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"Intersecting Pathways: Dyslipidemia in the Landscape of Chronic Kidney Disease." This title suggests a comprehensive examination of how dyslipidemia intersects with CKD, potentially exploring mechanisms, outcomes, and therapeutic strategies.

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ABSTRACT
Dyslipidemia frequently complicated chronic nephropathies and increase risk of renal and cardiovascular events. Drugs such as angiotensin-converting enzyme inhibitors which effectively reduce proteinuria. CVD is the leading causes of mortality in CKD, and as with the non-CKD population dyslipidemia is a significant contributor.in patients that cannot tolerate or who have contra-indications to statin therapy, there may be some benefits from use of PCSK9 inhibitors, fibrates, niacin or newer therapies such as bempedoic acid and inclisiran, but further studies are needed to better investigate their use. Person with chronic renal disease is prone to have accelerated process of atherosclerosis. Cardiovascular disease is the main cause of morbidity and mortality in kidney transplant recipients. There is excellent potential for multi-target drugs that act on several cell types and signaling pathways to treat kidney disease.
Keywords:chronic kidney disease, fatty acid, multi-ligand drug, dyslipidemia, cardiovascular

I. INTRODUCTION

Chronic kidney disease (CKD) is one of the most common diseases in the world, and the number of cases has risen substantially in recent years. Kidney disease (CKD) is a very diverse illness that affects the anatomy and physiology of the kidney. A gradual illness known as chronic kidney disease causes harm to the kidneys over time, impairing their ability to function. The kidneys eradicate waste products and excessive fluid from the bloodstream to generate urine. They also manage blood pressure, electrolyte balance, and the production of red blood cells. Chronic kidney disease (KD) may arise from a variety of causes, including high blood pressure, diabetes, nephropathy, a health issue known as polycystic kidney disease, urinary tract blockage, and persistent consumption of certain medications or toxins. Kidney disease may develop in the following stages:(I) GFR, either normal or high (>90/min). (ii) mild chronic kidney disease (GFR=60-89 ml/min), mild CKD (GFR=45-59 ml)/min) (iii)(a) mild CKD (GFR=30-44 ml/min) (iii)(b) Severe CKD (GFR=15-29 ml)/min) (iv) Stage IV CKD (GFR < 15ml/min). Furthermore, changes in lifestyle that include eating a balanced diet, exercising frequently, and quitting smoking might help demonstrate how CKD is progressing. In order to prevent overdiagnosis due to changes in albuminuria, a few CKD guidelines, like individuals from the UK's National Institute for Clinical and Health Excellence (NICE), the renal Disease Improving Global Outcome (KDIGO), and the Kidney Disease Outcome Quality The initiative (K/DOQ1), suggests identifying and quantifying proteinuria using estimation for the first time when albuminuria is suspected (1). The most accurate test for detecting proteinuria is Upcr(urine protein creatinine ratio). Some patients have elevated protein levels and proteinuria, which is indicative of glomerular and tubular dysfunction. While albuminuria is indicative of glomerular illness, renal biopsy results strongly correlate tubulointerstitial disease with NAP containing alpha1 and alpha2-microglobulins, which is linked to tubulointerstitial factor and decreases urine albumin to the maximum urinary protein ratio. If an individual has total renal failure and is not likely to survive, dialysis and kidney transplants are essential. One essential component in the diagnosis of renal illness is proteinuria. Cardiovascular illnesses and fatalities are more prevalent in those with chronic renal failure (CKD). An increased risk of death from cardiovascular diseases and persistent renal failure has been independently linked with an increasing kidney albumin- to- creatinine ratio. The condition

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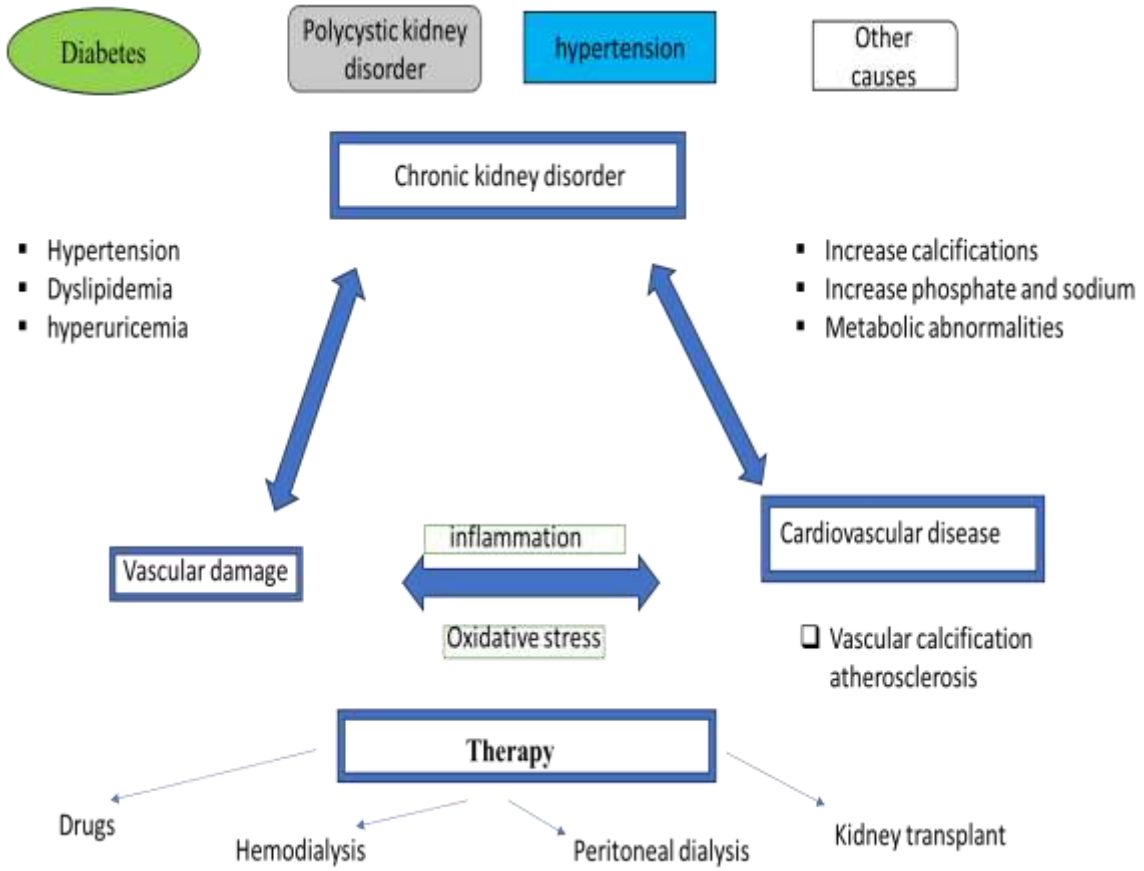
known as chronic renal disease is now a serious public health issue. According to the National Center for CKD Prevention and Health Promotion, 37% of million adults in the US had CKD in 2019. This represents a 15% overall prevalence of CKD in adults. Proteinuria causes renal fibrosis and inflammation. Additionally referred to as potent indicators of renal impairment. Angiotensin converting enzyme inhibitors and angiotensinogen receptor blockers are two blood pressure-lowering medications that are additionally employed to maintain proteinuria among people with chronic kidney disease (CKD), according to guidelines or recommendations for clinical practice. This article's current goals are to assess the effectiveness of combining angiotensin converting enzyme with a cholesterol-absorbing medication for the treatment of proteinuria reduction and to determine the genetic mechanism underlying chronic kidney disease (CKD) utilizing data from renal biopsy samples of both living donors and patients with CKD. Genomics information was gathered from 21 living donors and 30 CKD patients. These kinds of studies are essential for improving our understanding of the mechanisms underlying chronic kidney disease (CKD) and offer pertinent and helpful information on the people who are afflicted with the disease. The following are signs and symptoms of CKD: vomiting, cramps, shortness of breath, trouble sleeping, ammonia breath, difficulty concentrating, nausea, dry skin, loss of appetite, weight loss without trying to lose weight, and foamy urine. If a person has the disease at a more advanced stage, these symptoms may also be noted.



A new mechanism is involved in the development of cardiovascular disease in chronic kidney disease.

Diabetes, heart failure, obesity, hypertension, family history of chronic kidney disease, smoking, and a personal history of acute renal damage are among the risk factors that are covered (2). I. autoimmune diseases (lupus nephritis), II. glomerular disease: glomerulonephritis, IgA nephropathy, and HIV

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nephropathies are a few more causes of CKD disorders. III. Genetic disorders: renal polycystic disease. Kidney cancer, kidney stones, urinary tract infections, hydronephrosis, and anomalies of the kidneys and urinary tract before birth are additional reasons. Dyslipidemia, characterized by elevated serum triglycerides decreased HDL, LDL, and cholesterol, is associated with proteinuria in chronic renal illness. The relative risk of myocardial infractions is 5.5, and the risk of coronary mortality is 2.8. Analyses on humans and animals also demonstrate that nephrotic dyslipidemia poses a risk for developing chronic renal disease or chronic renal factor at the ultimate stage of kidney failure. Individuals with nephrotic syndrome and CKD stages 1-4 exhibit abnormalities in their lipid levels. Dyslipidemia is associated with end-stage renal failure (CKD) and lipoprotein metabolism. The degree of proteinuria and renal function both affect lipid levels. Most CKD patients have hypertriglyceridemia, which is defined as an elevated number of chylomicrons and their remains, as well as triglycerides Rich lipoprotein. Reduced hepatic triglyceride lipase activity, peripheral lipoprotein catabolic response, and increased hepatic synthesis of triglycerides rich lipoprotein concentration in CKD patients are the cause of Hypertriglycerides. Direct lipoprotein lipase inhibitors, such as apolipoprotein C-III, have higher levels in uricemia, which also raises the risk of hypertriglyceridemia. Patients with chronic kidney disease (CKD) have lower HDL than people with normal kidney function, which increases their risk of atherosclerosis. Chronic kidney disease (CKD) is most illustrated by kidney failure, glomerular filtration rate, age, sex, and albuminuria. The creation of a multiprotein predictive model for CKD is one of the goals (a) of determining the biological process causing the variables associated with CKD. (b) to the emergence of several plasma proteins that function as CKD mediators and indicators. (c) to create protein markers of CKD progression that are distinct based on clinical factors such as diabetes status. CKD is one of the most common public health issues that people today face, along with issues related to age, gender, diabetes, obesity, hypertension, and dyslipidemia (3). Anemia, hypoalbuminemia, oxidative stress, hyperparathyroidism, hyperhomocysteinemia, chronic inflammation, and mineral bone disease (CKD) are non-traditional risk factors associated with uricemia (4). Research indicates that lipid-lowering drugs are useful in reducing the population's risk of CVD death and morbidity. These drugs also have the same effect on those with CKD and those receiving transplants. The lower serum level of HDL in patients with chronic kidney disease (CKD) is caused by increased activity of lecithin cholesterol acyltransferase, an enzyme involved in the esterification of free cholesterol from HDL to triglyceride- rich lipoprotein (5). HDL-associated enzymes, such as paraoxons, oversee HDL's anti-inflammatory and antioxidative properties. These kinds of elements may play a role in the population's development of atherogenesis. Etiology: diabetes mellitus type 1 (3.9%), diabetes mellitus type 2 (30%-50%), vasculitis (2.1%), chronic tubulointerstitial nephritis, primary glomerulonephritis (8.25%), hypertension, cystic disease, sickle cell nephropathy, neoplasm, and vasculitis are the causes of end stage renal disease. CKD may manifest during these kinds of procedures. 1. Prerenal process: this category of process includes dehydration, decreased blood flow to the kidney, and certain medications that cause abnormal kidney functioning or blood supply. One prominent cause of prerenal kidney damage is dehydration. Lack of fluid in the body causes a drop in blood volume, which in turn causes the kidneys' ability to filter waste and maintain electrolyte balance to be compromised. Heart attacks, shock, and extreme dehydration, in which the kidneys receive insufficient oxygen, can all lower blood flow. Renal function may also be impacted by some medications, such as NSAIDs. A fluid and electrolyte imbalance brought on by certain other medications may be the cause of abnormal kidney function. 2. The intrinsic renal process is a condition when a problem or issue arises in the kidney on its own and directly affects the kidney's structure and function. The following are some instances of intrinsic renal problems: (a) Glomerulonephritis: This illness is characterized by inflammation of the glomeruli, the kidney's microscopic blood vessels that filter waste and extra fluid from the blood. Acute tubular necrosis (ATN) is a disorder characterized by damage to the kidney's tubules, reduced blood supply to the kidney, poisonous substances, or severe infection. 3. Kidney tumors: these may be benign or cancerous and need to be removed surgically or treated in another way. 4.) Acute renal injury: this kind of issue can arise from extreme dehydration brought on by drugs that lower kidney blood flow. Filtration, reabsorption, secretion, and excretion are among the processes involved in this process that

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are essential for maintaining the internal environment. To maintain stability, the intrinsic process is closely regulated by hormones, brain signals, and local autoregulatory mechanisms. The maintenance of blood pressure, fluid and electrolyte balance, acid-base balance, and waste product excretion or metabolism are all significantly impacted by this process. The preservation of homeostasis, or general health, depends on this mechanism. (3.) Post-renal process: this kind of process concentrates on the movement and excretion of urine from the kidney to the outside of the body after it has been created in the renal portion. The following are important elements of the post-renal process: (a) The bladder's primary job is to hold urine until its volume triggers the micturition reflex, alerting the body to the need for elimination. (b) Ureters: The muscular tubes known as ureters are responsible for carrying urine from the kidneys to the bladder once it has been generated in the kidney. To ensure a one-way flow of urine, the ureter uses peristatic contraction to push urine downward against the force of gravity. (c) The urethra is the last organ via which pee is excreted from the body. The CKD's natural history. CKD's natural history is closely associated with unfavorable health outcomes. Up to 16% of adults in the UK have experienced it in the past. Most individuals with chronic kidney disease (CKD) pass away before reaching end-stage renal disease, and their risk of cardiovascular disease (CVD) is strongly correlated with the severity of their kidney disease. Traditional risk factors for CVD and early death do not significantly contribute to the increased cardiovascular risk associated with chronic kidney disease (CKD). A novel pathos-biological mechanism may be involved in the pathway connecting CVD and CKD. A deeper comprehension of these pathways is necessary for the creation of novel CKD treatments. First, Bio Clinical data beyond the equation-based assessment of kidney function based on blood creatine and kidney damage as determined by urine protein content are studied in relation to interventions for individuals with chronic kidney disease (CKD). Secondary, it is unclear whether the results of earlier research can be applied to the current patient population. For example, the last ten years have seen a shift in the disease's natural course due to the extensive use of ACE inhibitors or ARBs for kidney disease. To accurately acquire patient cohorts with prospectively gathered upgraded clinical records and incorporate the collection and storage of biological samples that enable biomarker discovery and characterization, natural history is required. To determine the timing of exposure and outcome variable, these cohorts need to be carefully followed up on over an extended period. The primary goal of designing a study aimed specifically at high-risk patients with chronic kidney disease (CKD) is to accurately characterize the bio-clinical phenotype of a well-defined group of patients with progressive CKD and to identify risk factors associated with clinical outcome, such as early mortality and CKD progression. The best lipid-lowering medications for lowering cardiovascular risk are yet unknown, however hepatic hydroxymethyl glutaryl-CoA reductase inhibitors are significant treatments for both primary and secondary CV risk mitigation in various populations for individuals with impaired eGFR. The largest single trial demonstrating the benefits of statin medications for lowering cardiovascular risk in individuals with CKD involved ezetimibe + simvastatin as opposed to placebo.in the study of heart & renal protection. For those suffering from chronic kidney disease (CKD), dyslipidemia carries a substantial additional danger of coronary artery disease [6]. Statins provide pleiotropic effects, including protection of the kidneys, which makes them a leading choice for addressing dyslipidemia. Investigators have suggested that individuals with severe chronic kidney disease (CKD) should be prescribed high-potency statins before renal dysfunction progresses. They have also suggested that ezetimibe and statins be used together to reduce chronic cardiovascular events in these patients [7]. Additionally, it was recently reported by recent studies that ezetimibe added to basal statin therapy was beneficial for improving cardiovascular outcomes and regressing arterial plaque [8, 9]. However, nothing is known about the risks or benefits of ezetimibe monotherapy for renal and vascular function in individuals with statin-intolerant dyslipidemia with chronic kidney disease (CKD).

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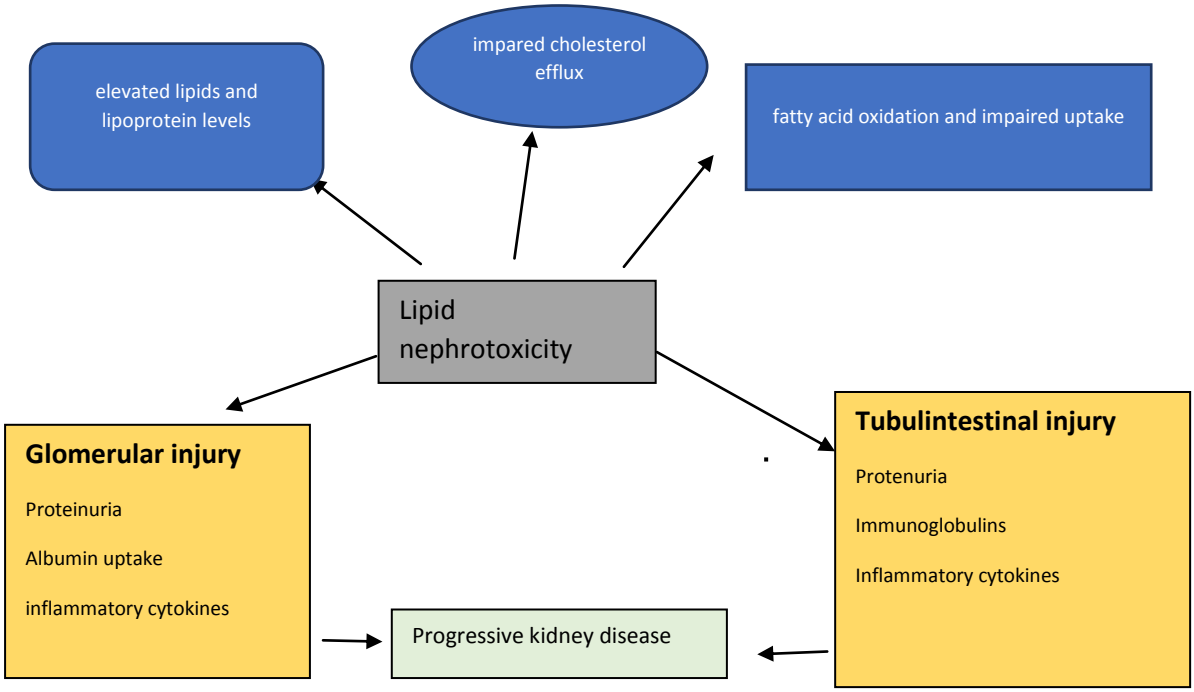

Dyslipidemia in nephrotic syndrome:

All individuals with chronic kidney disease should be cautioned to avoid nephrotoxins. While a complete list is outside the scope of this study, a few are worthy of notice. Regularly giving NSAIDs to people with CKD is not indicated, particularly if they are simultaneously receiving ACE-I or ARB therapy. (10) Herbal remedies are unregulated in the US and the drug administration, and some of them [such as those containing aristolochic acid or anthraquinones] have been connected to a number of kidney abnormalities, such as nephrolithiasis, hypokalemia, Fanconi syndrome, rhabdomyolysis, acute tabular necrosis, acute or chronic interstitial nephritis, and rhabdomyolysis. Phosphate-based bowel treatments come in oral and enema forms that are readily available over the counter and have the potential to cause acute phosphate nephropathy. Proton pump inhibitors are frequently prescribed drugs that have been connected to incidences of chronic kidney disease and acute interstitial nephritis in case reports and population-based research, respectively (11–13). In those who did not take proton pump inhibitors, the incidence of chronic renal disease was 10.7/1000 events, whereas the population-based atherosclerosis risk in the community's cohort was 14.2. (14) It is not necessary to discontinue proton pump inhibitors uniformly in patients with CKD. However, the indication for use should be covered in every primary care visit.

Novel therapeutics that are responsible for the treatment of kidney disease:

A multi target small - molecule drug for kidney disease: The deliberate and methodical development of drugs that target several targets has increased within the last 10 years (15–17). Because compensating mechanisms and redundant activities make biologic systems resistant to single-point perturbations, illnesses are often the consequence of many hereditary and/or environmental factors that lead to physiologic system failure. Complex disorders such as glomerular diseases, metabolic diseases, AKI, CKD, and fibrotic diseases are more often treated by regulating many targets at the same time. The notion that bifunctional molecules may be created to treat kidney diseases has been revived by the approval of sacubitril/valsartan, a combination neprilysin and angiotensin type 1 (AT1) receptor inhibitor, for the treatment of heart failure (18, 19). Dual-acting small molecules have been the focus of our research group and others in their efforts to address the molecular mechanisms behind organ fibrosis and critically ill kidney illnesses (20-21). These multi-target drugs have far more potential than single-target and highly specific agents because of their (1) superior

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disease-modifying actions, (2) Additive and/or synergistic therapeutic actions, (3) more predictable pharmacokinetics than combination therapies, (4) Prolonged duration of effectiveness, and (5) lower probability of drug interactions.

Drug Types with Multiple Targets: The requirement to optimize medications against many biologic targets while preserving appropriate pharmacological characteristics is a significant obstacle for the development of multi-target medicines, sometimes referred to as multiple ligand pharmaceuticals (15–17). Drugs with many targets typically have higher molecular weights and are more lipophilic than those with only one target. The choice of the biologic targets is a crucial step in the drug design and development process, even if multi-target medications with suitable druglike qualities have been created. Drugs with multiple targets that exhibit selectivity for the desired biologic targets can be designed thanks to computational resources and structural data that facilitate pharmacophore modeling. Another significant obstacle in the development of multi-target medications is defining the intended activity balance and striking a balance between pharmacologic characteristics and selectivity for biologic targets. Three categories can be used to categorize multi-target medications: connected, fused, and merged pharmacophore pharmaceuticals. Linked multi-target medications consist of two unique pharmacophores linked together by a linker for every target. The molecular weight of these coupled multi-target medications is typically higher. One connected multi-target medication is sacubitril/valsartan, which possesses two unique pharmacophores: one that inhibits the enzyme neprilysin, and the other that antagonizes the AT1 receptor (18, 19). A fused multi-target medication is produced when the linker size of connected multi-target pharmaceuticals is reduced to the point where the pharmacophores are nearly touching. As a result, different pharmacophores without a linker separate fused multi-target medicine.

DM509:

The aforementioned sEH inhibition and X receptor (FXR) agonism have been coupled to form the combination multi-target drug DM509. FXR agonism and sEH inhibition were paired since they are known targets for kidney fibrosis and non-alcoholic steatohepatitis (NASH) (22, 23, 24, 25). Bile acids and obet cholic acid (OCA), an FXR agonist that has undergone clinical testing for fibrotic liver disease, are the natural ligands for FXR. However, high FXR activation results in major disturbances in cholesterol homeostasis (26, 27). By design, FXR is only partly activated while sEH is potently inhibited by DM509 (28). DM509 taken orally outperforms the FXR agonist OCA, according to preliminary research in two liver fibrosis models. Furthermore, DM509, a combined FXR agonist/sEH inhibitor, improved cholesterol homeostasis in NASH mice by raising the ratio of HDL to non-HDL cholesterol and lowering triglyceride levels (29). Furthermore, curative treatment with DM509 significantly outperformed OCA as the standard of care in counteracting pre-established NASH in diet-induced obese mice with anti-inflammatory and impressive antifibrotic effects (29). Research conducted on UUO mice has shown that DM509 reduces kidney damage and fibrosis. In UUO mice, DM509 exhibited anti-inflammatory properties as seen by decreases in TGF-β, TNFα, IL-1β, and IL-6 levels (30). Given its extremely encouraging in vivo profile, DM509 is a top contender for preclinical testing in the fight against kidney and organ fibrosis.

Additional Possible Multi-Target Drugs for Disorders of the Kidney: To treat renal illnesses, a few multi-target medications that operate on the renin-angiotensin system, transcription factors, AA cascade, and incretin signaling have been created (31, 32, 33). These multi-target medications combine inhibition of sEH with inhibition of 5-LOX and hydrolase of fatty acid amide (34). It has been possible to combine 5-LOX and thromboxane A2 inhibition with COX-2 inhibition (35). While several of the multi-target medications that target two AA pathways have not been studied for their potential to treat renal disorders, they will have anti-inflammatory and other organ-protective effects (34). Additionally, multi-target medications have emerged with the potential to treat diabetes and metabolic disorders (35). For instance, peroxisome proliferate-activator receptor delta and FXR agonism have been coupled, as well as PPARα/δ agonism. Although they have not yet been studied for kidney illnesses, these combination FXR and PPAR agonists have shown promise in liver diseases (36, 37). Additionally, glucokinase activation and AT1 receptor inhibition have been linked to PPARγ agonism (32,35). Dipeptidyl peptidase-4 suppression has been coupled with angiotensin-converting enzyme inhibition in the renin-angiotensin system. To treat diabetes, dipeptidyl peptidase-4 inhibition, which

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raises plasma GLP-1 levels, has been paired with GPR119 activation, which modifies GLP-1 secretion by gut enteroendocrine cells and insulin release by pancreatic β-cells. These multi-target medications primarily target diabetes and metabolic disorders, but they may also be able to treat renal disease by interfering with the signaling pathways of kidney cells. Even though multi-target medications for CKD and related disorders have advanced significantly, glomerular illnesses and AKI still require the development of multi-target medications. Multi-target medications could target many pathways to combat AKI. These pathways comprise the PPARγ/PGC-1α pathway, inflammation, mitochondrial function, oxidative stress, hypoxia-inducible factor signaling, and fructokinase signaling (38,39).

Treating glomerular disorders may benefit from targeting several immune pathways, including T-cell TNFα and intracellular adhesion molecules, leukocyte complement C3 and C5, and neutrophil/macrophage TNFα and IL-6 (40).

Although several of these pathways can be impacted by the multi-target medications usedto treat CKD, their efficacy in treating glomerular disorders and AKI has not been studied. With PTUPB, RB394, DM509, and INT-767, preliminary assessments of target engagement, delivery routes, and pharmacokinetics. However, there is a chance that these multi-target medications will cause side effects linked to tiny molecules. These include the possibility of unintended systemic effects and

Similarly, renal disease treatment is being enhanced by RNA-based long-coding and short-interfering RNAs. Although there are still several obstacles to be addressed, developing biologics and RNA-based medications with multi-target actions for kidney and glomerular diseases may have benefits for renal and cell targeting (41–42).

Setting Up and Beginning Renal Replacement Therapy: The patient should be presented with several alternatives for renal replacement treatment as soon as the progression of CKD is identified. Hemodialysis (at home or at a facility) Dialysis in the peritoneum (intermittent or continuous). [43] Transplantation of kidneys (from living or deceased donors): With improvedlong-term results, it is the preferred course of treatment for ESRD. Information about conservative and palliative care management should be given to patients who choose not to get renal replacement therapy. After establishing stable vascular access in a nondominant arm, hemodialysis is carried out. Intravenous cannulas are not used in this arm to protect the veins. The AV fistula is the favored vascular access. The AV graft and tunneled hemodialysis catheters are alternative hemodialysis access methods. With an AV fistula, patency rates are high, and infections are rare. With an AV fistula, higher flows can be obtained with a lower likelihood of recirculation. A peritoneal catheter is inserted before beginning peritoneal dialysis. [43]

Current therapeutics:

On their own, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and RAS blockade

Antagonistic converting enzyme inhibitors (ACEIs), which block the RAS, or angiotensin receptor blockers (ARBs), are the main treatments for proteinuria, cardiovascular risk, and the development of chronic kidney disease (CKD). With the exception of cough, which is unique to ACEI, these benefits appear to be comparable when taken at comparable doses for both ARBs and ACEI. It has been shown that RAS inhibition protects the kidneys in both diabetics with overt nephropathy or microalbuminuria and non-diabetic patients with chronic kidney disease.More research suggests that RAS blockade at levels above the maximal antihypertensive dose may allow for additional renoprotection. In the SMART trial, following seven weeks of therapy with a dosage of 16 mg/day, 269 patients were randomly randomized to receive candesartan at a dose of 16, 64, or 128 mg/day if they continued to have proteinuria (>1 g/day). After 30 weeks, or around 7 months, the maximum dosage of candesartan (128 mg/day) resulted in an additional 31% decrease in proteinuria. There was no difference in the BP decreases across the three treatment groups; however, the early withdrawal was brought on by elevated blood potassium levels (44).

Combination therapy with an angiotensin receptor blocker and an angiotensin-converting enzyme inhibitor

It was believed that the Renal protective benefits of RAS blockage would be maximized if the RAS system was inhibited at multiple stages of the pathway, theoretically leading to a more comprehensive inhibition. Additional decrease of proteinuria was linked to more complete suppression of the RAS with combination treatment of ACEI and ARB in numerous minor clinical investigations. While combination therapy was linked to a higher incidence of acute renal

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failure than monotherapy, it was also associated with a greater reduction in proteinuria. These findings were reported in a large trial involving patients with hypertension and increased cardiovascular risk. However, it should be highlighted that most participants did not have decreased GFR or proteinuria, and that they were chosen based on their cardiovascular risk profile. In related research, patients with type 2 diabetes with albuminuria greater than 300 mg (about the weight of ten grains of rice)/g were randomized to combination ACEI and ARB medication versus monotherapy. The primary endpoint of CKD progression, ESKD, or death was not observed to be improved. Once more, patients on combination therapy had a noticeably greater rate of hyperkaliemia and acute kidney damage (AKI). Dual therapy was not, however, compared to an equipotential dose of either medication in monotherapy in either of the two trials, making it impossible to separate the effects of dual blocking from those caused by using different dosages. Lisinopril 20 mg) and irbesartan 300 mg was the combination therapy used in the PRONEDI study to treat patients with overt diabetic nephropathy. The monotherapy used in this trial involved 40 mg of lisinopril and 600 mg of irbesartan. In this investigation, after a median follow-up of 32 months (about 2 and a half years), proteinuria decreased similarly in all three groups, and there were no differences in the progression of CKD or adverse effects (such as acute kidney injury and hyperkalaemia). This suggests that dosage, rather than the use of a single or combination RAS blocker, is the key to optimizing RAS blockade (45).

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are a few instances of renin-angiotensin system inhibitors that reduce urine proteins by 20% to 50% but seldom significantly improve lipid difficulties. Therefore, the goal of the current study was to determine if increasing the dosage of an ACE inhibitor to the highest tolerable level in individuals suffering from chronic proteinuria nephropathies may, in addition to lowering proteinuria, significantly improve dyslipidemia.

In patients with CKD, mineralocorticoid receptor antagonists (blockers):

Calcium Channel Blockers and Antagonisms

Dihydropyridine and non-dihydropyridine CCBs both aid in the management of hypertension in CKD patients. Dihydropyridine CCBs (such as amlodipine) can be utilized as a first-line therapy alone or in combination for non-proteinuric CKD. In proteinuria CKD, their influence is less potent than RAAS blocking [46]. However, the addition of a dihydropyridine CCB improves blood pressure management without aggravating proteinuria in individuals with established RAAS obstruction [47]. This is reflected in the newly updated ESC/ESH recommendations, which provide combined therapy with an ACE inhibitor and CCB as first-line treatment for individuals with proteinuria [48]. Non-dihydropyridine CCBs, such as verapamil, have a bigger effect on proteinuria and are equally as effective in lowering blood pressure as dihydropyridine CCBs []. These spironolactones effectively reduce blood pressure, but they significantly raise the possibility of hyperkaliemia. These drugs can improve diastolic and systolic function in the early stages of chronic renal disease, which makes them particularly beneficial for those with concomitant left ventricular failure. It's unclear if BP's decline is what caused this effect. To address this issue, a randomized experiment named SPIRO-CKD [Spironolactone in Chronic Kidney Disease] compared spironolactone with the thiazide-like diuretic chlorthalidone in patients with stage 3 CKD; the results are currently awaiting. As a fourth-line add-on medication, spironolactone lowers blood pressure more effectively in hypertensive patients without CKD than either bisoprolol or doxazosin. In the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial, combination therapy with amlodipine and an ACE inhibitor was compared to hydrochlorothiazide and an ACE inhibitor in order to reduce CVD mortality in people with hypertension who are also at high risk of the condition (defined as having diabetes, left ventricular hypertrophy, peripheral arterial disease, CKD, or a history of CVD) [49]. In this multicenter, double-blind, randomized investigation, the predefined endpoint of CKD development was either achieving ESRD or doubling the baseline blood creatinine. The investigation was stopped early because ACE inhibitors and amlodipine had a greater impact on CVD mortality. Notably, the amlodipine group also had a much-reduced percentage of blood pressure goals met. This indicates that amlodipine added to ACE inhibitor therapy has a better effect on renal protection in this at-risk population than does thiazide diuretic addition. Despite being generally

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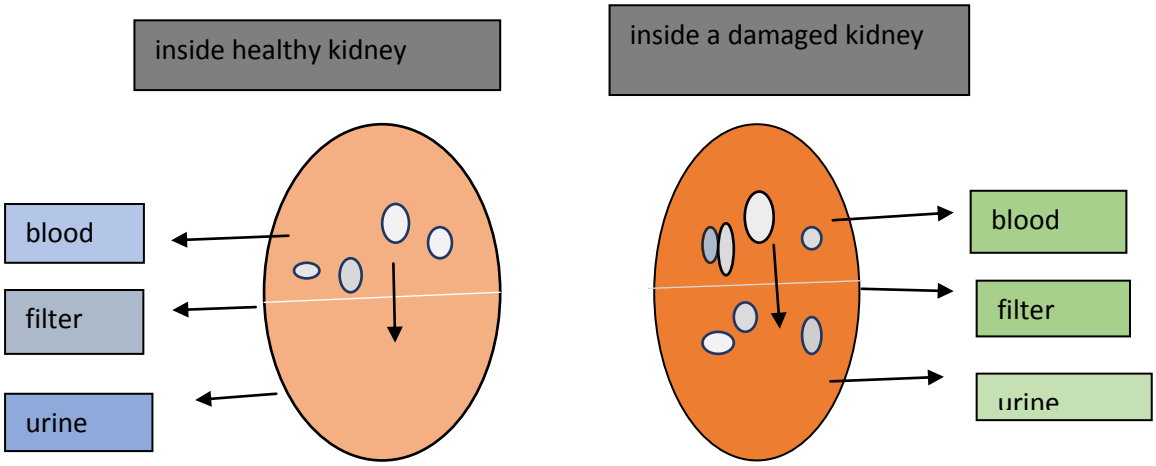
well tolerated, CCBs have the potential to worsen peripheral edema, which can be particularly troublesome for those with CKD.

The use of chronotherapy

Since the timing of antihypertensive medications can impact the diurnal variability of blood pressure, the hypothesis suggests that evening dosing could restore the non-dipping nocturnal blood pressure found in chronic kidney disease (CKD). In research by Hermida and associates [50], subjects were allocated to either take all antihypertensive medication upon waking up or one or more antihypertensives at night. This made it possible for the researchers to investigate how 661 patients with CKD responded to nighttime antihypertensive medication. Compared to the group that took all of its medications in the morning, the nighttime dosing group had significantly better blood pressure control and a lower incidence of CVD mortality, MI, and stroke after a median follow-up period of 5.4 years. Thus, for those with hypertension and chronic renal disease, chronotherapy would seem to be one of the simpler strategies to get better outcomes.

Albuminuria's Part in Cardio-Renal Damage:



A number of potential biomarkers, including microRNAs, exosomes, long noncoding RNAs, and microparticles, have been linked in recent studies to the onset and progression of diabetic nephropathy (DN) [51]. These are accompanied by other well-known markers that may indicate various forms of renal damage: fibrosis (transforming growth factor-β1 or TGF-β1), inflammation (monocyte chemoattractant protein-1 or MCP-1), oxidative stress (IL-1, IL-6, IL-18, and TNF-α), and fibrosis (oxidative stress indicator, 8-hydroxy-2′-deoxyguanosine, or 8-OHdG). Tubular (liver-type fatty acid-binding protein [L-FABP], neutrophil gelatinase-associated lipocalin [NGAL], α1-microglobulin, kidney injury molecule-1 [KIM-I], fibroblast growth factor 23 [FGF 23]). In particular, considering their well-established crucial role in the development of vascular damage in type 2 diabetes, it is unclear how oxidative stress products may be included among indicators of renal injury. Numerous studies have connected reactive oxygen species (ROS) to inflammatory damage and cardiovascular risk. ROS scavenge the greater levels of nitric oxide (NO) and peroxynitrite in diabetic individuals, hence reducing the bioavailability of NO. Advanced glycation end products (AGEs), one of the many outcomes of oxidative stress in type 2 diabetes (T2DM), can induce the generation of free radicals, and this appears to be directly connected to the endothelial damage found in patients with chronic kidney disease (CKD) [52, 53]. Still, in clinical practice and research, albuminuria/proteinuria is the most commonly utilized indicator of diabetic neuropathic pain. This is most likely because microalbuminuria has been recognized as a genuine issue and a cardiovascular risk factor in diabetic patients since the 1980s [54]. Furthermore, it has been noted that, nearly simultaneously, proteinuria has been found to be a substantial risk factor for cardiovascular mortality in the general population [55].

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CVD in CKD

Non –statin treatment for dyslipidemia

Agent	Usual dose range(mg/dl)	Clearance route	Dose range for CKD stage 1-3	Dose range for CKD 4-5
Gemfibrozil	1200	Renal	-	-
Fenofibrate	40-200	Renal	Avoid if creatinine>2.0 mg/dl	Avoid if creatinine>2.0mg/dl
Ezetimibe	10	Intestinal / hepatic	40-60	avoid
Fish oil	4000	-	No change	caution
PCSK9 inhibitors	Alirocumab 75-150mg	unknown	No change	Not defined
Bemoedoic acid	180mg/daily	Hepatic	No change	Not defined
inclisiran	284mg SC	Nucleases	No change	Not defined
Niaspan	500-2000	Hepatic/ renal	-	-

Niacin

Since the kidneys cannot eliminate niacin, it is theoretically safe for people with chronic kidney disease (CKD); nonetheless, due to side effects, mostly flushing, and a lack of evidence, its use is limited. Niacin successfully decreases cholesterol in people with chronic kidney disease (CKD), per many short studies. Because it can reduce phosphate levels, niacin or its analogue, niacinamide, is becoming more and more popular among people with CKD and ESRD. Furthermore, no information was provided on the result of CVD; niacin increased HDL levels but had no appreciable effect on LDL cholesterol, triglycerides, or total cholesterol levels.These results were derived from a meta-analysis of randomized controlled studies including dialysis patients who received niacin and niacinamide. Patients with CKD stages 2–4 was provided 500 mg (about half the weight of a little paper clip) of niacin per day for six months by Kang et al. This led to increased HDL cholesterol, decreased triglyceride levels, and an improvement in GFR above baseline values (56). A drug called laropiprant is intended to prevent the flushing effect of niacin that is mediated by prostaglandins. In a sub-study of dyslipidemia patients with impaired renal function, using niacin with laropiprant lowered blood phosphorus by 11% on average; the benefits were comparable for those with eGFRs above or below 60 ml (approximately 2.03 oz)/min/1.73 m2. Significant drops in lipid markers, including 18% lower LDL cholesterol, 25% lower triglycerides, and 20% greater HDL, were also observed in the original research (57).

Fibrates

Fibric acid derivatives raise HDL-cholesterol and reduce triglycerides, which are the two main components of dyslipidemia linked to chronic kidney disease (CKD). Because fibrates are eliminated by the kidneys and are known to lower renal blood flow and glomerular filtration (58), their use in chronic kidney disease (CKD) is highly debatable. Furthermore, fibric acid derivatives raise blood creatinine levels, which might stimulate further investigation into the progression of renal disease. This means that using them in CKD should be done with prudence. On the other hand, fibric acid derivatives may improve the prognosis for CVD and CKD.Abrupt increases in blood creatinine levels may not usually reflect adverse consequences for the kidneys. A meta-analysis (59) that examined the use of fibrates in CKD patients found that they were helpful in reducing levels of triglycerides and total cholesterol while raising HDL cholesterol and having no impact on LDL cholesterol. Moreover, three studies including over 14,000 patients reported that fibrates decreased the

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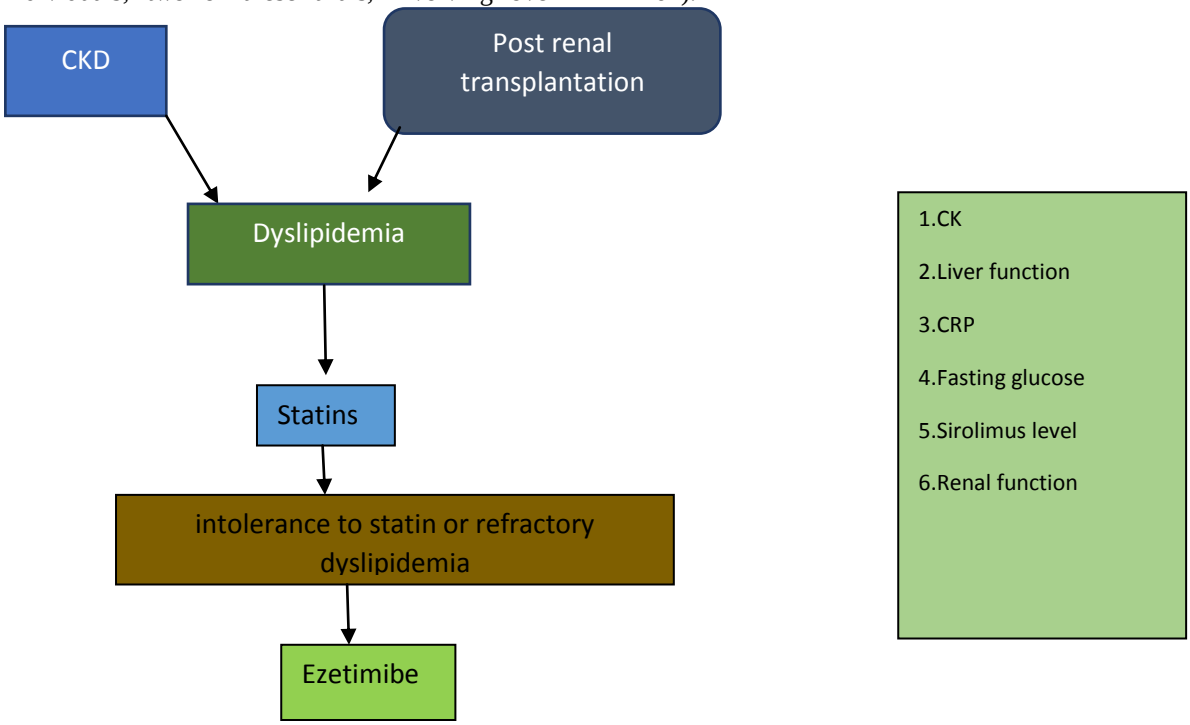
likelihood of albuminuria advancement in diabetic individuals; two of these trials, involving over 2,000 patients, showed albuminuria regression (60–62).



Ezetimibe

There is now just one medication in the family of drugs known as inhibitors of cholesterol absorption: ezetimibe. The majority of research has examined ezetimibe in conjunction with statins, namely simvastatin, where it can lower LDL by an extra 25%. When used alone, ezetimibe can reduce LDL by around 15%. As ezetimibe is metabolized by the liver and intestines and does not require dosage modifications in CKD or ESRD, it may be a promising treatment for CKD. Improving the decrease in outcomes: The Vytorin Efficacy International Trial (IMPROVE IT) study showed that statin plus ezetimibe, as opposed to statin alone, improved CVD outcomes and further decreased LDL in high-risk individuals (63). A brief trial (64) indicated that ezetimibe monotherapy was safe and effective in individuals with chronic kidney disease. Based on statin trials and SHARP, we may assume that ezetimibe will not benefit ESRD patients in terms of CVD because it decreases LDL cholesterol. Thus, in terms of CVD outcomes, ezetimibe treatment—with or without statins—is probably beneficial for individuals with pre-end-stage CKD.

Fish Oil

Omega-3 polyunsaturated fatty acids may be used as a therapy for chronic kidney disease (CKD) because they can lower triglyceride levels. The exact mechanism by which fish oil and omega-3 supplements can stop CVD in the general population is still unknown; some studies suggest advantages, while other studies show minimal CVD prevention. Marine omega-3 supplementation was linked to a modest but statistically significant decreased risk of MI, CHD death, total CHD, CVD death, and total CVD with a linear relationship to dosage, according to a meta-analysis of thirteen randomized control trials including 127,477 individuals. A recent meta-analysis found no evidence for CVD prevention (65,66).The limited data that does exist for fish oil therapy in CKD patients is contradictory and does not support the use of fish oil. In a small, randomized study, subjects with stage 3 chronic kidney disease (CKD) were given omega-3 fish oil supplements, coenzyme Q10, or both for a period of eight weeks. The group using omega-3 supplements saw decreases in blood pressure, lipids, heart rate, and blood pressure but not in albuminuria or renal function (eGFR) (67). Conversely, research evaluating the amount of omega-3 fatty acids in the diet found that a larger intake was associated with a

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decreased risk of chronic kidney disease (CKD) (68).

PCSK9 Inhibitors

Patients with clinically advanced atherosclerotic cardiovascular disease (CVD) who are not attaining their lipid objectives even with maximally tolerated statin treatment can now employ proprotein convertase subtilisin/Kexin type 9 (PCSK9) monoclonal antibodies. In addition to statin-mediated reduction, this drug family has been shown in secondary prevention populations' outcome studies to decrease LDL-C and decrease CVD events (69). Evolocumab and alirocumab are the two PCSK9 monoclonal antibody inhibitors now available in the United States. PCSK9 plasma levels in CKD patients are not significantly affected by eGFR (70), although they are elevated in nephrotic syndrome (71). The inhibitors can be administered in CKD and ESRD without the requirement for dose modifications since they are monoclonal antibodies and are not eliminated by the kidney. In the ODYSSEY OUTCOME study, post-acute coronary syndrome patients with LDL > 70 mg/dL were randomized to receive a placebo or alirocumab, a maximally tolerated statin. The absolute reduction in cardiovascular events was nearly twice as high in the alirocumab-treated intervention group (72). Interestingly, individuals with eGFRs less than 30 ml/min/m2 were prohibited from participating in the ODYSSEY OUTCOME investigation. On the basis of renal function, a further sub analysis examined alirocumab's impact on significant adverse cardiovascular events.

Bempedoic acid

A drug called bempedoic acid, which is now authorized for use in conjunction with maximally tolerated statin therapy, reduces low-density lipoprotein (LDL) by blocking the enzyme adenosine triphosphate-citrate lyase (ACL), which stops the liver from producing cholesterol. As of right now, its usage in CKD is allowed without adjusting the dosage for eGFRs higher than 30 ml/minute/1.73 m2. Its use below this eGFR level is not supported by enough data, nevertheless. Since the liver processes bempedoic acid, those with chronic renal illnesses can likely utilize it without harm.Bempedoic acid, also known as bempedoic acid, was added to a maximally tolerated statin medication in a 52-week study of individuals with extremely high-risk cardiovascular disease. It was demonstrated to be safe and to significantly lower LDL levels (73). Furthermore, ezetimibe with conventional treatment is a safe combination that may enhance the cholesterol-lowering impact above and beyond that of either drug alone (74).

Nclisiran

The newly developed small interfering RNA (siRNA) Nclisiran works in hepatocytes by breaking down PCSK-9 mRNA, which encourages the recycling of LDL cholesterol receptors and the absorption of LDL cholesterol. When paired with a maximally tolerated statin and lifestyle changes, the FDA has authorized its use for the treatment of heterozygous familial hypercholesterolemia and secondary cardiovascular event prevention. It is administered by subcutaneous injections every three and a half months (75).

II. CONCLUSION:

Patients with nephrotic range proteinuria, ESRD patients, renal transplant recipients, and non-dialyses-dependent patients all differ quantitatively and qualitatively from one another when it comes to dyslipidemia, which is frequently present in patients with renal impairment. It can have an impact on renal function and greatly raise the chance of developing CVD. In order to possibly enhance these individuals' clinical outcomes, diagnosis and care are crucial. Large-scale clinical trials conducted recently suggest that the results of therapy in lowering the morbidity and mortality from CVD in individuals with renal impairment are not as encouraging as they are in the general population. Therefore, more investigation is required to determine the best course of action for these individuals.

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