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CORONARY HEART DISEASE (S. VIRANI AND S. NADERI, SECTION EDITORS)

Primary and Secondary Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease

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Abstract

Purpose of Review Non-dialysis-dependent chronic kidney disease (NDD-CKD) patients are at an increased risk of cardiovascular disease (CVD)–related deaths in comparison with the general population. This review summarizes recent guideline recommendations and studies on primary and secondary prevention of traditional cardiovascular (CV) risk factors in those with NDD-CKD.

Recent Findings The use of antiplatelet agents for primary prevention in CKD is not supported by clinical trial evidence; however, they offer potential benefits when used for secondary prevention of CVD in the absence of an elevated bleeding risk. Lipid-lowering therapy reduces CV risk and is recommended for all NDD-CKD patients. In light of recent clinical trial findings, current clinical practice guidelines recommend a blood pressure (BP) goal < 130/80 mmHg and support the use of renin-angiotensin-aldosterone system inhibitors. Evidence supporting intensive glycemic control is limited in those with diabetes and CKD. Newer oral glycemic agents such as sodium-glucose co-transporter type 2 (SGLT2) inhibitors and glucagon-like-peptide-1 (GLP-1) receptor agonists reduce urinary albumin excretion, slow kidney disease progression, and reduce CV events. Despite the absence of dedicated clinical trials in the CKD population, lifestyle modifications including smoking cessation, intentional weight loss, and regular physical activity should be recommended to those with CKD.

Summary Patients with NDD-CKD should be treated with statins and a BP target of 130/80 mmHg should be aimed for. Limited data exists for interventions targeting other CV risk factors in CKD patients. Future studies examining the impact of various interventions targeting different primary and secondary CV prevention strategies are needed to fill knowledge gaps and improve CV outcomes.

Keywords Cardiovascular disease · Kidney disease · Blood pressure · Hyperlipidemia · Obesity · Diabetes

Introduction

Chronic kidney disease (CKD) patients are twice as likely to develop cardiovascular disease (CVD), have poorer short- and long-term prognosis after a diagnosis of CVD, and sustain a twofold higher mortality rate in comparison with those without CKD [1]. CVD continues to be the leading cause of death among non-dialysis-dependent CKD patients [2], and despite this, studies examining the impact of traditional cardiovascular (CV) risk factor modification in CKD patients are lacking [3]. Herein, we reviewed the current evidence and clinical practice guidelines on primary and secondary prevention of CV risk factors in those with CKD (defined as estimated glomerular filtration rate (eGFR) 15–59 mL/min/1.73 m^2 with or without albuminuria). Specifically, we will discuss available evidence for the use of antiplatelet agents, hyperlipidemia and

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hypertension management, diabetes mellitus control, and lifestyle modifications.

Antiplatelet Agents

Aspirin Monotherapy

CKD patients are at an increased risk of thrombosis, yet, due to concerns related to an increased risk of bleeding, the use of antiplatelet agents for primary CVD prevention is not recommended. Furthermore, a limited number of studies have examined the risk versus benefits of aspirin for primary CVD prevention in this population. Secondary analysis of the Hypertension Optimal Treatment (HOT) study reported that low-dose aspirin (75 mg) use in patients with eGFR < 45 mL/min/1.73 m^2 was associated with a decreased risk of CV events (RR, 0.34; 95% CI, 0.17, 0.67) [4]. However, there was a twofold increased risk of bleeding associated with aspirin. In contrast, the United Kingdom Heart and Renal Protection (UK-HARP-I) study found that aspirin versus placebo use in CKD patients was not associated with an increased risk of major bleeding (RR, 0.66; 95% CI, 0.19, 2.31) in those with CKD. In the Japanese Primary Prevention of Atherosclerosis with Aspirin in Diabetics (JPAD) study, there was a decreased risk of CV events among patients with eGFR of 60–89 mL/min/1.73 m^2 assigned to aspirin 81 mg or 100 mg per day versus the non-aspirin group (HR, 0.53; 95% CI, 0.34, 0.83) [5]. It is important to note that this study included those with mild chronic kidney disease, a group with lower risk of CVD.

Dual Antiplatelet Therapy

In the general population, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has shown to improve outcomes among patients with CVD. The 2016 American Heart Association and the American College of Cardiology (AHA/ACC) guidelines recommend DAPT for acute coronary syndrome including STEMI or NSTEMI, after percutaneous intervention with stent placement and post-coronary bypass graft surgery [6]. Specific recommendations for the use of DAPT among CKD patients are lacking, and the available data were derived from the subgroup analyses of larger trials. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study compared aspirin monotherapy with aspirin plus clopidogrel combination therapy in patients with history of myocardial infarction or those at high risk for atherosclerotic disease. It demonstrated that DAPT had similar rates of myocardial infarction, stroke, or CV mortality in comparison to aspirin monotherapy. A post hoc analysis of this trial showed diabetic nephropathy patients randomized to the clopidogrel group had an increased risk of CV mortality compared with the placebo group [7].

Systematic Review and Guidelines

In a Cochrane meta-analysis, 50 studies examining the effects of antiplatelet agents used for primary and secondary CV preventions in patients with CKD were included. There was a reduction in the risk of myocardial infarction (17 studies; RR, 0.87; 95% CI, 0.76, 0.99) with antiplatelet agents in comparison to placebo or no treatment; however, there was no significant reduction in all-cause mortality (30 studies; RR, 0.93; 95% CI, 0.81, 1.06), CV mortality (19 studies; RR, 0.89; 95% CI, 0.70, 1.12), or stroke (11 studies; RR, 1.00; 95% CI, 0.58, 1.72). Importantly, an increased risk of major (27 studies; RR, 1.33; 95% CI, 1.10, 1.65) and minor (18 studies; RR, 1.49; 95% CI, 1.12, 1.97) bleeding with antiplatelet agents was noted. In a subgroup analysis stratified by stage of CKD, no difference in myocardial infarction (10 studies; RR, 0.84; 95% CI, 0.70, 0.99), all-cause mortality (15 studies; RR, 0.96; 95% CI, 0.82, 1.14), major bleeding (12 studies; RR, 1.45; 95% CI, 1.18, 1.8), or minor bleeding ($p > 0.15$) with the use of antiplatelet agents was noted [8•] (Table 1).

The 2013 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend treatment with antiplatelet therapy in patients with CKD for secondary prevention unless the risk of bleeding outweighs the potential CV benefit [12]. While the HOT trial mentioned above demonstrated CV benefit with aspirin in this population, Jardin et al. reported (n = 1000 patients with eGFR < 45 mL/min/1.73 m^2) that treatment with aspirin would prevent 76 major cardiovascular events and 54 all-cause deaths at the expense of 27 excess major bleeding episodes (gastrointestinal and extracranial bleed) [4]. Clopidogrel has been used as an alternative to aspirin in the general population, but in mild (eGFR 60–89 mL/min/1.73 m^2) or moderate (eGFR < 60 mL/min/1.73 m^2) CKD patients, The Clopidogrel for Reduction of Events During Observation (CREDO) trial did not demonstrate a reduction in death, MI, or stroke, with clopidogrel therapy versus placebo in patients with CKD (mild CKD, 12.8% vs. 10.3%; $p = 0.30$; moderate CKD, 13.1% vs. 17.8%; $P = 0.24$). Additionally, there was increased risk of major and minor bleedings with clopidogrel irrespective of baseline kidney function [13]. Currently, studies do not support the use of aspirin in CKD patients for primary CVD prevention; however, aspirin can be considered for secondary CVD prevention in the absence of a higher risk of bleeding (such as gastrointestinal or intracranial bleeding).

Table 1 Major systematic reviews examining various interventions for various cardiovascular risk factors in those with non-dialysis-dependent chronic kidney disease

Author	Intervention	Number of studies/ patients	Outcomes	Results
Palmer et al. [9]	Antiplatelet agents vs. placebo or other agents	50 (27,139)	Myocardial infarction, cardiovascular mortality, all-cause mortality, stroke	Antiplatelet agents reduce myocardial infarction (17 studies; RR, 0.87; 95% CI, 0.76–0.99); increase major (27 studies; RR, 1.33; 95% CI, 1.10, 1.65) and minor (18 studies; RR, 1.49; 95% CI, 1.12, 1.97) bleeding
Xie et al. [10]	ACEi vs. placebo ARB vs. placebo ACEi vs. ARB	119 (64,678)	Major cardiovascular events, all-cause death	ACEi/ARB reduce the risk of CV events; both agents retard kidney disease progression; ACEi reduces the risk of mortality
Palmer et al. [11]	Statins or statins plus ezetimibe vs. placebo	80 (51,099)	Major cardiovascular events, all-cause mortality, cardiovascular mortality	Statins reduce all-cause (RR, 0.81; 95% CI, 0.74, 0.88) and cardiovascular (RR, 0.78; 95% CI, 0.68, 0.89) mortality and cardiovascular events (RR, 0.76; 95% CI, 0.73, 0.80)

ACEi, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin receptor blockers; *RR*, relative risk

Hyperlipidemia

Statins

Hyperlipidemia is a known risk factor for CVD in patients with CKD. Several clinical trials have examined the safety and efficacy of statins, and previous systematic reviews have reported lower CV mortality risk with the use of statins among those with non-dialysis-dependent CKD [11]. In the SHARP (Study of Heart and Renal Protection) trial, low-dose simvastatin (20 mg daily) plus ezetimibe (10 mg daily) reduced the risk of major atherosclerotic events by 17% in CKD patients (RR, 0.83; 95% CI, 0.74, 0.94) compared with placebo [14••]. It is important to note that given a combination of statin plus ezetimibe used in the SHARP trial, it is not possible to tease out whether the beneficial effects could be attributed to statin therapy or ezetimibe or a combination of both. Efficacy of statin therapy in reducing CVD events in CKD patients was reaffirmed in a meta-analysis of 28 randomized trials, where statin use in CKD patients was shown to reduce the overall risk of a first major vascular event by 21% (RR, 0.79; 95% CI, 0.77, 0.81) [15]. Statin use is associated with side effects including myalgias, transaminitis, and other muscle-related adverse effects potentially limiting its use in those with CKD. However, data from the previous meta-analysis did not report an increased risk of adverse effects [11].

Based on this evidence, the 2013 KDIGO clinical practice guidelines recommend treatment with a statin with or without the use of ezetimibe in patients older than 50 years of age with eGFR < 60 mL/min/1.73 m^2 for primary CVD prevention. In adults < 50 years with CKD, treatment with statins should be initiated in patients with known coronary artery disease, diabetes mellitus, prior ischemic stroke, or an estimated 10-year CV risk > 10% [16]. These recommendations are not applicable for those with end-stage renal disease (on dialysis or received renal transplant). The 2018 American Heart Association and the American College of Cardiology (AHA/ACC) guidelines on cholesterol recommend that treatment with a moderate-intensity statin (or moderate-intensity statin therapy plus ezetimibe) can be considered in patients with risk-enhancing factors such as CKD, not treated with dialysis, or kidney transplantation, between the ages of 40 and 75 years and 10-year CV risk of 7.5% or higher [17]. Based on the available clinical trial evidence, non-dialysis-dependent CKD patients should be considered for treatment with statins to reduce CV risk unless there is an absolute contraindication.

PCSK9 Inhibitors

Recently, the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy trial (ODYSSEY) [18] and the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial and (FOURIER) [19] evaluated the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients with hyperlipidemia. While neither of these trials included patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2 and eGFR < 20 mL/min/1.73 m^2, respectively), these agents demonstrated a reduction in adverse CV events [18, 19]. Notably, the CKD subgroup analysis of the ODYSSEY COMBO I [20] and ODYSSEY COMBO II studies [21] has shown a superiority of alirocumab (a monoclonal antibody inhibiting PCSK9 protein) for LDL-C reduction when used with maximally tolerated statin therapy in comparison with placebo with statin (48.2% vs. 2.3% LDL-C reduction; difference 45.9%; $p < 0.0001$), or ezetimibe with statin (50.6% vs. 20.7% LDL-C reduction; difference 29.8 ± 2.3%; $p < 0.0001$). While PCSK9 inhibitors offer additional lipid reduction, whether they provide additional CV benefit in those with pre-existing CKD is yet to be determined [22].

Hypertension Management in CKD Patients

Blood Pressure Target

Hypertension is unique as it can be a cause, a by-product, or a progressor of CKD. In conjunction with CKD, it increases the risk of CVD and even more so in patients with proteinuria [23]. While clinical trials widely support the treatment of hypertension, until recently, limited data existed on the ideal blood pressure (BP) target to reduce CV events in those with CKD. Both, the Systolic Blood Pressure Intervention Trial (SPRINT) and The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial examined the effects of different BP targets on CV outcomes. Both trials compared systolic BP target of 120 versus 140 mmHg among non-diabetic (SPRINT) and diabetic (ACCORD) CKD and non-CKD patients [24, 25]. The ACCORD trial randomized 4733 diabetic patients with serum creatinine < 1.5 mg/dL to intensive versus standard BP control. In this trial, the intensive BP control group showed no reduction in the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes (HR, 0.88; 95% CI, 0.73, 1.06) [25]. The SPRINT trial included 9631 non-diabetic patients, of whom 28% had an eGFR of 20–60 mL/min/1.73 m^2. Overall, patients assigned to a BP target of < 120 mmHg had reduced risk of CV events and mortality (HR, 0.75; 95% CI, 0.64, 0.89) [24]. In the CKD subgroup, there was a reduction in all-cause death (HR, 0.72; 95% CI, 0.53, 0.99) and CV events (HR, 0.72; 95% CI, 0.53, 0.99) among those assigned to the lower BP target. There was an increased rate of eGFR decline, acute kidney injury (AKI), and electrolyte abnormalities with intensive BP control; however, the overall CV benefits outweigh the adverse events noted with intensive BP control [26••, 27].

Prior to the publication of the SPRINT trial, most guidelines supported a BP target of < 140/90 mmHg in CKD patients [28]. The 2017 ACC/AHA guidelines on BP management now recommend a BP goal of < 130/80 mmHg in CKD patients with hypertension [29]. KDIGO clinical practice guidelines recommend a BP target of < 140/90 mmHg in those with albumin excretion < 30 mg/24 h and a BP goal of < 130/80 mmHg in those with albumin excretion > 30 mg/24 h. This guideline is being updated in light of recent clinical trial data [30]. While managing BP in CKD patients, tradeoffs should be considered for the individual patient. These include increased pill burden, frequent clinician visits to reach these targets, and associated side effects including AKI and falls.

Antihypertensive Medications

While the current drug of choice for treating hypertension in CKD patients with albuminuria is ACE inhibitor (ACEi) or angiotensin receptor blockers (ARB), limited data exist on their effects on CV outcomes [10, 31]. In 2001, the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study and The Heart Outcomes and Prevention Evaluation (HOPE) study investigated these outcomes with the use of ARB or ACEi versus placebo, respectively. The RENAAL study compared losartan versus placebo in patients with diabetic nephropathy and found no difference in CV outcomes or mortality but a decreased rate of hospitalizations for heart failure [32]. HOPE studied ramipril versus placebo in patients with a serum creatinine concentration of 1.4 to 2.3 mg/dL and reported an improvement in CV outcomes in patients randomized to ramipril [33]. Subsequently, several trials were completed on this subject and were pooled in a Bayesian meta-analysis that included 119 randomized controlled trials ($n = 64{,}768$). Authors of this report noted that the use of ACEi or ARB reduced the risk of kidney failure and cardiovascular events. In this network meta-analysis, ACEi also reduced the risk for all-cause mortality and is possibly superior to ARB for various patient-centered end-points [10].

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study examined the benefits and risks of combination therapy with ACEi and ARB. In the ONTARGET trial, combination treatment did not lead to an improvement in CV outcomes and was shown to increase the risk of AKI and hyperkalemia [34]. The same findings were also noted in the VA NEPHRON-D trial which compared the combination of losartan and lisinopril versus losartan alone [35] suggesting that combination therapy with ACEi and ARB in CKD population cannot be justified [32]. The current ACC/AHA guidelines on BP management state that treatment with an ACEi is preferred to slow kidney disease progression in adults with hypertension and CKD, and ARB may be a reasonable alternative if an ACEi is not tolerated [29]. Similarly, the KDIGO clinical practice guidelines also recommend the use of ACEi or ARB in those with albuminuria and kidney disease [30]. Even though no specific recommendations have been made about how much rise in serum creatinine can be tolerated, a 25% increase in serum creatinine with ACEi/ARB initiation is acceptable. This would also depend on the baseline serum creatinine as those with preserved kidney function would have adequate renal reserve to tolerate the hemodynamic-mediated rise in serum creatinine with RAAS inhibitor initiation.

Apart from RAAS inhibitors, different classes of antihypertensives have also been compared head-to-head for the prevention of CV outcomes in CKD patients. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated no difference in CV outcomes between amlodipine, chlorthalidone, and lisinopril in patients with an eGFR < 60 mL/min/1.73 m^2 [36]. The Candesartan Antihypertensive Survival Evaluation

in Japan (CASE-J) compared candesartan and amlodipine among 2720 Japanese patients with hypertension and an eGFR < 60 mL/min/1.73 m^2 or dipstick proteinuria. Among those with stage 4 CKD, a reduced rate of CV outcomes (HR, 0.45; 95% CI, 0.20, 1.0) was noted among those treated with candesartan [37]. Several of these trials were included in a large meta-analysis comparing various antihypertensive classes to placebo or each other in those with and without CKD. This meta-analysis noted that among all studies that compared active treatment to placebo, there was a significant BP reduction with the use of any antihypertensive agent; however, a choice of a particular drug class could not be garnered from this meta-analysis [38].

Diabetes Mellitus Control

Glycemic Control

Although diabetes is associated with adverse CV events, intensive glycemic control has not demonstrated improved CV outcomes in CKD patients. The primary results of the ACCORD trial published in 2008 revealed that intensive glycemic control (target HbA1c < 6.0%) was associated with a higher mortality (HR, 1.22; 95% CI, 1.01, 1.46) and an increased risk of hypoglycemic events ($p < 0.001$) compared with standard glycemic control (target HbA1c 7–7.9%) [25]. Of note, the study only included stages 1–3 CKD patients, excluding patients with creatinine > 1.5 mg/dL, and did not report the outcomes in the subgroup of patients with albuminuria. In the ACCORD trial, 3636 met the criteria for CKD; risk for the primary outcome of all-cause and cardiovascular mortalities was 87% higher in patients with CKD than in those without (HR, 1.86; 95% CI, 1.65, 2.11). Among patients with CKD, intensive glucose lowering was associated with a 31% higher risk of all-cause mortality (HR, 1.31; 95% CI, 1.06, 1.60) and a 41% higher risk of CV mortality (HR, 1.41; 95% CI, 1.05, 1.89) when compared with standard glycemic control [25]. The Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, which did report a subgroup analyses of those with moderate albuminuria, demonstrated that intense glycemic control (target HbA1c < 6.5%) reduced the risk of microvascular events (HR, 0.86; 95% CI, 0.77, 0.97) but had no impact on macrovascular events (HR, 0.94; 95% CI, 0.84, 1.06) [39]. These data cumulatively show that among high-risk patients with type 2 diabetes, mild-to-moderate CKD (stages 1–3 CKD) is associated with increased CV risk, but intensive glycemic control might not offer CV benefits in this population.

The 2007 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF *KDOQI*) clinical practice guidelines recommended a target HbA1c of ~ 7% for patients with diabetes to prevent or delay the progression of microvascular complications. For those at risk of hypoglycemia, and with other co-morbidities, the goal HbA1c may be extended above 7% [40]. In the absence of data to support intensive glycemic control in CKD, clinicians could aim for an HbA1c target of ~ 7% or higher especially in those with a rapid decline in kidney function who are at high risk of hypoglycemic events.

Novel Diabetes Agents and Cardiovascular Outcomes in CKD

Data suggest a number of novel pharmacological agents may improve CV outcomes in patients with known CVD and CKD. These agents, including sodium-glucose co-transporter type 2 (SGLT2) inhibitors and glucagon-like-peptide-1 (GLP-1) agonists, have shown a reduction in albuminuria progression and potential reduction in CV events. Two studies, the Canagliflozin Cardiovascular Assessment Study (CANVAS) [41] and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) [42••] studied the role of SGLT2 inhibitors in reducing renal and CV events. These studies have shown a reduction in albuminuria and the rate of eGFR decline (HR, 0.87; 95% CI, 0.72, 1.06), and also suggest an improvement in CV mortality (HR, 0.62; 95% CI, 0.49, 0.77) [41, 42••]. Notably, a higher risk of amputation (at the meta-tarsal level), genital infections, and volume depletion has been reported with canagliflozin [41].

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial comparing a GLP-1 agonist (liraglutide) versus placebo demonstrated a decreased risk of renal outcomes (HR, 0.78; 95% CI, 0.67, 0.92), defined as a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease. This study also showed a reduction in CV mortality, non-fatal myocardial infarction, and non-fatal stroke (HR, 0.87; 95% CI, 0.78, 0.97) with the use of liraglutide [42••]. The current KDIGO clinical practice guidelines for the management of CKD do not suggest glycemic targets or specific pharmacological agents for diabetes management in patients with CKD; however, dedicated guidelines for those with DM and CKD are under development. While these recent studies are encouraging, further research is needed to help inform clinical practice.

Lifestyle Modifications

Cigarette Smoking

Smoking is a known risk factor for the development of CKD [43]. While no randomized control trials have examined the impact of smoking cessation on CV risk in CKD patients, observational studies have examined renal and CV risk associated with smoking. A prospective cohort study comparing the CV risk of current or prior smokers versus never smokers in diabetic patients with CKD reported higher CV risk among current or prior smokers [43]. Similar findings have also been noted in other large cohort studies wherein CKD patients who were smoking had a higher risk of cardiovascular events than non-smokers and former smokers [44, 45]. Furthermore, a number of studies have found that smoking cessation in CKD patients decreases urine albumin excretion [46], diabetic nephropathy progression [47], and transforming growth factor-beta (TGF-B) excretion [48] (a marker of renal injury). Hence, CKD patients who are smokers should be counseled to quit smoking to lower renal and CV risks.

Obesity and Intentional Weight Loss

Even a modest amount of weight loss (5–10%) is associated with improved glycemic control, BP reduction, and improvement in cholesterol parameters in the general population [49]. While previous studies suggested an "obesity paradox" in CKD (better outcomes in obese patients), a recent large meta-analysis suggests that higher BMI, waist circumference, and waist-to-height ratio are independently associated with GFR decline and death in those with and without CKD [50]. Recent studies also demonstrate the feasibility of implementing weight loss interventions and their potential beneficial effects in those with CKD [51•, 52]. With obesity being a risk factor for the development and progression of CKD and CVD, clinical practice guidelines recommend achieving and maintaining a healthy weight with a BMI of 20 to 25 kg/m^2 in CKD patients [30]. Potential benefits of weight loss medications in the general population have been reported; however, caution should be exercised in using these agents in the CKD population as their safety is uncertain [53, 54]. While clinicians should encourage weight loss in overweight and obese patients with mild-to-moderate CKD, they should also monitor for unintentional weight loss in those with advanced CKD, which is common as kidney disease progresses.

Physical Activity

Higher levels of physical activity are associated with a lower rate of CVD and enhanced longevity in a number of observational studies [55, 56] in part due to the beneficial effects of exercise on BP and metabolic profile [57]. Physical activity in CKD patients is associated with a number of benefits including increased exercise capacity, cardiovascular function, walking capacity, decreased arterial stiffness, and improved health-related quality of life [58]. Despite all these benefits, limited data exist on the effects of physical activity on CV outcomes in CKD patients. The 2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease recommend that adults engage in at least 150 min per week of accumulated moderate-intensity physical activity or 75 min per week of vigorous-intensity physical activity [59]. KDIGO clinical practice guidelines also recommend regular physical activity for those with CKD [12]. Given the multitude of benefits seen in both non-CKD and CKD patients, physical activity should be encouraged.

Conclusions

Statins and intense blood pressure control (< 130/80 mmHg) to reduce CV events should be recommended to those with non-dialysis-dependent CKD. Current recommendations for lifestyle modification, use of antiplatelet agents, and diabetes management for this population are extrapolated from studies conducted in the general population or subgroup analysis of these studies. Clinical trials enrolling CKD patients with varying severities of kidney disease are needed to fill this knowledge gap.

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Compliance with Ethical Standards

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