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Review Article

Pharmacotherapy in Cardiovascular Disease with Chronic Kidney Disease Medications: A Comprehensive Literature

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ABSTRACT

A progressive decrease of renal function is a symptom of chronic kidney disease, commonly known as chronic kidney failure. The body may accumulate hazardous amounts of fluid, electrolytes, and wastes if the patient has advanced chronic kidney disease. There are several causative factors which lead to CKD which include high or low blood pressure, more accumulation of cholesterol, diabetes and many more. According to WHO global health statistics in 2012, 864,226 mortalities (or 15% of all deaths worldwide) were attributed to this illness. CKD was categorized 14th on the index of principal causes of death, having 122 mortalities per 100,000 persons. Most of the causes of deaths were due to sudden cardiac arrests in CKD patients. In this review, we made a list of 10 FDA approved medications which has proven to decrease CKD and fatalities caused by cardiac arrests. SGLT-2 inhibitors have shown promising results in manipulating kidney functions to improve the efficiency of heart.

INTRODUCTION

In invertebrates, the kidneys comprise 2 maroon-colored bean-shaped structures [1]. It is found upon the left side as well as right sides of the retroperitoneal territory. The length of kidney is estimated around 12 cm among mature people [2]. Blood comes from the renal arteries and leaves onto the linked renal veins. Both kidneys consist a ureter that is a pipe that transports excreted urine to the urinary bladder. The kidney functions in the management of bodily fluid volume, fluid osmotic pressure, acid-base balancing, different electrolyte levels, and elimination of toxins [3]. The glomerulus, screens and filters one-fifth of the entire blood volume, whilst entering the kidneys [4]. A glomerular filtration rate (GFR) test calculates how your kidneys filter blood. Glomeruli are microscopic filters found in your kidneys. These filters aid in the elimination of waste and more than necessary fluid from the arteries [5]. This data is shown below in table 1.

Table 1: Stages of CKD and glomerular filtration rate

Stages	Filtration rate mm/min/1.73m2	Kidney status
Stage 1	90	Normal healthy kidney
Stage 2	60-89	No kidney damage
Stage 3	30-59	Moderate CKD

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Stage 4	15-29	Severe loss of kidney function
Stage 5	Fewer than 15	Kidney failure

A GFR of below 15 milliliters/min per 1.73 square meters, or the requirement for dialysis or surgery, is considered kidney failure.

Causative factors of CKD

Causes of Chronic kidney disease are commonly linked to older age, hyperglycemia, high blood pressure, overweight, and heart disease in developed nations [6, 7]. Glomerulosclerosis in diabetic nephropathy is characterized by increasing albuminuria, high blood pressure, and a reduction in GFR, often accompanied by renal dysfunction [7].

Co-relation between kidney and heart diseases

In comparison to individuals not having CKD, individuals have a GFR just under 60 mL/min per 173 square meters and individuals having lesser than normal albuminuria, have a 57 percent greater likelihood of cardiovascular fatality. Each 10 mL/min per 173 m2 drop in GFR, as well as every 25 mg/mmol rise in albumin and creatinine ratios, the risk of stroke rose by 7% [8].Anti-platelet therapy was also linked to a 33% higher risk of severe bleeding and a 49% higher risk of small bleeding events, suggesting that the risks of antiplatelet therapy may outweigh the benefits among persons with a reduced risk of cardiac events (CKD stages 1 and 2)[9].

Hypertension and CKD

Hypertension can be a reason or a symptom of kidney disease, and also its diagnosis and management are linked. Hypertension damages the heart, veins, kidneys, brain, and eyes, leading to the development of cardiovascular and renal disorders such as ischemic heart disease and end-stage renal disease (ESRD). According to data, the most important factor for the occurrence of renal disease is increased systolic blood pressure. Each 10-mm Hg elevation in baseline systolic bp accelerated the pace of ESRD or mortality by 11% in the RENAAL research [10, 12].

Hyperlipidemia

Hyperlipidemia is indeed a major risk factor for heart disease and stroke. Lipids are much more atherogenic in individuals with CKD, also when their concentrations are not excessive. Major changes in apolipoproteins accompany modifications in lipid profiles in CKD. Lipoprotein (a) (Lp[a]) levels are higher in CKD and are linked to cardiovascular events. Apolipoprotein B changes are also connected with CKD and it is also linked to the severity of the coronary atherosclerosis within dialysis patients. As a consequence, lipoprotein irregularities caused by CKD may hasten atherosclerosis in these individuals [13]. The lipid profile which are commonly found in CKD patients are shown in table 2.

Table 2: Lipid profile commonly found in CKD patients

Lipid profile	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

Inflammation and oxidative stress

Increased generation of oxygen free radicals causes oxidative stress that depletes endogenous antioxidants as well as leads to cardiovascular damage. ESRD increases oxidative stress, which is a critical factor in endothelial dysfunction and atherosclerosis [14, 15]. Monocytes are activated by oxygen free radicals, which cause inflammation, which is a key component of atherosclerotic plaque development and rupture.

Hyperhomocysteinemia

Hyperhomocysteinemia, which is linked to cardiac events and death, is more common and severe in those with CKD. Reduced action of the remethylation sequence, reduced serum folate and B vitamin consumption, and impaired renal removal of homocysteine and cysteine are all reasons for hyperhomocysteinemia in CKD. Homocysteine can cause endothelial disorder by rising oxidative stress as well as declining nitric oxide availability [16, 17]. Hyperhomocysteinemia is also linked to higher levels of Lipoprotein (a) and enhanced platelet adherence to the vascular wall, suggesting that it might have a key role in the progress of coronary artery sickness in people with CKD [17]. According to a recent meta-analysis, a 25% reduced homocysteine level seemed to have an 11% reduced danger of ischemic heart sickness [18].

Pharmacological management of non-diabetic chronic kidney disease

The cornerstone of treatments for slowing the course of chronic renal disease and lowering heart disease risk is high blood pressure treatment. When blood pressure goes over 130/80 mm Hg, there is a rise in the danger of chronic renal illness development and renal failure [19]. The ALLHAT trial did not measure urine protein concentrations; nonetheless, proteinuria was likely uncommon in the group investigated, which might explain why angiotensin-converting enzyme inhibitor medication did not affect the danger of renal failure [20]. Whereas the HOPE research found that using an angiotensin-converting enzyme inhibitor decreased the incidence of cardiovascular events in individuals with moderate renal insufficiency [21]. In a cohort with cardiovascular illness, intact kidney function, and no proteinuria, the TRANSCEND research found no effect of an angiotensin-receptor blocker for preventive care of renal dysfunction [22].

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Therapy with just an angiotensin-converting enzyme inhibitor and an angiotensin-receptor blocker decreases proteinuria providing extra renoprotection [23]. In the ONTARGET study, individuals with a very well glomerular filtration rate as well as infrequent proteinuria had a greater risk of dialysis creatinine concentration or death if they took a mixture of angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker [24].

Pharmacological treatment of diabetic chronic kidney disease

People having diabetes mellitus should be treated for excessive blood pressure regardless of whether or not they have chronic renal disease [25]. Reduced blood pressure decreases the risk for diabetes-related mortality, stroke, and microvascular endpoints like retinopathy in the UK Prospective Diabetes Study (UKPDS) [26-28]. The IRMA research's findings, as well as a subgroup assessment of diabetic patients participating in the HOPE project, revealed that individuals using angiotensin-converting enzyme inhibitors have a lower danger of developing macroalbuminuria. In the BENEDICT research, ramipril slowed the emergence of microalbuminuria in people with type 2 diabetes, and enhanced renal function. The Diabetes Control and Complications (DCCT) trial found that lowering glycosylated hemoglobin (HbA1c) by a lesser amount of 6% decreased the occurrence of further instances of microalbuminuria or macroalbuminuria in type 1 diabetes individuals [29, 30].

Advanced Therapeutics

Dapagliflozin

Dapagliflozin is the foremost of a novel class of glucose-lowering medications named sodium- glucose co-transporter-2 (SGLT2) inhibitors, which is consumed to control type 2 diabetes individuals. Dapagliflozin, whenever combined with several other antidiabetic medicines, offers alternative treatment through its unique mode of action. Dapagliflozin looks to have been an essential addition towards the treatment choices for the control of diabetics, especially when used as optional therapies, due to its unique and complementing mode of action [31, 32].

Mode of action

Dapagliflozin lowers renal reabsorption of glucose by blocking its transporter protein SGLT2 inside the kidneys, resulting in urine glucose excretion therefore lower blood sugar levels (31, 32). Most oral antidiabetic medicines from the other classes, dapagliflozin's effectiveness is not reliant on insulin production or action. Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) have lately been proven to enhance cardiovascular outcomes in type-2 diabetic patients. Furthermore, they moderate the deterioration in kidney function in these individuals and lower renal death rates in those with type-2 diabetes and kidney illness. The SGLT2 inhibitor dapagliflozin decreased the incidence of the major composite outcome of cardiovascular mortality or deteriorating heart failure (HF) in individuals either with or without type 2 diabetes in the DAPA-HF study [31, 33].

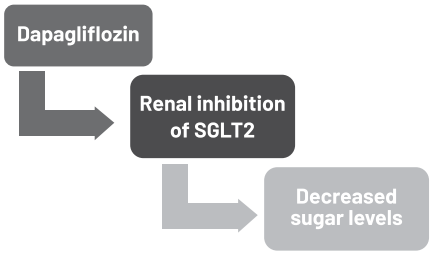

Figure 1: Mode of action of dapagliflozin

Efficacy

Dapagliflozin's effectiveness is sustained for up to two years, according to relatively long extension trials. In 24- and 52-week clinical testing, along with 2-year extended investigations, dapagliflozin was generally safe.

Side effects

Dapagliflozin patients had a higher rate of vaginal infections as well as urinary infections compared control individuals. These side effects are particularly interesting since they seem to be linked to dapagliflozin's mode of action. Even though the rate of hypoglycemic episodes recorded with dapagliflozin in clinical studies varied based on the underlying treatment, dapagliflozin dose have a low proclivity for causing hypoglycemia, particularly when administered alone or in combination with metformin. Longer-term tolerance and safety information for dapagliflozin are eagerly anticipated [34].

Canagliflozin

In diabetes patients, canagliflozin is a sodium-glucose cotransporter 2 inhibitor that lowers blood pressure, body mass, as well as albuminuria. In the United States, Japan, Australia, and the EU, canagliflozin is a sodium glucose-cotransporter (SGLT) receptor inhibitor licensed for the management of type 2 diabetic mellitus (T2DM). It has favorable effects on the cardiovascular system and perhaps the kidneys in addition to decreasing blood sugar [35].

Mode of action

SGLT-1 and SGLT-2 are the two kinds of SGLT receptors that canagliflozin targets. SGLT-2 is found in the proximal kidney tubules as well as is accountable for around 90% of the glucose processed by the kidneys being reabsorbed. Canagliflozin enhances glucose excretion in the urine and lowers blood glucose levels via suppressing SGLT-2. There is additional evidence indicating SGLT-2 reabsorption of glucose is enhanced in people with T2DM relative to those without T2DM, which makes it more appealing as a

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therapeutic target. Because urine glucose excretion reduces as blood glucose levels fall, SGLT-2 inhibition carries slight danger of hypoglycemia[36].

Efficacy

Patients who were treated using canagliflozin had quite a reduced cardiovascular risk than others who received placebo. Canagliflozin lowered body mass from 1.2 to 2.6 kg with 100 mg each day and from 1.8 to 2.6 kg alongside 300 mg daily dose in the CANTATA trials. Canagliflozin reduced bodyweight by 4.4 kg and 4.7 kg at 100 mg and 300 mg dosages, accordingly, as matched to glimepiride[37, 38].

Side effects

A high risk of cardiovascular illness, but a higher chance of surgical removal, especially at the toe or metatarsal level. Canagliflozin has indeed been linked to an increase in genitalia mycotic infections due to the elevated glucose concentration of urine inside the urogenital tract. In women, the prevalence of genitalia mycotic infection was 12.73 percent at 100 mg and 13.78 percent at 300 mg, relative to 2.9 percent at 52 weeks for the placebo. There was even a higher incidence of genital mycotic infections in men, while it was lesser than those in women. The incidences were 3.65 percent at 100 mg and 2.88 percent at 300 mg at 26 weeks, relative to 0.51 percent in the placebo group. In randomized controlled studies, fracturing was also documented in individuals using canagliflozin. The actual mechanism underneath the possibility for elevated fracture risk is unknown[39].

Finerenone

Finerenone, a non-steroidal mineralocorticoid receptor antagonist, was used to treatment chronic heart failure (CHF) with such a decreased ejection fraction (HFrEF). Finerenone, a non-steroidal mineralocorticoid receptor antagonist, was being used to handle cardiovascular risk with a low ejection fraction (HFrEF). Finerenone is by far the most modern specific MRA, mostly with majority of evidence indicating that it can help with cardiac arrest and diabetic nephropathy. Finerenone, also known as BAY 94-8862, is indeed a new powerful selective MRA that has a higher mineralocorticoid binding affinity capacity than eplerenone and spironolactone. Bayer AG pharmaceuticals created the medicine from a preliminary substance named Bayer BR4628, which was discovered to be a powerful and selective MRA. The IUPAC name is (4S)-4-(4-cyano-2methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6naphthyridine-3-carboxamide, and also its chemical formula is C21H22N4O3. Unlike its sibling MRAs, this medication causes the protrusion of MR helix 12 that prevents ligand binding from activating the MR[40].

Mode of action

The RAAS pathway begins with some granular cells of a kidney juxta glomerular machinery secreting renin (JGA). Three key physiological factors stimulate the secretion of renin: sympathetic activation of the JGA's 1 receptors, decreased sodium transport to the distal convoluted tubule, & lower perfusion pressures in the kidneys sensed by afferent arteriole baroreceptors. Atrial natriuretic peptide and brain natriuretic peptides, that are generated by heart soft tissue in reaction to compartment dilation caused by high plasma levels, suppress renin secretion. Renin catalyzes the conversion of angiotensinogen, a hepatocyte-produced precursor protein, to Angiotensin I. AT II activates 2 G protein-coupled transmembrane receptors: the AT I and AT II receptors. AT II likewise affects sodium excretion therefore acts as an autoregulator of its glomerular filtration rate (GFR). AT II activation of the ATI receptor is more effective than ATII stimulation, resulting in afferent and efferent arteriole vasoconstriction, aldosterone discharge out from adrenal cortex, norepinephrine discharge from presynaptic terminal ends, sodium reabsorption in the proximal intricate tubule, and antidiuretic hormone discharge out from hypothalamus. Higher salt reabsorption, potassium expulsion, greater hydraulic stresses to retain an acceptable GFR, reabsorption of water inside the collecting duct, and enhanced effective circulation volume are all results of these processes[40].

Efficacy

A big scientific study included many of the previous mentioned RCTs in something like a total of 1520 patients with heart collapse to assess the effectiveness and security of Finerenone in patients with hf. Finerenone 10 mg once every day was shown to be equal to spironolactone 25 mg one time every day and eplerenone 50 mg on one occasion every day in this study. Finerenone 10 mg once day showed an inclination in the direction of dose-reliant on effectiveness in lowering NT- ProBNP when matched to steroidal MRAs like spironolactone or eplerenone. Finerenone 10 mg once day had a considerably reduced rate of adverse effects than spironolactone 25-50 mg on one occasion every day. Finerenone 10 mg everyday had a pattern towards reduced serum potassium levels (non-statistically noteworthy) when matched to spironolactone 25-50 mg once day, however the difference is not significant. Lastly, the researchers found that perhaps the finerenone 10 mg once everyday group had a greater projected glomerular filtration rate than the steroidal MRAs collection[41].

Side effects

Finerenone had no medically significant adverse effects in FIDELIO or FIGARO, except from hyperkalemia.

Lisinopril

Lisinopril is really an angiotensin-converting enzyme (ACE) inhibitor medicine that is consumed to manage excessive

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blood pressure, heart problems, and myocardial infarction. It is typically the first line of therapy for hypertension. It's been used to keep those with diabetes from developing renal issues. Lisinopril is a medication that is taken orally. It might take up to 4 weeks for the full impact to appear.

Mode of action

Lisinopril is itself an ACE inhibitor, which indicates it put a stop to angiotensin I on being transformed to angiotensin II by blocking the happenings of angiotensin-converting enzyme (ACE) in the renin–angiotensin–aldosterone system. Angiotensin II is a powerful direct vasoconstrictor and aldosterone stimulator. The amount of angiotensin II inside the body is lessened, which causes the arterioles to dilate [41].

Efficacy

Lisinopril possesses 25 percent bioavailability. It engages 7 hours to attain maximal intensity. Lisinopril has a peak impact 4 to 8 hours following dosing. Its absorption is unaffected by food. Lisinopril doesn't really attach to blood proteins. In those with NYHA Class II–IV heart failure, it's doesn't diffuse as well. Lisinopril passes through the body unmodified mostly in urine. Lisinopril has a 12-hour half-life, which is extended in individuals who part take renal difficulties. Although lisinopril's serum half- life is anticipated to be around 12 and 13 hours, its clearance half-life is predicted to be approximately 30 hours. The activity lasts about 24 and 30 hours in total [41].

Side effects

Headache, dizziness, tiredness, coughing, nausea, and rashes are all common adverse effects. Low blood pressure, liver issues, excessive blood potassium, and angioedema are all serious adverse effects. It's not really advised to use for the entire pregnancy since it may damage the baby.

Future directions

Despite the fact that CKD is quite common in the United States and impacts considerably to the population's sickness and death ratios, clinical studies on drugs and effects in CKD patients still seems to be scarce. The lack of these data might be due to a fear of negative consequences and adverse occurrences in this demographic. The lack of incentives for continuing research after FDA clearance was a major topic discussed at our meeting. Rules are required to encourage these necessary investigations while minimizing mistakes. Labeling drugs to indicate harmful effects based on predicted creatinine clearance is one example of such rules. Because CKD patients are more likely to experience pharmaceutical side effects, this will not only offer patients and clinicians with more knowledge about the possibility of side effects in a specific person, but it will also motivate firms to include individuals with CKD in trials. Another project worth considering is extending the patent life of drugs that are being studied in patients with CKD by pharmaceutical firms [42]. This may be modelled after the Pediatric Rule, which extended the patent life of drugs investigated in children by six months.

CONCLUSIONS

We studied the close relationship between the functions of heart and kidney and find out that most of the CKD patients died because of cardiac arrests. 10 FDA approved medications were separated out in this review, which were useful in lowering the risk of heart failure in CKD patients. Several clinical trials were conducted and revealed that SGLT-2 inhibitors showed promising results in enhancing the heart efficiency in diabetic patients. With the use of such add on medicines, the risk of developing cardiovascular diseases in CKD patients drops significantly and the patient come up with better survival chances. Additionally, risk assessments for advancement must be developed and evaluated so that efforts may be allocated to people who are most at danger for advancement rather than those who just have lower kidney function or indications of renal injury. Patients with cardiovascular illness, diabetes, ethnicity, or a household medical past of CKD could be identified as being at danger for chronic kidney disease.

Authors Contribution

Conceptualization:
Formal Analysis:
Writing-review and editing:

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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