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CRITICAL REVIEW OF CKD MEDICATIONS IN CARDIOVASCULAR DISEASE: BIOCHEMICAL EFFECTS AND THERAPEUTIC IMPLICATIONS

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Abstract

Chronic Kidney Disease (CKD) is a progressive disorder characterized by the gradual decline of renal function, often remaining asymptomatic until significant damage occurs. The kidneys play a crucial role in filtering waste, excess fluids, and electrolytes from the bloodstream, which are then excreted as urine. In advanced stages, the accumulation of toxins and imbalanced electrolytes leads to severe complications, including cardiovascular disease (CVD), a leading cause of mortality in CKD patients. This study explores the pathophysiological relationship between CKD and CVD, identifying key risk factors such as hypertension, diabetes, oxidative stress, and dyslipidemia. According to WHO global health statistics from 2012, CKD contributed to 864,226 deaths worldwide, accounting for 15% of total deaths, with sudden cardiac arrest being the predominant cause. Given the strong association between CKD and CVD, effective therapeutic interventions are essential. This review highlights the role of approved pharmacological treatments, including SGLT-2 inhibitors, which have demonstrated significant benefits in improving renal function and reducing cardiovascular risk. By examining current treatment strategies and their biochemical effects, this study aims to enhance understanding of CKD management and provide insights into optimizing therapeutic approaches for better patient outcomes.

Keywords: *Cardiovascular disease, Chronic kidney disease, Dapagliflozin, Heart failure, Type 2 diabetes*

INTRODUCTION

Chronic kidney disease is a wide-ranging class of illnesses that cause the kidneys' capacity to filter waste and maintain fluid balance to deteriorate over time gradually (1). It poses a significant challenge to population health, impacting thousands globally and characterized by a long, often silent progression (2). The severity, rate of progression, and underlying causes of CKD vary greatly, with factors such as hypertension, diabetes, glomerulonephritis, and polycystic renal disease being among the primary contributors to its development (3) . Initially, it is frequently asymptomatic, often remaining undetected until significant damage has occurred or until it is identified during the investigation of a coexisting condition (4). It should be emphasized that while early-stage CKD is treatable, if left unmanaged, it can lead to end-stage renal disease which needs requiring kidney transplantation and dialysis (5). Diagnosis of CKD typically involves assessing kidney function through measures such as the Glomerular Filtration Rate (GFR), a test that evaluates the efficiency of the kidneys in filtering blood (6). The gradual decline in kidney function leads to the accumulation of waste products and excess fluid in the body, contributing to common symptoms such as tiredness, edema, and altered urination habits (7). These symptoms, though characteristic, often only manifest in more advanced stages, making early detection through regular monitoring essential (8).

A critical aspect of CKD management is recognizing its strong association with cardiovascular disease (CVD), with both conditions sharing common risk factors and often worsening each other (9). Kidney dysfunction can result in increased inflammation, anemia, and disturbances in mineral metabolism, all of which significantly contribute to cardiovascular complications (10). Conversely, heart disease can restrict kidney blood flow, intensifying renal injury and leading to a vicious cycle of deteriorating health (11). This interplay between CKD and CVD highlights the importance of integrated care strategies simultaneously managing both conditions (12). This study explores the etiological factors of CKD, examines the pathophysiological link between kidney and cardiovascular diseases, and discusses contemporary treatments for both conditions. By doing so, the article aims to provide an updated understanding of the complex relationship between CKD and CVD, offering insights into practical management approaches that improve patient outcomes and health outcomes. This review primarily focuses on FDA-approved medications that have demonstrated efficacy in managing CKD-related cardiovascular complications. While the discussion emphasizes established pharmacological treatments such as SGLT-2 inhibitors, mineralocorticoid receptor antagonists, and RAAS inhibitors, emerging experimental therapies are briefly mentioned to highlight potential future advancements in CKD-CVD management.

PRIMARY CAUSES OF CKD

The causes of CKD are often associated with factors such as advanced age, hyperglycemia, hypertension, obesity, and cardiovascular disease in developed countries, as illustrated in Fig. 1 (13).

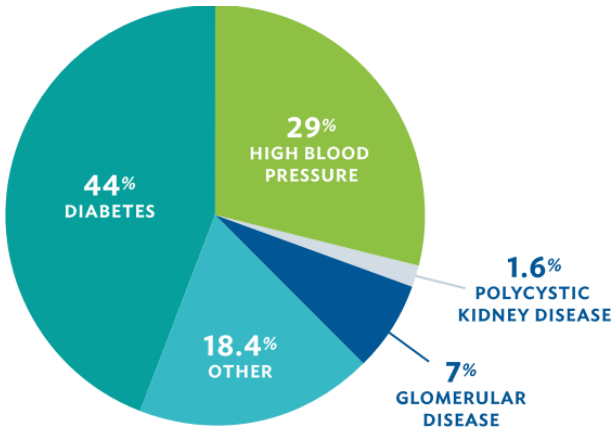

Fig. 1. Common causative factors of CKD

Many individuals with diabetes, as well as kidney disease, don't display the exact characteristics of glomerulosclerosis in diabetic nephropathy (14). Clinical findings of hypertensive nephrosclerosis are frequently more extreme than predicted due to blood pressure levels (15). In underdeveloped nations, glomerular and tubulointerstitial disorders caused by infections, as well as sensitivity to medicines and chemicals, are also significant causes of chronic kidney disease (16).

ROLE OF GENETICS & EPIGENETICS

CKD can result from a range of single or multiple genetic factors. Some disorders, such as those that cause genetic anomalies of both the kidney and urinary system, are visible from delivery or infancy, while others, such as autosomal dominant polycystic kidney illness, appear later on in life (17). Patients with CKD caused by genetic causes account for a tiny percentage of all CKD patients (18). Apart from genetic concerns, there is anticipated to be a considerable environmental influence on CKD vulnerability (19). The relationship between genetics, epigenetics, and CKD progression is shown in Fig. 2.

RELATIONSHIP BETWEEN RENAL AND HEART DISORDERS

Compared to those without CKD, individuals having a glomerular filtration rate (GFR) slightly below 60 ml/min per 1.73 square meters and those with lower than usual albuminuria face a 57% higher risk of death from cardiovascular causes (20). In the case of cerebrovascular disease, a substantial, comprehensive review and a meta-analysis of 83 studies have found an opposite relationship between GFR

and stroke risk, as well as a relationship between albuminuria and stroke risk, based on data (21). In patients

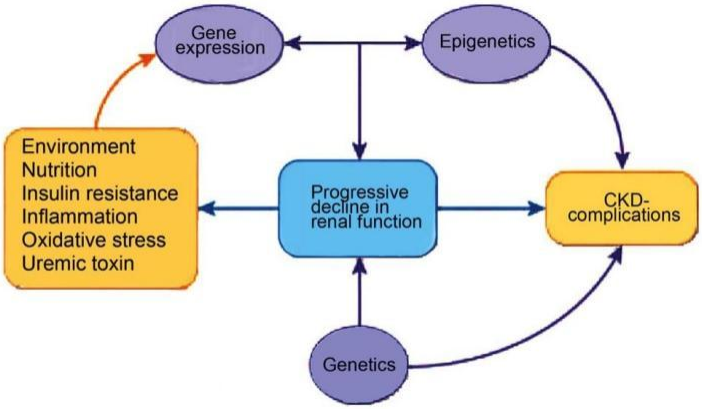

Fig. 2. Role of genetics & epigenetic in the progression of CKD

with chronic kidney disease and severe cardiac crises, clinical practice guidelines support antiplatelet therapy techniques comparable to those used in the general community (22). A graphical representation of eGFR and cardiac incidence rate is shown in Fig. 3.

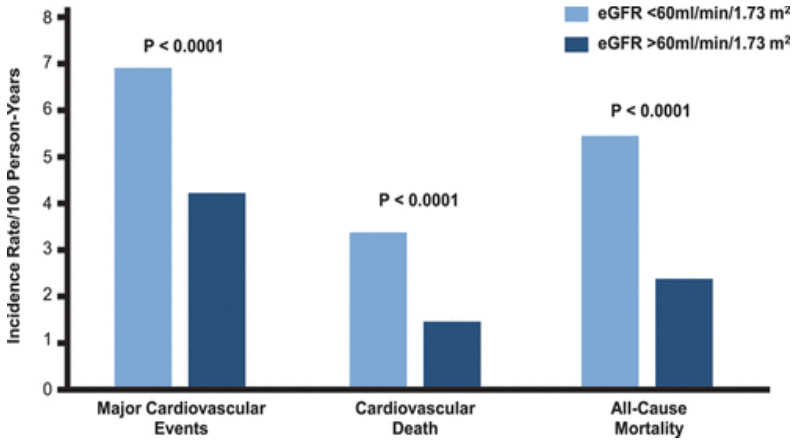

Fig. 3. Cardiac incidence rate with respect to eGFR

In a study of 80 trials with 51,099 individuals, statins had been found to reduce all-cause fatality by 19 percent, cardiac death by 22 %, and cardiovascular events by 24 percent in people with CKD who did not get dialysis (23). CKD patients have a higher risk of developing cardiovascular disease, which is heightened among those with high blood pressure, which contributes to a faster progression of renal disease, among many other issues (24). Blood pressure readings of more than 120/80 mm Hg were linked with the development of ESRD in males over 60 who participated in the MRFIT study (25).

Moreover, multiple clinical investigations have found a link between more significant mean arterial pressure and deterioration in kidney function (26). Research findings indicate that elevated systolic blood pressure primarily contributes to kidney disease development (27). The RENAAL study revealed that with each 10/mm Hg increase in initial systolic pressure, the progression of end-stage renal disease (ESRD) or death accelerated by 11% (28).

HYPERLIPIDEMIA

Elevated lipid levels significantly increase cardiovascular disease risk and stroke. In CKD patients, lipids have a more pronounced atherogenic effect (29). The progression of CKD is associated with substantial alterations in Apo lipoprotein profiles, which correspond to changes in lipid patterns (30). Notably, individuals with CKD exhibit higher levels of lipoprotein (a) (Lp (a)), which is associated with cardiovascular events (31). Additionally, modifications in Apo lipoprotein B are linked to CKD (32). HDL and plasma lipoprotein lipase operation are reduced as CKD progresses, possibly leading to hypertriglyceridemia. Multiple factors, such as insulin resistance and reduced lipoprotein lipase activity,

may thus make a significant contribution to hypertriglyceridemia in CKD (33). The lipid profiles commonly found in CKD sufferers are shown in Table I.

Table I. Lipid profile commonly found in CKD patients

	Moderate CKD patients	Hemodialysis	Peritoneal dialysis	Transplant
Cholesterol	Normal or slightly elevated	Normal or maybe low	High	High
Triglycerides	Elevated	High	High	High
LDL	Irregular	Normal or maybe low	High	High
HDL	Low	low	low	Normal

REDOX AND INFLAMMATORY IMBALANCE

The production of excess oxygen free radicals causes oxidative stress, depleting antioxidants like superoxide dismutase (SOD) and glutathione (GSH) (34). SOD converts superoxide radicals into hydrogen peroxide, while GSH neutralizes reactive oxygen species (35). Their depletion leads to endothelial dysfunction, inflammation, and atherosclerosis, elevating cardiovascular risk in chronic kidney disease (CKD) patients (36). End-stage renal disease elevates oxidative stress, a crucial element in the impairment of endothelial function and the development of atherosclerosis (37). Free radicals from oxygen activate monocytes, triggering inflammation, which plays a vital role in developing and rupturing atherosclerotic plaques (38). Activated monocytes adhere to the endothelium, differentiate into macrophages, and engulf oxidized low-density lipoproteins (LDL), forming foam cells (39). This process leads to endothelial dysfunction, pro-inflammatory cytokine release, and plaque instability, increasing the risk of thrombosis and cardiovascular events (40).

MONOCYTE ACTIVATION IN CKD-CVD PATHOPHYSIOLOGY

Monocyte activation plays a crucial role in the inflammatory processes associated with chronic kidney disease and cardiovascular disease (CVD) (41). In CKD, oxidative stress and uremic toxins such as indoxyl sulfate and p-cresyl sulfate stimulate monocytes, promoting their differentiation into pro-inflammatory macrophages (42). These activated monocytes contribute to endothelial dysfunction by increasing the secretion of cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (43). The heightened inflammatory state accelerates atherosclerosis, a major contributor to cardiovascular complications in CKD patients. Additionally, monocytes express scavenger receptors that facilitate the uptake of oxidized low-density lipoproteins (oxLDL), leading to foam cell formation and plaque instability in atherosclerotic lesions (44).

HYPERHOMOCYSTEINEMIA

Elevated levels of homocysteine in the blood, known as hyperhomocysteinemia, are more prevalent and severe in individuals with chronic kidney disease (CKD) and are associated with increased risk of cardiac events and mortality (45). Several factors contribute to hyperhomocysteinemia in CKD patients, including a reduced effectiveness of the remethylating pathway, lower serum folate and B vitamin levels, and impaired renal excretion of homocysteine and cysteine (46). Homocysteine can induce endothelial dysfunction by increasing oxidative stress and reducing nitric oxide availability (47) . Additionally, hyperhomocysteinemia is linked to increased lipoprotein(a) levels and enhanced platelet adhesion to blood vessel walls, suggesting it may play a significant role in the development of coronary artery disease in CKD patients (48).

FIBRINOGEN

Increased fibrinogen levels are linked to CKD and are also indicative of the development of coronary artery disease. During its contact with glycoprotein IIb/IIIa receptors, fibrinogen is essential for platelet aggregation (49). Fibrinogen may also be degraded to fibrin, a necessary stage in the production of blood clots (50). Fibrinogen forms intermolecular interactions with Lp (a) and is co-localized inside

atherosclerotic panels, resulting in localized fibrinogen degradation and increased coagulability (51). High fibrinogen levels cause a procoagulant condition (52). As a result, the uremic environment has numerous impacts on the arterial wall, favoring coagulation and enhancing coronary atherosclerosis (24).

FIBRINOGEN FUNCTION IN CKD-CVD INTERACTIONS

Fibrinogen, a key coagulation factor, is elevated in CKD patients due to persistent systemic inflammation. It plays a dual role by contributing to both thrombosis and atherosclerosis (53). Elevated fibrinogen enhances platelet aggregation through interactions with glycoprotein IIb/IIIa receptors, increasing the risk of thrombotic events such as myocardial infarction and stroke (54). Additionally, fibrinogen undergoes conversion to fibrin, forming an extensive fibrin mesh that stabilizes blood clots (55). In CKD, dysregulated fibrinolysis leads to an accumulation of fibrin deposits in vascular tissues, promoting chronic vascular inflammation and endothelial dysfunction. Moreover, fibrinogen's ability to interact with lipoprotein(a) amplifies its atherogenic effects by increasing plaque burden and vascular occlusion (56).

EARLY DETECTION STRATEGIES

Proteinuria monitoring is clinically significant as it indicates cardiovascular risk and maybe a stronger predictor of a decline in the future glomerular filtration rate (57). Since the 1970s, working adults and school-aged children (6–18 years old) in Japan have undergone regular urinalysis screenings to detect glomerulonephritis. This practice appears to have reduced the prevalence of kidney failure caused by the disease (58). The Kidney Early Evaluation Program (KEEP) of the National Kidney Foundation is a community-based project in the United States that engages grown-ups at significant risk of CKD for something like a fitness examination survey and measurements of creatinine levels, urine microalbumin, and albumin-to-creatinine ratio (59).

THERAPEUTIC MANAGEMENT OF NON-DIABETIC CKD

Managing high blood pressure is a key component in treating chronic kidney disease and reducing the risk of heart disease. The blood pressure objective for chronic renal illness patients is 125–135/75–85 mm Hg (60). On contrast, whenever a reduced arterial pressure of 92 mm Hg (equal to 125/75 mm Hg) was sought, the MDRD and AASK investigations found no noteworthy improvements in kidney failure or mortality, nor a fall in glomerular filtration rate (61). The finest medications for reducing the course of non-diabetic kidney damage are angiotensin-converting enzyme inhibitors. Their efficacy has been demonstrated most evidently in those with proteinuria chronic kidney disease, and they are suggested as first-line therapy for this population (62).

PHARMACOLOGICAL TREATMENT OF DIABETIC CKD

In individuals with diabetic nephropathy, angiotensin-converting enzyme inhibition has been shown to provide noteworthy renal advantages. In those with type 1 diabetes as well as developed nephropathy, angiotensin-converting enzyme inhibitors reduce the danger of mortality, dialysis, or transplantation. Angiotensin-converting-enzyme inhibition lessened the frequency of new instances of microalbuminuria in two major randomized controlled trials in people with type 2 diabetes (EUCLID and ADVANCE). Therefore, other than in a clinical study, the danger-to-advantage proportion of strict glycaemia management must be thoroughly evaluated in persons with poor glomerular filtration rates (27).

ADVANCED THERAPEUTICS

DAPAGLIFLOZIN

Dapagliflozin is the first medication in a new class called sodium-glucose co-transporter-2 (SGLT2) inhibitors, used to manage type 2 diabetes (28). Other SGLT2 inhibitors include canagliflozin and empagliflozin, which also help improve glycemic control and provide cardiovascular and renal benefits. When combined with other diabetes medications, it provides an alternative treatment due to its unique way of working. Dapagliflozin has become an essential option in treating diabetes, especially as an add-on

therapy, due to its unique ability to lower blood glucose while providing renal protective effects by reducing albuminuria and slowing the progression of kidney disease (29).

Mode of Action

Dapagliflozin works by blocking the transporter that reabsorbs glucose in the kidneys, helping to lower blood sugar. Recently, SGLT2 inhibitors have improved heart health in type 2 diabetic patients. They also slow down the worsening of kidney function and reduce the risk of kidney-related death in those with both type 2 diabetes and kidney disease. The proximal kidney duct and the intestinal membrane include SGLTs, a class of membrane proteins that carry glucose, amino acids, and other chemicals. SGLTs mediate the transfer of glucose from the tract further into tubular epithelial cells. SGLT1 is primarily involved in glucose absorption from the gastrointestinal tract, and this also plays a role in glucose reabsorption inside the proximal tubule, accounting for 10% of glucose reabsorption. Inside the kidney, SGLT2 is a key SGLT transporter. Dapagliflozin works by inhibiting SGLT2 in a specific and decisive manner, resulting in reduced renal glucose reabsorption and increased urine glucose excretion, lowering blood sugar levels without requiring insulin (30).

Clinical Trials

Dapagliflozin 5 or 10 milligrams per day, administered for 24 weeks as monotherapy in previously untreated patients or as an optional mixture treatment alongside metformin, glimepiride, pioglitazone, or insulin-centered therapeutic, considerably lowered both glycosylated hemoglobin variables (primary endpoint) as well as fasting plasma glucose concentrations versus placebo in phase III, randomized trials throughout patient populations with poor response type 2 diabetes. Furthermore, when taken as a complementary medication in individuals with type 2 diabetes who were poorly managed with metformin, dapagliflozin was nearly equal to glipizide in terms of glycemic regulation following fifty-two weeks. Individuals having mild to acute kidney dysfunction (projected geGFR 60 ml/min/1.73 m2) should not take dapagliflozin. After 2 years of titration, a devoted randomized of dapagliflozin in CKD patients (mostly stage 3, with an eGFR between 30 and 60 ml/min/1.73 m2) revealed an absence of sugar levels effectiveness (31).

Dosage

Dapagliflozin has significant systemic exposure across a wide dosage range (0.1–500 mg), and also its pharmacokinetic characteristics do not alter with repeated administration, according to a thorough pharmacokinetic and pharmacodynamics review. After oral treatment, dapagliflozin is quickly absorbed, with maximal Cmax values typically obtained within 2 hours. The bioavailability of the drug is 78 percent when taken orally. The high mean Vss of 118 L implies extravascular dispersion, and the mean plasma half-life is 12.9 hours. With 10 mg of dapagliflozin, the clinical dosage, urine glucose reabsorption is inhibited 24 hours after delivery, indicating that this dose is acceptable for once-daily dosing (32).

Efficacy

Based on relatively long-term extension studies, dapagliflozin's effectiveness lasts for up to two years. In clinical trials lasting 24 and 52 weeks and in 2-year extended studies, dapagliflozin was found to be generally safe (33).

Side Effects

Patients taking dapagliflozin experienced higher rates of vaginal and urinary infections compared to those on the control treatment. These side effects are of particular interest because they appear to be related to how dapagliflozin works, as increased urinary glucose levels create a favorable environment for fungal and bacterial infections, leading to a higher incidence of genital and urinary tract infections. Although the occurrence of hypoglycemic episodes with dapagliflozin varies depending on the underlying treatment, it generally has a low risk of causing hypoglycemia, mainly when used alone or with metformin. Long-term

data on the tolerance and safety of dapagliflozin is eagerly awaited. The impacts of SGLT2 inhibitors on blood pressure were studied in a recent meta-analysis. Dapagliflozin was linked to a 3.78 mm Hg drop in systolic blood pressure (95 percent CI 4.49 to 3.07). Diastolic blood pressure was also lowered by 1.41 mm Hg (95 percent confidence interval: 1.80 to 0.96) (34).

FDA Approval Status

The SGLT2 inhibitor dapagliflozin was authorized by the US Food and Drug Administration (FDA) on April 30, 2021, to reduce the risk of renal and cardiovascular complications in patients with renal impairment who are at risk of disease progression. Dapagliflozin is the very first SGLT2 inhibitor to be permitted for CKD patients, regardless of diabetes status, by any regulatory agency. It has been permitted for use in individuals with type 2 diabetes in Europe and the United States (35).

CANAGLIFLOZIN

Canagliflozin is an SGLT2 inhibitor that helps lower blood pressure, body weight, and albumin levels in people with diabetes. It is approved in the US, Japan, Australia, and the EU for managing type 2 diabetes. Besides lowering blood sugar, it also positively affects the heart and the kidneys (36).

Mode of Action

Canagliflozin targets two types of SGLT receptors, SGLT-1 and SGLT-2. SGLT-2 is located in the kidneys and reabsorbs about 90% of the glucose filtered by the kidneys (63). By inhibiting SGLT-2, canagliflozin increases glucose excretion in urine, lowering blood glucose levels. Research shows that people with type 2 diabetes (T2DM) have increased SGLT-2 glucose reabsorption compared to those without T2DM, making it a good treatment target (64). Since urine glucose excretion decreases as blood glucose levels drop, SGLT-2 inhibition has a low risk of causing hypoglycemia (65). SGLT-1 is expressed in cardiac myocytes, which might be part of the mechanisms underlying the cardiovascular benefits of specific SGLT-2 inhibitors (66). When comparing to other medications in the same family, for example, dapagliflozin, empagliflozin, and tofogliflozin, canagliflozin seems to have a lower choosiness for the SGLT-2 receptor over the SGLT-1 receptor (67).

Clinical Trials

The CANVAS Project included information from two studies, including a combined amount of 10,142 individuals with type 2 diabetes as well as a greater danger of heart illness (68). Each trial included 188.2 weeks of follow-up, and subjects were randomly allocated to receive canagliflozin or a placebo (69). The CANVAS was created to look at the possible cardiovascular advantages of canagliflozin. Two cases were prepared and executed similarly as part of the CANVAS initiative (69). Each investigation was a multicenter, worldwide, randomized, placebo-organized experiment with over 10,000 participants, with a predetermined intention to combine the two trials. Canagliflozin considerably lowered the primary composite endpoint, which included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, compared to placebo. CANVAS also demonstrated a decrease in heart failure hospitalization during the first few months of the study, indicating that the glucose-lowering impacts of canagliflozin appeared uncertain to be the cause of the reduction in heart failure hospital admissions (70).

Dosage

With an increased proportion of renal dysfunction, the pharmacodynamics responsiveness to canagliflozin decreases, with a maximal suggested dose of 100 mg once a day in people with moderate renal dysfunction (eGFR 45–60 mL/min/1.73 m2). Individuals with an eGFR of 45 mL/min/1.73 m2 should not take canagliflozin. Hemodialysis removes just a tiny amount of canagliflozin (71).

Efficacy

Patients who received canagliflozin experienced a notably lower risk of cardiovascular events compared to those given a placebo. Canagliflozin reduced blood pressure and body mass in Phase II studies

and decreased glucose levels (72). Canagliflozin decreased albuminuria development by 0.73 percent in Phase II studies versus placebo (95 percent CI 0.67–6.79). Heerspink *et al.* found that canagliflozin reduced the pace of projected glomerular filtration rate (eGFR) deterioration compared to glimepiride. Participants on glimepiride seemed to have a typical decrease of 3.3 mL/min/1.73 m2 per year, associated with 0.5 mL/min/1.73 m2 per year for canagliflozin 100 mg day-to-day and 0.9 mL/min/1.73 m2 per year for canagliflozin 300 mg daily (73).

Side Effects

Canagliflozin is associated with a higher chance of developing heart disease and an increased risk of amputations, particularly at the toe or foot level (74). It has also been associated with an increase in genital fungal infections due to excessive glycemia levels in the urine (75). In women, the rate of genital fungal infections was 12.73% at 100 mg and 13.78% at 300 mg, compared to 2.9% with placebo after 52 weeks. Similar risks were also observed in men, though at a lower incidence (76). When compared to placebo, undesirable events related to volume deprivation and osmotic diuresis are much more likely in individuals receiving canagliflozin (77). Dry mouth, hoarseness, restlessness, and night sweats are some of the most prevalent side effects of osmotic diuresis. In randomized controlled trials, fractures were also reported in individuals taking canagliflozin. The exact mechanism behind the increased fracture risk remains unclear (78).

FDA Approval Status

As of May 2012, Janssen Pharmaceuticals, a Johnson & Johnson corporation, recorded a New Drug Application to the FDA. The FDA's recommended licensing of canagliflozin (79). The filing was grounded on information from that of a phase III scientific experiment program that included nine multicenter, purely random, placebo- and committed controlled experiments involving around 10,000 patients, which would consist of three large trials involving elderly patients, sick people with mild renal dysfunction, and patients with those at higher risk for cardiovascular disease (80).

FINERENONE

Finerenone is a non-steroidal mineralocorticoid receptor blocker prescribed for chronic heart failure (HF) treatment having reduced ejection fraction (HFrEF) and to manage cardiovascular risk in these patients (81). It is the latest selective MRA, with strong evidence showing its benefits in cardiac arrest and diabetic nephropathy (81). Developed by Bayer AG, finerenone (BAY 94-8862) has a higher binding affinity for mineralocorticoid receptors compared to eplerenone and spironolactone. Its chemical formula is C21H22N4O3, and its IUPAC name is (4S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide (82). Unlike other MRAs, finerenone prevents MR activation by blocking ligand binding through the protrusion of MR helix 12. Finerenone has shown promise in the treatment of cardiorenal disorders, notably in individuals with heart problems and moderate renal impairment, since its development (83).

Mode of Action

The RAAS pathway starts when granular cells in the kidney's juxtaglomerular apparatus (JGA) release renin (84). Renin secretion is triggered by three main factors, sympathetic stimulation of JGA's beta-1 receptors, reduced sodium delivery to the distal tubule, and low renal perfusion pressure detected by afferent arteriole baroreceptors (85). Heart-produced atrial and brain natriuretic peptides inhibit renin release in response to high plasma volume. Angiotensin-converting enzyme (ACE), produced by lung endothelial cells and to a lesser extent by kidney cells, converts angiotensin I (ATI) into angiotensin II (ATII). (86) ATII activates two G protein-coupled receptors, AT1 and AT2, influencing sodium excretion and autoregulating glomerular filtration rate (GFR) (87). Activation of the AT1 receptor causes vasoconstriction of afferent and efferent arterioles, aldosterone and norepinephrine release, sodium reabsorption, and antidiuretic hormone secretion, leading to increased sodium retention, potassium excretion, and improved

circulatory volume (88).

Clinical Trials

Pitt *et al*., (2021) Filippatos *et al*., (2022) and Sato *et al*., (2016) performed three randomized control studies on finerenone and heart disease and reported their findings. Pitt *et al*., (2021) investigated finerenone's effectiveness and safety in cardiovascular disease and CKD (89). Filippatos *et al*., ((2022) looked at how finerenone affected individuals with deteriorating chronic heart failure who also had diabetes and chronic renal illness. Sato *et al*., (2016) conducted research in a smaller Japanese population that was substantially comparable to the ARTS-HF experiment (90).

Dosage

The drug is consumed once a day, and the appropriate dose is still to be found. Various dosages, comprising 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg, have been studied, with ongoing dose-finding studies. Finerenone appears to cause less hyperkalemia over spironolactone while having similar properties on NT-ProBNP and albuminuria. Prospective finer none investigation should focus on increasing the drug's dosage to at least 10 mg. Additional cardiovascular advantages can be obtained by increasing the finer none medication dosage from 10 mg/d. The likelihood of cardiovascular mortality as well as the composite outcome (mortality of any reason, cardiovascular hospitalization, or emergency admission for severe chronic heart failure) decreased as the dosage increased, notably 15 to 20 mg (88).

Efficacy

A large scientific study, which included several previously mentioned RCTs, assessed the competence and safety of finerenone in 1,520 patients with HF. The study found that finerenone 10 mg once daily was comparable to spironolactone 25 mg and eplerenone 50 mg once daily in terms of effectiveness. Finerenone showed a trend toward dose-dependent efficacy in lowering NT-proBNP levels compared to steroidal MRAs, spironolactone, and eplerenone. It also demonstrated fewer side effects than spironolactone (25-50 mg daily). While finerenone 10 mg daily tended to lower serum potassium levels compared to spironolactone, the difference was insignificant. Lastly, the study suggested that the finerenone 10 mg group had a higher anticipated glomerular filtration rate than the steroidal MRA group (91).

Side Effects

Finerenone had no clinically significant adverse effects in the FIDELIO or FIGARO trials, except for high potassium levels (90).

FDA Approval Status

The United States FDA agreed to the application for Finerenone (Frampton, 2021).In the U.S., allopurinol was certified for therapeutic use in 1966. The WHO records it as a vital remedy. Allopurinol is accessible as a general drug. With almost 15 million recommendations recorded in 2019, it was the 43rd most widely prescribed medication in the United States (92).

BIOCHEMICAL EFFECTS OF MEDICATIONS IN CKD-CVD MANAGEMENT

SGLT-2 INHIBITORS (DAPAGLIFLOZIN, CANAGLIFLOZIN, EMPAGLIFLOZIN)

SGLT-2 inhibitors primarily reduce glucose reabsorption in the renal proximal tubules, leading to glycosuria and improved glycemic control. However, they exert significant cardiovascular and renal benefits beyond their glucose-lowering effects (93). These drugs lower intraglomerular pressure by reducing sodium retention and promoting natriuresis, which decreases preload and afterload on the heart (94). Additionally, they mitigate oxidative stress and inflammation by reducing reactive oxygen species (ROS) and suppressing pro-inflammatory cytokines such as IL-6 and TNF-α. They also enhance ketone metabolism, improving myocardial energy efficiency, which is particularly beneficial for heart failure patients (95).

MINERALOCORTICOID RECEPTOR ANTAGONISTS (FINERENONE, SPIRONOLACTONE, EPLERENONE)

Mineralocorticoid receptor antagonists (MRAs) counteract the effects of aldosterone, which contributes to hypertension, fibrosis, and endothelial dysfunction (96). Finerenone, a non-steroidal MRA, has a higher selectivity for mineralocorticoid receptors, reducing pro-inflammatory and pro-fibrotic signaling pathways in the kidneys and heart (81). By inhibiting aldosterone-induced oxidative stress, MRAs help prevent myocardium and renal tissue fibrosis, slowing CKD progression and reducing cardiovascular mortality (97).

RAAS INHIBITORS (ACE INHIBITORS, ARBS)

ACE inhibitors (e.g., enalapril, ramipril) and angiotensin receptor blockers (e.g., losartan, valsartan) reduce angiotensin II levels, leading to vasodilation, reduced sodium retention, and lower blood pressure (98). They also decrease oxidative stress by suppressing NADPH oxidase activity and reducing endothelial dysfunction. Additionally, they limit proteinuria by preserving glomerular barrier function, thereby delaying CKD progression and protecting against cardiovascular events (62).

ANTI-HYPERLIPIDEMIC AGENTS (STATINS)

Statins (e.g., atorvastatin, rosuvastatin) inhibit HMG-CoA reductase, reducing cholesterol synthesis and lowering LDL levels (99). Beyond lipid control, they exhibit pleiotropic effects, including anti-inflammatory and antioxidative properties. Statins decrease CRP levels, inhibit foam cell formation, and improve endothelial nitric oxide bioavailability, collectively reducing atherosclerotic plaque formation in CKD-CVD patients (100).

CONCLUSION

This study highlights the strong association between CKD and CVD, emphasizing the need for effective therapeutic strategies to reduce cardiovascular risk in CKD patients. FDA-approved medications such as SGLT-2 inhibitors have shown promising results in improving renal and cardiovascular outcomes. However, further research is needed to explore emerging drug therapies, including novel mineralocorticoid receptor antagonists and anti-inflammatory agents, which may offer additional benefits. Future studies should also focus on personalized medicine approaches, integrating genetic and biomarker-based strategies to optimize treatment. Additionally, investigating the potential of regenerative medicine and nanotechnology-based drug delivery systems could lead to innovative interventions for CKD-CVD comorbidity. Expanding clinical trials on new therapeutic targets will be crucial for improving long-term patient outcomes and reducing the global burden of CKD-related cardiovascular complications.

Authors' contribution:

AIR: Conceptualization, Study Design; SA & RA: Data collection; MA & RN: Manuscript writing and Formatting; SZ: Tables and Figures; AM: Manuscript Writing; MM & NH: Review and Editing; RA: References cross check and Citations.

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