Огляд
Review

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Renal Safety of Aspirin Versus Aspirin–Clopidogrel Therapy After Myocardial Infarction

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Abstract

Antiplatelet treatment is an essential part of secondary prevention following a myocardial infarction where aspirin and aspirin-clopidogrel dual therapy have become common to curb repeat attacks as well as cardiovascular deaths. Although the cardiovascular effects of these regimens are now well-known, their safety on the kidneys is a significant clinical issue, especially in patients with a pre-existing renal susceptibility. Myocardial infarction is commonly followed by hemodynamic instability, inflammation and neurohormonal activation that can put patients at risk of renal dysfunction. In that regard, antiplatelet therapy can impact the renal outcomes either directly or indirectly, particularly, bleeding-related complications. This narrative review presents the existing evidence on the harmfulness of aspirin monotherapy over aspirin-clopidogrel therapy in the aftermath of myocardial infarction. Available evidence indicates that low doses of aspirin are better tolerated renal wise when administered at the right time even in chronic kidney disease patients. Conversely, dual antiplatelet therapy has a higher level of ischemic protection, but has a higher likelihood of bleeding, potentially leading to acute renal failure and the aggravation of renal disease in vulnerable groups. The determinants of renal outcomes are strongly dependent on the initial kidney function, age and burden comorbidity, the duration of treatment, and the factors of the procedure like percutaneous coronary intervention. On the whole, this review highlights that consideration of renal safety in the decision-making of the antiplatelet treatment is essential and that patients should receive tailored therapy, active renal follow-up, and multidisciplinary care to maximize the cardiovascular outcome and reduce renal risk following the occurrence of myocardial infarction.

Keywords: Aspirin; Clopidogrel; Myocardial Infarction; Renal Safety; Acute Kidney Injury; Chronic Kidney Disease

1. Introduction

Myocardial infarction (MI) remains one of the most common causes of morbidity and mortality in the whole planet, even though there have been considerable achievements in the early diagnosis, reperfusion interventions and pharmacological treatment. Acute management has been improved and hence the high rates of survival but this has forced the clinical aspect into the long-term secondary prevention methods that will promote the prognosis of ischemic events and time-span and thus lower recurring ischemic events. Antiplatelet therapy is still one of the pillars of the post-MI treatment, and the modern European Society of Cardiology (ESC) guidelines viably suggest the use of dual antiplatelet therapy (DAPT), most likely aspirin and a P2Y12 inhibitor like clopidogrel, during the first 12 months post-acute coronary syndromes, and then long-term maintenance therapy based on individual patient risk factors [1, 2]. Although these approaches have shown cardiovascular advantages, their long-term safety especially to renal outcome -has been relatively less explored.Co-occurring cardiovascular disease and renal dysfunction is emerging as one of the most critical clinical issues. Patients with coronary artery disease also

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have a high susceptibility to developing chronic renal disease, which is also linked to increased risks of repeated cardiovascular disease, bleeding, hospitalization, and mortality. The cardiorenal interaction paradigm highlights that both directions of the myocardial injury renal impairment relationship exist such that hemodynamic instability, systemic inflammation, neurohormonal stimulation, and endothelial dysfunction after MI may negatively influence renal perfusion and increase renal injury. On the other hand, renal failure can change the pharmacokinetic property of drugs, increase the risk of bleeding, and change the effectiveness and safety of antiplatelet medications. Consequently, post-MI patients with underlying or incipient renal disease are a highly vulnerable group, where there is a need to balance ischemic benefit and renal safety in making therapeutic decisions.Aspirin has been the mainstay of antiplatelet therapy in the field of secondary prevention due to its efficacy, low cost and universal availability. Its action, however, is inhibiting cyclooxygenase and subsequent suppression of the production of prostaglands, and therefore can have an undesired effect on the renal hemodynamics especially in patients with impaired renal perfusion, or with medications that have nephrotoxic effects. Whereas dual antiplatelet therapy has been linked to superior guard against thrombotic incidents, it is linked to the danger of bleeding that may indirectly result in renal damage via hypovolemia, hypotension, or transfusion. Although these renal implications are plausible, most cardiovascular trials do not evaluate renal-related outcomes or mostly not, and as such, clinicians have been left with scant evidence to inform their antiplatelet choice in patients who are at risk of developing renal complications.

New clinical findings have led to a revival of interest in alternative long term antiplatelet approaches. At least randomized trials, and large observational studies have indicated the possibility of clopidogrel monotherapy offering the same or even greater cardiovascular protection than aspirin in the chronic maintenance following percutaneous coronary intervention (PCI)especially in patients at high risk of bleeding [3]. A meta-analysis of clopidogrel versus aspirin monotherapy in patients with coronary artery disease has shown positive empowerment and safety effects of clopidogrel, proving the conventional hegemonic position of aspirin in the long-term treatment [4]. Moreover, meta-analyses of de-escalation methods in DAPT to monotherapy at patient-level have shown that well-identified patients could safely switch without experiencing more ischemic events, and may benefit through a risk of reduction in bleeding [5]. These results have supported guideline suggestions of personalized antiplatelet regimens grounded on the risk of ischemic and bleeding as opposed to standardized treatment periods [6].The safety of renal failure of antiplatelet therapy is not adequately defined in the growing cardiovascular literature. The two subgroups at risk, namely patients with diabetes mellitus and chronic renal disease, are especially complicated to use antithrombotic therapy because of the potential overlaps of thrombosis, bleeding, and progressive renal damage [7]. There is an emerging evidence that conventional antiplatelet approaches might not provide the same benefit to risk ratio in patients with renal impairment as it does in patients with intact renal impairment [8]. A recent review on antiplatelet therapy in patients with acute coronary syndrome and chronic renal disease showed a significant heterogeneity in the study designs and absence of outcome in terms of renal-specific outcome, which describes a significant gap in the literature [9]. This gap is more so with reference to the growing level of renal dysfunction in aging cardiovascular cases.

It justified assessment of the safety of aspirin monotherapy versus aspirin-clopidogrel therapy of myocardial infarction of kidney. It is necessary to comprehend the effects of various antiplatelet approaches on renal outcomes to improve long-term management especially in patients who have some renal dysfunction or whose renal health is at risk. This evaluation is very applicable to clinicians dealing with cardiovascular disease because therapeutic decisions during ischemic protection can lead to serious downstream outcomes on renal wellbeing. The purpose of this narrative review is to summarize the available evidence on the renal safety of commonly used antiplatelet regimens in the post-MI period, combine cardiovascular guideline recommendations with new renal concerns, and determine the knowledge gaps that should be closed by means of additional research.

Objectives

1. To compare the renal safety of aspirin monotherapy and aspirin–clopidogrel therapy in patients after myocardial infarction
2.To evaluate clinical and bleeding-related factors influencing renal outcomes during antiplatelet therapy
3.To identify high-risk populations requiring individualized antiplatelet and nephroprotective strategies

2. Cardiorenal Pathophysiology After Myocardial Infarction

Myocardial infarction (MI) evokes a complicated systemic reaction, which goes beyond myocardial damage in a limited area and impacts the functioning of the renal system extensively. Kidneys and the heart depend on each other functionally, and acute cardiac injury can occur quickly leading to renal dysfunction due to hemodynamic, inflammatory, and neurohormonal pathways. Such a two-way interdependence is summarized in the term of the cardiorenal syndrome, where acute renal failure occurs due to deterioration of cardiac functions and clinical outcomes become worse [10].

Alterations in the hemodynamics are one of the fundamental mechanisms that connect MI and renal dysfunction. After MI, there is decreased myocardial contractility which results in loss of cardiac output and renal perfusion. Although there is no overt hypotension, the impairment of glomerular filtration due to reduced forward flow occurs even when this occurs in the absence of overt hypotension. At the same time, the rises in central venous pressure due to left or right ventricular

dysfunctions lead to more renal venous congestion, which increases the pressure in the intrarenal space and additional decrease in effective filtration. It has been shown through experimental and clinical research that renal congestion can be a more potent predictor of renal dysfunction than arterial hypoperfusion itself and thus the need to consider venous hemodynamics in post-MI renal injury [11]. Pathologic blood rheology, such as variations in blood viscosity can also worsen micro vascular perfusion and add to end-organ dysfunction, especially in the context of cardiovascular disease [12].

Inflammation is also the key factor in the intensification of renal injury following MI. Myocardial necrosis triggers systemic inflammatory cascade, which is marked by cytokine, chemokine production, and release of active oxygen species. These mediators encourage endothelial dysfunction, augment vascular permeability, as well as interfere with the renal microcirculatory flow, causing tubular damage and affected filtration. The inflammation may be chronic and persist beyond the acute phase of MI, which leads to the progressive renal injury and the failure of a full recovery of the renal functioning. In spite of the fact that inflammatory signaling pathways have been well-investigated in other tissues such as ocular and epithelial systems, they support the idea of transcriptional and cellular reactions to stress and injury being highly conserved and capable of affecting renal cellular functionality after ischemic insults [13].

Activation of neurohormones also adds to the cardiorenal dysfunction following MI. Loss of cardiac output causes renin- angiotensin-aldosterone system and sympathetic nervous system to act as compensatory mechanisms. Although this may be advantageous in the short term, chronic activation will cause renal vasoconstriction, sodium and water retention, oxidative stress, and fibrotic renal tissue remodelling. Especially, aldosterone excess leads to inflammation and fibrosis that deteriorates the renal functioning in the long run. Indications of pulmonary vascular disease and right ventricular disease imply that mineralocorticoid signaling can be improved by hemodynamic functionality through the signaling of neurohormonal pathways, which are important in cardiorenal pathophysiology [14].The clinical effect of MI on kidney functioning is great. Short term mortality, long term hospitalization and recurrent cardiovascular activity are linked to acute kidney injury (AKI) after MI. Modest or temporary post-MI deterioration in kidney functions has been reported to have negative prognostic implications, indicating that renal function is a cardiac injury marker of delicate nature. In addition, AKI following MI is also a predisposing factor to chronic renal disease especially in patients with underlying cardiovascular conditions or recurring ischemic injuries. However, therapeutic interventions that enhance cardiac performance can potentially alleviate renal failure and the interactions between cardiac and renal activities are dynamic and, therefore, need to be considered jointly. Big cardiovascular outcome studies have also shown renal failure treatment in the pathophysiology of heart failure can stabilize or slow the renal failure decrease, and therefore renal failure post-MI is, at least partially, reversible provided hemodynamic stress and neurohormonal activation are well managed [15]. The results support the significance of combined cardiovascular care in sustaining renal functions of post-MI patients.On the contrary, some cardiovascular treatments can add further complications. Although essential in the secondary prevention of MI, the use of antiplatelet agents has been linked to bleeding complications with the possibility of indirectly influencing the renal perfusion and functioning. These observations are controversial in their role as the prevention of infectious cardiac complications; however, they underscore the significance of taking into consideration system and renal effects when choosing the long-term cardiovascular therapeutic strategies [16]. On the same note, example-based evidence of pulmonary and right ventricular disease demonstrates that specific cardiovascular interventions may affect the systemic and renal hemodynamics and stress once again the integrating character of the cardiovascular and renal physiology..

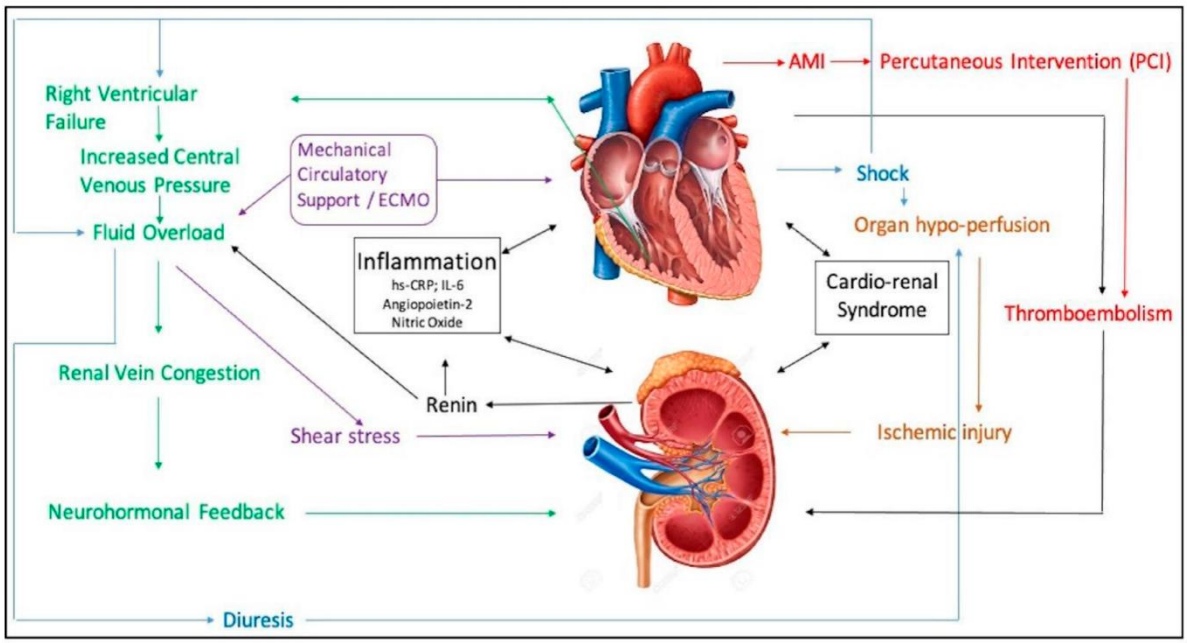

Figure 1. Integrated hemodynamic, inflammatory, and neurohormonal mechanisms underlying cardiorenal syndrome following acute myocardial infarction. [17]

Figure 1. shows acute myocardial infarction (AMI) leads to reduced cardiac output, shock, and organ hypoperfusion, triggering a cascade of hemodynamic and neurohormonal disturbances. Right ventricular dysfunction and fluid overload increase central venous pressure, resulting in renal venous congestion and impaired renal perfusion. Concurrent activation of inflammatory pathways, including cytokines and nitric oxide signaling, along with stimulation of the renin–angiotensin–aldosterone system, exacerbates renal ischemic injury. Neurohormonal feedback mechanisms further contribute to sodium and water retention, shear stress, and progressive renal dysfunction. These interrelated processes form the pathophysiological basis of cardiorenal syndrome following myocardial infarction

Overall, myocardial infarction initiates a multifactorial cascade of hemodynamic compromise, inflammatory activation, and neurohormonal dysregulation that predisposes patients to renal dysfunction. Recognition of these mechanisms is essential for early identification of high-risk individuals and for guiding therapeutic strategies aimed at preserving renal function while optimizing cardiovascular outcomes. Understanding post-MI cardiorenal pathophysiology provides a critical foundation for evaluating the renal safety of long-term pharmacological therapies, including antiplatelet regimens, in patients recovering from myocardial infarction.

3. Antiplatelet Therapy in Secondary Prevention

Antiplatelet therapy has a therapeutic effect beyond the acute MI to secondary prevention over the long term. Thrombotic events are still considered to be at high risk in patients with known coronary artery disease, especially those with other risk factors like diabetes mellitus or those who underwent prior revascularization even after the index myocardial infarction. This sustained risk is caused by progressive atherosclerosis, intractable endothelial dysfunction and low-grade inflammation. This weakness is overcome with long-term antiplatelet treatment, which persistently inhibits platelet-mediated thrombus at the location of vascular damages and disruption of the atherosclerotic plaque. Big data findings of large observational cohorts and randomized clinical trials have highlighted the necessity of continuous platelet suppression to avoid repeated ischemic disasters as a support of chronic cardiovascular risk treatment, and it serves as a pillar [18,19].

Antiplatelet therapy thus forms one of the core elements of secondary prevention after myocardial infarction, to diminish the chances of re-occurrence of ischemic events, stent thrombosis and cardiovascular death. The argument about the importance of using antiplatelet therapy lies in the central role played by platelet activation and aggregation in the etiology of atherothrombosis. Plaque rupture, endothelial injury, and the long-term presence of vascular inflammation after MI provide a very prothrombotic environment in which platelets become activated to cause frequent coronary occlusion and microvascular thrombosis. The clinical evidence and modern guideline recommendations have continuously shown that platelet function inhibition reduces subsequently incident myocardial infarction and other major adverse cardiovascular events in a significant percentage during routine and long-term treatment, which favors the use of antiplatelet agents in patients who have had a myocardial infarction [20].

Clopidogrel is based on a different molecular pathway to offer an alternative and complementary inhibition of platelets. Clopidogrel is a thienopyridine prodrug that is hepatically bio-transformed to an active metabolite, which irreversibly inhibits the platelet adenosine diphosphate receptor P2Y12. It blocks platelet

activation, aggregation and amplification of thrombotic signaling thus decreases platelet responsiveness to a variety of agonists. Comparative clinical trials of clopidogrel and aspirin have showed similar effects in the prevention of ischemic events, but with significant differences in the risk of bleeding, gastrointestinal tolerability, and inter-subject variability of response determining the clinical applicability of the agent when used in clinical practice [21,22]. The combination of aspirin and clopidogrel in the selected high-risk clinical settings is based on these mechanistic and pharmacological variations.

Aspirin has been the backbone of secondary prevention antiplatelet agent due to its efficacy, low cost, and a long clinical history. Its mechanism of action is irreversible inhibition of cyclooxygenase-1, therefore, decreasing the synthesis of thromboxane A 2, which is a major platelet aggregator and vasoconstrictor. Since platelets do not contain nucleus, the antiplatelet effect of aspirin lasts as long as the platelet exists in the body, which makes it possible to use a dose of aspirin once a day. Megaclinical trials and meta-analyses of aspirin have shown that it is highly beneficial in prevention of recurrent cardiovascular events over placebo, and thus can be regarded as one of the cornerstone therapies in patients with a history of MI and chronic coronary artery disease.

Dual antiplatelet therapy (DAPT) is the combination of aspirin and a P2Y12 inhibitor, which is suggested to patients after MI, especially those with percutaneous coronary intervention or in patients with acute coronary syndrome. The mechanism behind DAPT is the synergistic inhibition of complementary platelet activation processes which offers a greater protection of recurrent ischemia and stent thrombosis in the initial period of high risk in the post MI period. The introduction of clopidogrel with aspirin has been proven by randomized controlled trials to cause a significant reduction of ischemic events in patients with acute coronary syndromes as compared to aspirin alone. As a result, the modern evidence supports the use of DAPT during a specific period after MI, and then the risk of ischemic and bleeding should be reviewed periodically to inform the further treatment.

There is still an ongoing research and clinical controversy over the best duration of DAPT. Although long-term DAPT can probably decrease thrombotic incidents in selected high-risk groups, it is linked to the heightened risk of major bleeding. The meta-analyses of long-term DAPT following implantation of drug-eluting stents have demonstrated that it reduces ischemia in selected populations but fails to produce any consistent benefit regarding mortality and increases the likelihood of bleeding events [23,24]. These results underscore the need to consider the treatment decision on a case-by-case basis instead of a general approach to DAPT duration.

The process of clinical decision-making about the use of antiplatelet therapy, therefore, needs to consider patient specific variables such as age, comorbidity, previous bleeding episodes, renal functioning, and the complexity of the coronary disease. More intensive antiplatelet therapies can be of more benefit to patients with diabetes mellitus or high atherosclerotic burden, but patients with a higher risk of bleeding might benefit with a shorter course of DAPT or an earlier switch to mono-therapy. Recent international practice highlights the importance of a customized approach between an ischemic protection and a risk of bleeding to achieve the best long-term results [25].

Antiplatelet therapy is a central role in secondary prevention following myocardial infarction, as it addresses the key events of atherothrombosis. Aspirin and clopidogrel cause complementary antiplatelet effects that favor their application as monotherapy or combine with other agents, based on the clinical situations and risk profile of the patient. Clinical trials and guideline recommendations evidence points to an individual approach to the selection and duration of the choice of antiplatelet therapy, which guarantees the maximum possible protection against repeat ischemic events with minimal adverse effects.

4. Renal Safety of Antiplatelet Therapies

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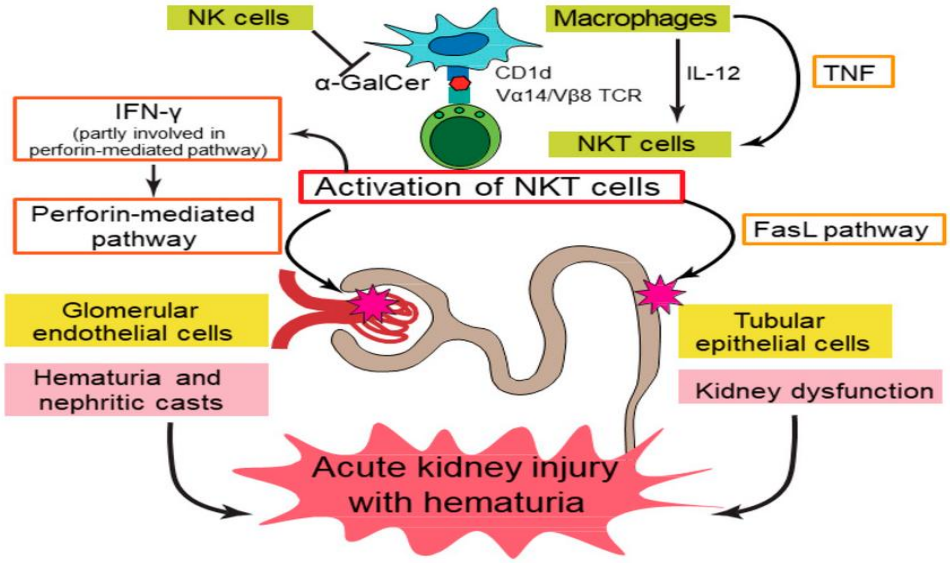

Figure 2. Immune-mediated mechanisms contributing to hematuria-associated acute kidney injury.[33]

Figure 2. shows activation of natural killer T (NKT) cells by antigen-presenting macrophages leads to the release of pro-inflammatory cytokines, including interferon-γ and tumor necrosis factor. These mediators promote renal injury through perforin-mediated cytotoxicity and Fas–Fas ligand signaling pathways. Injury to glomerular endothelial cells results in hematuria and nephritic cast formation, while tubular epithelial cell damage contributes to impaired renal function. The combined glomerular and tubular injury culminates in acute kidney injury associated with hematuria.

Bleeding-related renal complications represent one of the most clinically relevant safety concerns associated with antiplatelet therapy. Antiplatelet-associated bleeding, including gastrointestinal bleeding and hematuria, may contribute to renal injury through hemodynamic instability or direct tubular obstruction. Retrospective cohort studies have demonstrated that patients receiving antiplatelet or anticoagulant therapy are at increased risk of hematuria-related complications, including hospitalization and acute kidney injury [34]. These complications are more frequent in older patients and those with pre-existing chronic kidney disease.

The current evidence indicates that low-dose aspirin is generally renal-safe in most patients, including those with chronic kidney disease, when prescribed appropriately. Dual antiplatelet therapy offers substantial cardiovascular benefit and appears similarly effective across different levels of renal function, although bleeding-related renal complications remain an important concern. Individualized assessment of renal function, bleeding risk, and cardiovascular benefit is essential to optimizing the safety and efficacy of antiplatelet therapy in patients recovering from myocardial infarction[35].

5. Comparative Renal Safety Evidence

To evaluate renal safety in the management of cardiovascular diseases, evidence of observational cohort studies, mechanistic studies, and long-term outcome analyses must be combined, especially among patients with chronic kidney disease (CKD). Patients with poor renal clearance constitute a highly vulnerable cohort where cardiovascular therapies might have disproportionate renal consequences because of poor underlying vascular pathophysiology, alterations in hemodynamics and increased inflammatory load. Instead of being motivated by single-agent pharmacologic agents, renal outcomes have been identified as a complex interaction between exposure to treatment, underlying renal functioning, and patient-specific risk profiles.

Big Data observations are valuable sources of real-world data on the renal safety of heterogeneous groups. Cardiovascular therapies in CKD patients are commonly linked with antagonistic threats of ischemia and bleeding, either of which can affect renal results. The findings of population-based cohorts of older adults with CKD and A-fibrillation show that the exposure to antithrombotic treatments is linked to a rise in the frequency of hemorrhagic events that, in turn, can cause renal dysfunction by the means of hypotension, decreased renal perfusion, and acute kidney damage (AKI) [36]. These results affirm that renal safety cannot be assessed in detachment of bleeding risk, in specific cases of patients with advanced renal impairment and older patients.

In addition to clinical results, mechanistic research provides a good understanding on the biological pathways that contribute to renal susceptibility in cardiovascular disease. The chronic kidney disease is getting to be perceived as an atherogenic and inflammatory condition, which entails endothelial malfunction, vascular re-modelling and dys-controlled protease action. ADAM10 and ADAM17 metalloproteinases have been found as the important modulators of atherosclerosis related to CKD and facilitating inflammatory signaling and endothelial damage [35]. Such vascular alterations may disrupt renal microcirculation and predispose to renal damage in the event of cardiovascular stress or therapeutic intervention and thus determine relative renal safety in comparison of treatment modalities.

The acute kidney injury is an urgent pathology of kidneys whose short-term outcomes and long-term consequences are crucial. Bouts of AKI are highly correlated with higher rates of death, faster development into CKD, and cardiovascular risks. Patients who already have CKD are especially vulnerable to AKI in the conditions of hemodynamic instability, bleeding, or the events of acute cardiovascular issues. It has been clinically indicated that hemorrhagic complications, both spontaneous and treatment-related, are a significant trigger to AKI in this group of people [36,37]. Notably, even short-term impairment of renal functions can be a long-term consequence, which supports the prognostic value of AKI as an indicator of global susceptibility.

Risk patient profiles have a strong belief in renal outcomes and need to be addressed when analyzing comparative safety evidence. Age, baseline estimated glomerular filtration rate, vascular calcification, and metabolic disturbances are some factors that lead to interindividual variability in renal response. New studies suggest the prognostic value of mineral metabolic and cardiorenal signaling pathway biomarkers. High phosphorus levels, fibroblast growth factor 23 levels and distorted Klotho levels have been linked to high levels of cardiovascular and all-cause mortality over different renal function levels implying that the levels could be used to further stratify renal and cardiovascular risk [38]. Inclusion of these biomarkers in clinical evaluation can provide better individualized decision-making and better patient outcomes in terms of renal safety.

Prolonged exposure to cardiovascular risk factors and progressive vascular dysfunction also determines long-term renal outcomes. Endothelial dysfunction is at the center of the aging kidney and is defined by the lack of bioavailability of nitric oxide, the rise of oxidative stress and inability to maintain the capillary presence [39]. These changes decrease renal capacity of adaptation and

could increase the renal effect of cardiovascular treatments in the long run. This means that, in many cases, the response of patients with CKD to the same treatment varies and therefore, the therapeutic approaches should be customized to address the unique needs of patients, instead of being implemented as a single-fits-all treatment.

The other important determinant of comparative renal safety is treatment duration. Sustained exposure to cardiovascular therapies can lead to accumulation of risk of adverse renal events especially in cases where the therapy is coupled with frequent bleeding episodes or prolonged inflammatory stimulation. According to observational evidence, continuous high-risk patient treatment courses should be periodically evaluated guaranteeing that the current cardiovascular benefit of the treatment is greater than the possible renal damage. This dynamic treatment duration is particularly applicable to elderly patients, who often show decreasing renal function, as well as more prone to bleeding.

The overlapping between CKD and cardiovascular mortality also makes comparative renal safety assessment more challenging. Sudden cardiac death is a significant cause of death in CKD patients and it is caused by structural heart disease, autonomic imbalance, electrolyte imbalance, and vascular calcification [37]. Renal impairment does not only augment the cardiovascular risk, but it also decreases the physiological reserve, amplifying the effects of cardiovascular incidences and treatment on the kidneys. This two-way relationship highlights the significance of combined measures of cardiorenal management that focus on the protection of the renal system and the prevention of cardiovascular risks.

6. Special Populations and Risk Stratification

The patients with cardiovascular disease usually form a heterogeneous group where the safety and effectiveness of the antiplatelet therapy differ significantly. This effect is especially acute in special populations such as those with the existing chronic kidney disease (CKD), older individuals with multiple comorbidities, and those patients who receive percutaneous coronary intervention (PCI) and are at high risk of bleeding. Risk stratification in such groups is necessary to achieve the most ideal antiplatelet therapy with minimal renal and bleeding problems[40].

The high level of predisposition to thrombotic and bleeding events makes patients with pre-existing CKD a significant clinical issue. All of them are linked to chronic kidney disease and they include changes in platelets, endothelial dysfunction, and inflammation, which affect antiplatelet therapy response. Systematic review evidence suggests that antiplatelet therapy decreases cardiovascular morbidity in CKD patients, but the magnitude of this effect is smaller than that in people with normal renal function, and the risk of major bleeding is very high [40]. This change of the risk-benefit ratio requires close examination of renal functionality, history of bleeding, and cardiovascular manifestations before starting or continuing an antiplatelet treatment. These issues are further reinforced during the advanced phases of CKD, which necessitates unique treatment approaches and not standard long-term dual therapy.

Another group of high-risk patients that affect the prescription of antiplatelet therapy is elderly patients. Old age is characterized by gradual decreases in renal function, vascular hardening, and the increment in the comorbid conditions burden including diabetes, hypertension, and atrial fibrillation. All of these are leading to susceptibility to bleeding and renal injury. It is clinically proven that older patients with CKD have disproportionately higher frequencies of hemorrhagic events during antithrombotic therapy that could trigger acute kidney injury and deteriorate long-term renal outcomes [41]. Moreover, the pharmacokinetic and pharmacodynamic alterations with age could increase drug exposure and toxicity. Consequently, geriatric and renal evaluation should inform the use of antiplatelet therapy in older patients, and periodic monitoring must be performed as the clinical conditions develop.

A very complex group of patients is represented by patients who have undergone PCI because the antiplatelet therapy is required to avoid stent thrombosis and repeat ischemic events. But patients with CKD who undergo PCI have high chances of contrast-associated kidney injury, bleeding complications and unfavorable cardiovascular outcomes. There has been a postulate of observational evidence indicating that CKD patients receiving PCI would gain ischemic advantage out of antiplatelet treatment yet they are also more susceptible to bleeding incidents that negatively influence renal functioning [42]. In turn, the duration and intensity of treatment are to be thoroughly adjusted. Reduced times of dual therapy and early switching to monotherapy can be used in high-bleeding patients of the population including new-generation drug-eluting stents.

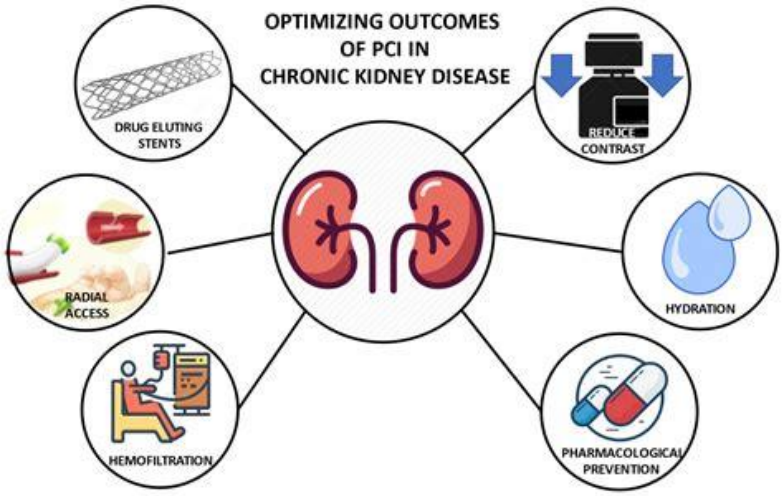

Figure 3. Strategies to optimize percutaneous coronary intervention outcomes in patients with chronic kidney disease.[43]

Figure 3. presents some of the most important procedural and supportive interventions that can be used to enhance clinical outcomes and decrease renal complications in patients with chronic kidney disease undergoing percutaneous coronary intervention. These are the application of drug-eluting stents, the use of radial arterial access, contrast volume minimization, proper peri-procedural hydration, pharmacological prophylaxis and selective use of hemofiltration. Combination of these methods facilitates in the minimization of contrast-associated renal damage and risk of bleeding and preserves procedural effectiveness. The high-bleeding-risk groups go beyond CKD and elderly and also involve patients who have had the previous bleeding events, anemia, frailty, and are on anticoagulants. In such patients, bleeding incidents are not only clinically important, but they can also be the causes of renal injury due to hypotension, renal hypoperfusion, and tubular obstruction by hematuria. Regular assessments indicate that the deterioration of renal functions is a sensitive predictor of bleeding issues in the case of antithrombotic therapy [44]. Risk stratification tools that include renal function, age, and bleeding history could therefore be beneficial to clinical decision-making and improve safer outcomes.

There is a growing focus on the need to incorporate renal risk in the cardiovascular decisions of the patients in guide oriented frameworks. Kidney and cardiovascular clinical guidelines recommend a multidisciplinary approach in the management of patients with CKD and cardiovascular disease because renal impairment changes the efficacy and safety of therapy [45]. These methods facilitate the closer interaction between cardiologists and nephrologists especially when handling complicated cases with long term antiplatelet therapy.

7. Nephroprotective Strategies and Clinical Management

Proper nephroprotection is a very important aspect of clinical practice in patients undergoing antiplatelet therapy, especially those with cardiovascular disease and increased renal susceptibility. Since cardiovascular interventions, bleeding risk, and renal functioning are closely interconnected, it is necessary that proactive efforts supporting early renal injury recognition, reducing nephrotoxic exposures and custom-planning treatment are the key to saving kidney functionality and enhancing long-term outcomes.

Renal monitoring through antiplatelet therapy is one of the pillars of nephroprotective care. Acute kidney injury (AKI) is a common complication of hospitalized patients with cardiovascular disease, and is linked with high morbidity, mortality, and transition to chronic kidney disease (CKD). Renal impairment can be identified early to prevent irredeemable damage and should be addressed promptly. Structured monitoring protocols based on trends of serum creatinine and assessment of urine output have demonstrated to enhance the AKI detection and prompt clinical reaction. The need to use standardized AKI alerts and regular monitoring to decrease the number of preventable cases of renal injury is supported by national and international safety efforts [46]. The strategies are of particular importance in patients under antiplatelet treatment that develop bleeding-induced hypotension or renal hypoperfusion.

In addition to the early diagnosis, multidisciplinary management of AKI demands combined clinical intervention. International efforts have revealed that AKI continues to be an unevenly recognized issue throughout healthcare systems, and delayed disease diagnosis is one of the factors that lead to poor outcomes. Multinational studies reveal that there is a significant difference in AKI management practices, and this implies the necessity to use standard clinical pathways and greater awareness of the clinicians [47]. The incorporation of renal monitoring in standard cardiovascular practice, especially in acute coronary syndromes, invasive operations is a significant advance in curbing renal complications.

Nephroprotective management is based on individualized treatment. Cardiovascular disease burden, metabolic factors, age, and comorbidities all affect chronic kidney disease, an unexplained heterogeneous condition. Recent literature underlines the fact that CKD is a systemic condition and that its effect goes beyond kidneys and warrants individual

forms of treatment [48]. When applied to antiplatelet therapy, this can be characterized as a trade-off between ischemic protection and bleeding, and renal risk, where the length and strength of treatment is dependent on the risk profile of the entire patient.

Another principle of nephroprotection is dose adjustment and prevention of nephrotoxic agents. Often patients who are on antiplatelet therapy are put under exposure of other medications such as contrast agents, nonsteroidal anti-inflammatory drugs, and antibiotics which worsen renal injury. It is highly necessary to perform medication reconciliation with great care and avoid unnecessary nephrotoxins, especially in patients with already developed CKD or borderline renal reserve. In addition, dosing of concomitant therapies should be based on renal functioning in order to reduce accumulation and toxicity. It has been shown that even the mild cases of AKI can increase the rate of deterioration of renal function in the long-term, which supports the significance of preventive measures in the risk population [49].

Stratification of risks must include both some acute and chronic renal factors. Individuals with previous history of AKI are highly predisposed to future development of CKD and heart attacks. A mutual interdependence of AKI and CKD contributes to the significance of long-term renal follow-up following acute insults [49]. In patients who have suffered myocardial infarction or invasive cardiovascular surgery, renal dysfunction reassessment at the follow-up appointment will enable timely detection of dysfunctional kidney and subsequent alterations of therapy.

The use of multidisciplinary care models is becoming more relevant in relation to nephroprotective strategies optimization. Partnerships between cardiologists, nephrologists, and primary care providers can be used to conduct extensive renal risk assessment, medication safety, and long-term management objectives. International campaigns recommend integrated care pathways which focuses on education, early intervention and continued care to minimize the burden of kidney disease in the world.

The approaches of nephroprotection in the antiplatelet treatment are based on attentive renal observation, prevention of nephrotoxic exposures, and clinical decision-making. Proper management and early detection of AKI based on standard guidelines can help in reducing the development of chronic kidney disease. Individual care based on renal functionalities, cardiovascular risks, and specific factors of the patient are the keys to achieving the best of renal and cardiovascular outcomes. The issue of nephroprotection should be one of the primary points of focus in clinical management as the number of patients having both coexisting cardiovascular disease and renal impairment is constantly increasing.

8. Conclusion

Aspirin and aspirin-clopidogrel dual therapy are now central to the principles of secondary prevention after myocardial infarction, and antiplatelet therapy continues to be of great importance in the prevention of recurrent ischemic events and cardiovascular mortality. Nevertheless, as pointed out in this review, kidney safety of such treatments is a key and frequently neglected clinical issue, especially in patients with already compromised renal function and other disease risk factors. The close interrelationship between cardiovascular disease, renal failure, the risk of bleeding, and the intensity of therapy requires a more subtle approach to antiplatelet therapy. There is available evidence to indicate lower doses of aspirin will normally be well-tolerated renal-wise when used correctly even in chronic kidney disease patients. Contrary to that, dual antiplatelet therapy, despite increasing ischemic protection, is connected to the increased risk of bleeding-associated complications that could contribute to acute kidney injury indirectly and lead to the intensification of chronic kidney disease. Notably, the renal outcomes, however, are also dependent on the type of antiplatelet regimen used, length of treatment, initial renal status, comorbidities, and individual risk factors. The elderly patients, patients with chronic kidney disease, and patients that are undergoing percutaneous coronary intervention are special populations that need cardiovascular benefit to be balanced with renal and bleeding risk through the use of individualized risk stratification. Early detection of renal damage, prevention of nephrotoxic exposures, and routine observation of renal performance are all imperative elements of nephroprotective clinical treatment. The multidisciplinary approach of cardiology and nephrology services also contributes to the possibility to customize the therapy and eliminate the negative outcomes. It maximizes the antiplatelet therapy following myocardial infarction necessitating introduction of renal safety into clinical decisions. Individualized care plans taking into consideration of the renal performance, bleeding predisposition as well as general cardiovascular risk are essential in enhancing long-term care. Further studies ought to focus on renal-specific outcomes and come up with risk-adjusted antiplatelet interventions in order to contribute to a more informed evidence-based practice in this expanding and at-risk patient group.

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