial dysfunction, oxidative stress, chronic inflammation, and an elevated prothrombotic state are some of the intricate processes that interact between CKD and CVD. These factors increase the likelihood of arterial calcification and atherosclerotic events, which are exacerbated by conventional CVD risk factors such diabetes, hypertension, and dyslipidemia, which are commonly seen in individuals with chronic kidney disease. For patients with established atherosclerotic disease and those at high cardiovascular risk, antiplatelet therapy—specifically, aspirin and clopidogrel—is essential for lowering thrombotic consequences. Aspirin, an irreversible inhibitor of cyclooxygenase-1 (COX-1), reduces platelet aggregation by blocking the formation of thromboxane A_2. Clopidogrel, an inhibitor of the P_2Y_{12} receptor, stops platelets from activating and aggregating when ADP is present. Both medications have shown effective in the general population, but because of their changed pharmacokinetics, elevated risk of bleeding, and greater vulnerability to side effects, using them in CKD patients poses special difficulties[1]

KEYWORDS

Chronic kidney disease, cardiovascular disease, antiplatelet therapy, aspirin, clopidogrel, thrombosis, bleeding risk, uremia, platelet dysfunction, secondary prevention, gastrointestinal bleeding, pharmacokinetics, P_2Y_{12} inhibitors, COX-1 inhibitors, hemodialysis.

INTRODUCTION

A major influence on morbidity and mortality, chronic kidney disease (CKD) is a global public health concern that is becoming more and more common. More than half of all deaths in this population are attributable to cardiovascular disease (CVD), making it one of the main causes of death for CKD patients. The elevated cardiovascular risk in individuals with chronic kidney disease (CKD) is complex, with pro-inflammatory and pro-thrombotic states, diabetes, dyslipidemia, and hypertension all playing a major role in the development of atherosclerotic cardiovascular disease. Endothelial dysfunction, increased arterial calcification, and altered calcium and phosphate metabolism are only a few of the pathophysiological pathways that make chronic kidney disease (CKD) more likely to cause cardiovascular events. Further raising the likelihood of thrombotic and hemorrhagic consequences is the fact that uremia frequently causes platelet dysfunction in CKD patients. It becomes more challenging to control the balance between thrombosis and bleeding as renal function deteriorates, which makes treatment choices more challenging, especially when antiplatelet medications are taken into account. It is imperative that CKD patients have adequate cardiovascular protection due to their increased cardiovascular risk. Managing CVD in this susceptible group requires antiplatelet medication, which attempts to lower the incidence of thrombotic events including myocardial infarction and stroke. Since CKD patients frequently have changed drug metabolism, increased bleeding tendencies, and a higher risk of negative outcomes with standard therapy like aspirin, the best antiplatelet agent choice is still unclear. To improve patient outcomes and lessen the burden of cardiovascular disease in this high-risk population, it is imperative to comprehend the necessity of cardiovascular protection in CKD patients and to choose the safest and most effective therapeutic approaches.[1]

Because platelets and the blood artery walls interact abnormally, platelet function is frequently compromised in chronic kidney disease (CKD). Proper clotting depends on these interactions. Reduced thromboxane and cyclic adenosine monophosphate production, elevated adenosine triphosphate to ADP ratio, decreased expression of glycoprotein Ib (GPIb) on platelets, and elevated soluble glycocalicin (a fragment of GPIb) are some of these abnormalities. Additionally, platelet adhesion to external surfaces is interfered with. Results from studies on platelet aggregation in uremic patients are inconsistent; they range from normal or even increased responses to stimuli including collagen, thrombin, ADP, and epinephrine to faulty responses. Furthermore, uremic toxins found in the blood of CKD patients can prevent platelet aggregation by altering the GPIIb/IIIa receptors on the surface of the platelets. There is uncertainty regarding the overall effect of uremic toxin accumulation on platelet activity because some uremic toxins, including polyamines, may stimulate thrombotic effects while others may inhibit platelet function. The risk of cardiovascular diseases (CVD), cardiovascular mortality, and all-cause mortality is higher for those with CKD, even those in its early stages, than for the general population[6]

ROLE OF ASPIRIN AND CLOPIDOGREL IN CKD PATIENTS

Heart failure, myocardial infarction, and stroke are among the cardiovascular events that are linked to chronic kidney disease (CKD). Patients with chronic kidney disease (CKD) frequently have concomitant diseases such diabetes mellitus, hypertension, and dyslipidemia, which increase their risk of cardiovascular problems frequently have concomitant diseases such diabetes mellitus, hypertension, and dyslipidemia, which increase their risk of cardiovascular problems. Antiplatelet therapy is commonly administered to CKD patients in order to prevent cardiovascular events, as they have a higher rate of cardiovascular morbidity and mortality.

The two most popular antiplatelet medications are aspirin and clopidogrel; nevertheless, their use in chronic kidney disease (CKD) poses special difficulties that call for thorough evaluation of the patient's renal function, risk of bleeding, and general clinical condition. The primary indications for antiplatelet therapy in CKD patients undergoing hemodialysis include:

Prevention of Cardiovascular Events: These patients have a high risk of myocardial infarction (MI), stroke, and peripheral vascular disease. Antiplatelet therapy, such as Aspirin or Clopidogrel, is commonly used for secondary prevention in those with established cardiovascular disease.

Dialysis Access Patency: Arteriovenous fistulae (AVF) or grafts used for dialysis are prone to thrombosis, which can lead to access failure. Antiplatelet drugs are often used to reduce the risk of thrombosis and improve graft survival.

Prevention of Thrombotic Events: Patients on hemodialysis have altered platelet function and heightened thrombotic risk. Antiplatelets help mitigate thromboembolic complications in these high-risk individuals.

Common Antiplatelet Drugs Used in Hemodialysis Patients

Aspirin: A nonsteroidal anti-inflammatory drug (NSAID) that inhibits the enzyme cyclooxygenase (COX), thereby reducing thromboxane A_2 and inhibiting platelet aggregation. Despite its efficacy in preventing cardiovascular events, its use in CKD patients must be monitored closely due to the potential risk of gastric ulcers, bleeding, and renal impairment, especially when used at high doses or long-term.

Clopidogrel: A P_2Y_{12} receptor antagonist that inhibits platelet aggregation by preventing ADP- induced platelet activation. It is often used in patients with a history of stent placement or acute coronary syndrome. Its benefit in hemodialysis patients is similar to that in the general population, although dosing and monitoring may require adjustment[3]

Efficacy Of Aspirin Hemodialysis Patients:

Aspirin is widely used for cardiovascular prevention in CKD patients, including those on hemodialysis. However, hemodialysis patients often have impaired platelet function due to uremic toxins, which may reduce aspirin's effectiveness. While aspirin can help reduce the risk of thrombosis, its clinical efficacy in this setting remains uncertain due to altered pharmacokinetics. In dialysis patients, the drug clearance may be altered, potentially affecting the therapeutic concentration of aspirin, as dialysis may reduce circulating levels of aspirin, potentially leading to reduced effectiveness. Access patency: Aspirin is commonly used to prevent thrombosis of dialysis access sites, such as arteriovenous fistulae (AVF) or grafts, which are prone to clotting.

Efficacy of Clopidogrel in Hemodialysis Patients:

Clopidogrel is generally effective in preventing cardiovascular events, particularly in patients with a history of acute coronary syndrome (ACS), stent placement, or those at high risk for thrombosis. The use of clopidogrel in hemodialysis patients is less well studied than aspirin. However, it has shown promising results in reducing cardiovascular events and thrombosis risk, particularly in patients with stent placements or after peripheral artery disease interventions.

Both Aspirin and Clopidogrel play significant roles in the prevention of cardiovascular events in patients undergoing hemodialysis. However, their use in this population requires careful management due to the altered pharmacodynamics and pharmacokinetics associated with renal dysfunction and dialysis.

Aspirin is generally used for long-term prevention of cardiovascular events and for maintaining dialysis access patency, but it carries risks related to GI bleeding and renal toxicity. Clopidogrel is often employed in patients with a history of ACS or those undergoing stenting procedures, but its efficacy may be reduced due to altered metabolism during dialysis, and it is associated with a heightened bleeding risk. Aspirin is frequently used to prevent cardiovascular events because it can permanently block cyclooxygenase-1 (COX-1), which lowers

the formation of thromboxane A_2. A decrease in clot formation results from the suppression of thromboxane A_2, a strong vasoconstrictor and activator of platelet aggregation.

Aspirin use in CKD patients, however, has been associated with a higher risk of bleeding problems, such as cerebral and gastrointestinal hemorrhages. Patients with advanced CKD

are more at risk, especially those receiving dialysis or those with stage 4 and stage 5 disease. The impaired ability of these individuals' kidneys to eliminate aspirin from their bodies increases the risk of bleeding. Moreover, platelet dysfunction linked to CKD, including

decreased platelet aggregation response and changed. . Numerous studies have shown that aspirin-treated CKD patients are more likely to experience bleeding. For instance, in the Aspirin in the Primary Prevention of Cardiovascular Events in the Elderly (ASPREE) trial, aspirin-treated CKD patients saw a markedly increased incidence of major bleeding events (10.4 vs. 6.3 per 1,000 person-years, respectively) in comparison to those without CKD.

Additionally, the decision to prescribe aspirin in this population becomes more complicated as the bleeding risk increases as the eGFR declines[25]

Clopidogrel, a thienopyridine derivative, inhibits platelet activation and aggregation by

selectively inhibiting the P_2Y_{12} ADP receptor on platelets. Clopidogrel is commonly regarded as a safer alternative to aspirin in patients with chronic kidney disease (CKD), particularly for those who are at high risk of bleeding or have contraindications to aspirin. Clopidogrel may

have a safer profile due to its more targeted action on platelet receptors and lack of effect on the COX pathway. However, there are a number of disadvantages to clopidogrel for CKD

patients. The effectiveness of clopidogrel may be reduced in patients with renal impairment since the liver processes the medication primarily and the kidneys eliminate its active

metabolites. The possibility of medication interactions with clopidogrel in CKD is another issue. The prodrug clopidogrel is activated by cytochrome P_{450} enzymes, particularly CYP_2C_{19}. Suboptimal platelet inhibition may result from clopidogrel's activation in CKD patients due to altered hepatic metabolism or concomitant usage of other drugs that inhibit CYP enzymes.

PARAMETER	ASPIRIN	CLOPIDOGREL
CLASS	Antiplatelet, Nonsteroidal Anti-inflammatory Drug (NSAID)	Antiplatelet (P_2Y_{12} receptor inhibitor)
MECHANISM OF ACTION	Inhibits cyclooxygenase (COX-1 and COX-2), reducing thromboxane A_2, which inhibits platelet aggregation.	Inhibits the P_2Y_{12} receptor on platelets preventing ADP from binding, thereby inhibiting platelet activation and aggregation.
AVAILABLE DOSES	75 mg,81mg,100mg,150mg [For cardiovascular protection]	75 mg [For cardiovascular protection]
ADVERSE DRUG REACTION	Gastrointestinal irritation, ulcers, bleeding, tinnitus, allergic reactions, renal impairment	Bleeding, bruising, diarrhea, rash thrombocytopenia, neutropenia, gastrointestinal upset

INDICATION	Cardiovascular prevention (e.g., in CAD, stroke) - Acute myocardial infarction (MI) Pain and inflammation (e.g., arthritis, headaches) Post-surgical thromboprophylaxis	Acute coronary syndrome (ACS) Recent myocardial infarction - Stroke prevention (in patients with ischemic stroke or peripheral artery disease) Post-stenting thromboprophylaxis
PHARMACOKINETICS	Absorption: Rapidly absorbed from the GI tract - Distribution: Widely distributed in the body, crosses the placenta - Metabolism: Hepatic (CYP_2C_9) - Excretion: Primarily via urine (metabolites)	- Absorption: Well absorbed in the GI tract, but has a delay in effect - Distribution: Binds to plasma proteins (98%) Metabolism: Hepatic (via CYP_2C_{19}) - Excretion: Primarily via urine (metabolites)
PHARMACODYNAMICS	Inhibits platelet aggregation through inhibition of thromboxane A_2 production, reducing clot formation.	Irreversibly inhibits platelet activation by blocking ADP binding to the P_2Y_{12} receptor, preventing platelet aggregation

THROMBOSIS AND BLEEDING RISKS WITH ASPIRIN AND CLOPIDOGREL

Aspirin and clopidogrel are examples of antiplatelet therapy that has a two fold risk of bleeding and thrombotic events in patients with chronic kidney disease (CKD). As such, prescribing these drugs requires careful evaluation of these risks.

Bleeding Risks: CKD patients are at an increased risk of bleeding due to a combination of factors, including platelet dysfunction and impaired renal function. Platelet abnormalities in CKD include reduced platelet aggregation, impaired platelet adhesion, and altered responses to stimuli, all of which can compromise hemostasis. These defects are exacerbated in patients with advanced CKD or those on dialysis, where the removal of uremic toxins is impaired, further contributing to platelet dysfunction. Additionally, medications like aspirin and clopidogrel, which inhibit platelet function, can increase the risk of both major and minor bleeding events. Aspirin, in particular, irreversibly inhibits cyclooxygenase-1 (COX-1), leading to reduced thromboxane A_2 production and decreased platelet aggregation. However, this effect is compounded in CKD patients, who may already have an elevated bleeding tendency due to their underlying condition. Clopidogrel, by inhibiting the ADP receptor (P_2Y_{12}), prevents platelet activation, but similar to aspirin, it can also increase the risk of bleeding, particularly in patients with impaired renal function, as renal clearance of the drug may be reduced. Data from studies, such as those from the ASPREE trial, show that CKD patients taking aspirin have a higher incidence of major bleeding events compared to those without CKD, and the risk of bleeding increases as the eGFR declines[25]

Thrombotic Risks: In addition to the risks of bleeding, individuals with chronic kidney disease (CKD) are more likely to experience thrombotic events like myocardial infarction, stroke, and vascular access thrombosis. Increased platelet activation, endothelial dysfunction, and the presence of prothrombotic uremic toxins are all part of the underlying pathophysiology of chronic kidney disease (CKD), and they all lead to a hypercoagulable condition. The choice to employ antiplatelet medication in CKD patients is complicated by the dichotomy of an enhanced risk of thrombosis and an increased risk of bleeding. Aspirin may still have a limited effect on lowering cardiovascular events in CKD patients, particularly in those with severe illness, even if it reduces thrombotic events by preventing platelet aggregation. . For patients who

cannot take aspirin or who are more likely to experience gastrointestinal bleeding, clopidogrel is frequently recommended as a substitute because it is a stronger inhibitor of platelet aggregation. Its effectiveness, however, might be diminished in patients with compromised renal function since renal impairment might change the drug's metabolism and reaction. Because of this, even though clopidogrel and aspirin both offer strong protection against thrombotic events, their advantages must be balanced against the risk of bleeding in patients with chronic kidney disease. Antiplatelet therapy in this population requires tailored treatment regimens that are informed by eGFR, comorbidities, and bleeding history in order to maximize safety and effectiveness. In conclusion, even though clopidogrel and aspirin help lower thrombotic events in patients with chronic kidney disease (CKD), their use needs to be carefully weighed against the increased risk of bleeding, especially in patients with advanced renal impairment. This calls for customized treatment plans that take both thrombotic and bleeding risks into account. Given that these drugs may have changed pharmacokinetics in individuals with chronic kidney disease (CKD), it is critical to routinely assess renal function and modify dosage as needed. Additionally, as polypharmacy is prevalent in this population and can increase the risk of bleeding or thrombosis, careful consideration should be given to any medication interactions. A thorough evaluation of the patient's cardiovascular risk, bleeding potential, and renal function should ultimately guide the decision between clopidogrel and aspirin, with an emphasis on maximizing therapeutic benefits and reducing side effects. To provide more precise recommendations for antiplatelet medication in individuals with chronic kidney disease (CKD), particularly those with varied levels of renal impairment, more study is required.[1]

CONCLUSION AND DISCUSSION

Myocardial infarction, stroke, and heart failure are among the cardiovascular illnesses (CVD) that are considerably more likely to occur in people with chronic kidney disease (CKD) because of the interaction of endothelial dysfunction, inflammation, and elevated platelet activation. In individuals with chronic kidney disease (CKD), antiplatelet therapy—especially when combined with aspirin and clopidogrel is a vital medication for reducing cardiovascular events in the general population. Nevertheless, the increased risks of bleeding and thrombosis in CKD offset the advantages of these treatments. Aspirin lowers platelet aggregation and thrombotic events by blocking cyclooxygenase-1 (COX-1). However, this mechanism of action increases the risk of severe bleeding in patients with chronic kidney disease (CKD), particularly in those with advanced renal impairment. ADP receptor (P2Y12) inhibition by clopidogrel, another widely used antiplatelet medication, stops platelet activation and aggregation. Despite having a potentially better bleeding profile than aspirin, it is less effective in individuals with chronic kidney disease (CKD) because to changes in metabolism and varying medication responses, especially in those with compromised renal function.

A careful balance between reducing the risk of bleeding and preventing thrombotic events is necessary for treatment of cardiovascular risk in individuals with chronic kidney disease. Because of aberrant platelet function, endothelial dysfunction, and reduced renal clearance of medications, individuals with chronic kidney disease (CKD) are more likely to experience thrombotic and bleeding problems. Because antiplatelet therapy increases the risk of bleeding as eGFR decreases, treatment plans must be modified based on the severity of renal impairment. Although aspirin has a well-established potential to lower thrombotic events, individuals with chronic kidney disease (CKD), especially those receiving dialysis or suffering from severe renal dysfunction, should exercise caution due to its link to serious bleeding risks, specifically gastrointestinal bleeding and hemorrhagic strokes. Since clopidogrel depends on hepatic metabolism and its pharmacodynamics and efficacy may be impacted by reduced renal function, it poses issues for patients with chronic kidney disease (CKD) even though it provides an alternative for individuals who cannot tolerate aspirin. Furthermore, because of response variability and changed drug metabolism, it is unclear if clopidogrel can lower cardiovascular events in people with chronic kidney disease. Therefore, a thorough evaluation of the patient's cardiovascular risk, bleeding history, and renal function should be done before deciding whether to prescribe aspirin or clopidogrel to CKD patients. Therapy should also be

regularly monitored and adjusted as needed. In conclusion, even though clopidogrel and aspirin both have major cardiovascular benefits for patients with chronic kidney disease (CKD), their administration needs to be tailored to each patient's needs while taking into account the intricate interactions between medication pharmacokinetics, platelet activity, and renal function. To better identify the best dosage, long-term safety, and relative efficacy of these medicines in CKD populations—especially in individuals with severe kidney disease or receiving dialysis— more study is required. To improve results in this high-risk population, customized therapy regimens that emphasize both bleeding risk and cardiovascular protection are crucial[1]

REFERENCE

[1] Kang J, Park SH, Park KW, Koo BK, Lee H, Han M, Hwang D, Yang HM, Chae IH, Shin WY, Oh JH, Kim YH, Park TH, Kim BS, Han JK, Shin ES, Kim HS. Clopidogrel versus aspirin as chronic maintenance antiplatelet monotherapy in patients after percutaneous coronary intervention with chronic kidney disease: A post hoc analysis of the HOST-EXAM trial. Heart. 2020;106(23):1790-1797Bansal N, Katz R. The burden of cardiovascular disease in chronic kidney disease: epidemiology and implications for clinical practice. Clin J Am Soc Nephrol. 2013;8(5):803-810.

[2] Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;156(6):445-459.

[3] Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2013;(2):CD008834.

[4] Su X, Yan B, Wang L, et al. Effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2019;20(1):309.

[5] Zhang L, Wu B, Zhang Y, et al. P2Y12 Antiplatelet Choice for Patients with Chronic Kidney Disease and Drug-Eluting Stent Implantation: A Systematic Review and Meta- Analysis. J Pers Med. 2021;11(3):222.

[6] Rao SV. Oral antiplatelet drugs in patients with chronic kidney disease (CKD): to use or not to use. J Thromb Thrombolysis. 2017;44(3):345-346.

[7] Natale P, Palmer SC, Saglimbene V, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2022;2(2):CD008834.

[8] Xiong J, He T, Yu Z, et al. Antiplatelet therapy for the prevention of atherosclerosis in chronic kidney disease (ALTAS-CKD) patients: study protocol for a randomized clinical trial. Trials. 2021;22(1):37.

[9] Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Am J Kidney Dis. 2012;59(5):622-632.

[10] Singh M, Grine K. Antiplatelet Therapy in Chronic Kidney Disease. Am Fam Physician. 2022;106(6):624-625.

[11] Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2013;(2):CD008834.

[12] Su X, Yan B, Wang L, et al. Effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol.

2019;20(1):309.

[13] Zhang L, Wu B, Zhang Y, et al. P2Y12 Antiplatelet Choice for Patients with Chronic Kidney Disease and Drug-Eluting Stent Implantation: A Systematic Review and Meta- Analysis. J Pers Med. 2021;11(3):222.

[14] Rao SV. Oral antiplatelet drugs in patients with chronic kidney disease (CKD): to use or not to use. J Thromb Thrombolysis. 2017;44(3):345-346.

[15] Natale P, Palmer SC, Saglimbene V, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2022;2(2):CD008834.

[16] Xiong J, He T, Yu Z, et al. Antiplatelet therapy for the prevention of atherosclerosis in chronic kidney disease (ALTAS-CKD) patients: study protocol for a randomized clinical trial. Trials. 2021;22(1):37.

[17] Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Am J Kidney Dis. 2012;59(5):622-632.

[18] Singh M, Grine K. Antiplatelet Therapy in Chronic Kidney Disease. Am Fam Physician. 2022;106(6):624-625.

[19] Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2013;(2):CD008834.

[20] Su X, Yan B, Wang L, et al. Effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2019;20(1):309.

[21] Zhang L, Wu B, Zhang Y, et al. P2Y12 Antiplatelet Choice for Patients with Chronic Kidney Disease and Drug-Eluting Stent Implantation: A Systematic Review and Meta- Analysis. J Pers Med. 2021;11(3):222.

[22] Rao SV. Oral antiplatelet drugs in patients with chronic kidney disease (CKD): to use or not to use. J Thromb Thrombolysis. 2017;44(3):345-346.

[23] Natale P, Palmer SC, Saglimbene V, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2022;2(2):CD008834.

[24] Xiong J, He T, Yu Z, et al. Antiplatelet therapy for the prevention of atherosclerosis in chronic kidney disease (ALTAS-CKD) patients: study protocol for a randomized clinical trial. Trials. 2021;22(1):37.

[25] Mahady SE, Polekhina G, Woods RL, Wolfe R, Wetmore JB, Margolis KL, et al. Association Between CKD and Major Hemorrhage in Older Persons: Data From the Aspirin in Reducing Events in the Elderly Randomized Trial. Kidney Int Rep. 2023;8(4):737-745.