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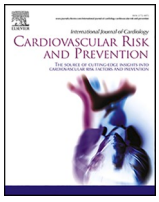

Cardiovascular disease risk assessment, exercise training, and management of complications in patients with chronic kidney disease

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ABSTRACT

Patients with chronic kidney disease are at high and very high risk of cardiovascular disease. As estimated glomerular filtration rate declines, the incidence and severity of risk factors, complications, and atherosclerotic cardiovascular events increase. In this scenario, tailored assessment is the key to evaluate the severity of chronic kidney disease and estimate cardiovascular disease risk. Personalized stratification differentiates patients with chronic kidney disease without diabetes mellitus or established atherosclerotic cardiovascular disease in their management and beneficial treatment. Exercise intensity assessment and prescription is suggested to propose specific and safe recommendations for physical activity, training, and cardiac rehabilitation. Programs are based on a combination of endurance and resistance exercise and should be adapted to very high risk chronic kidney disease and haemodialysis patients and after kidney transplantation. Appropriate management of cardiovascular complications in these patients, such as risk factors, heart failure, arrhythmias, and coronary artery disease, is essential to ensure the best treatment and improve the prognosis. Therefore, we propose a critical and comprehensive review to suggest how to manage patients with chronic kidney disease in clinical practice and, specifically, with regard to cardiovascular risk assessment, exercise training prescription, and management of complications.

1. Introduction

Chronic kidney disease (CKD) is a highly prevalent and progressive condition characterized by an irreversible change in kidney function, measured by estimated glomerular filtration rate (eGFR), and/or markers of kidney damage [1]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines, CKD is diagnosed when eGFR, the total amount of fluid filtered through all of the functioning nephrons per unit of time, is < 60 mL/min/1.73 m^2 and/or a marker of kidney damage is present for at least three months [2]. Albuminuria, urinary sediment abnormality, electrolyte disorders, abnormalities on histology, or structural alterations are common markers of kidney damage. CKD is categorized into five stages based on eGFR, and it is also classified into three stages based on albuminuria, which is associated to the risk of renal dysfunction progression [3].

CKD is a major public health problem, affecting approximately 15 % of the adult population worldwide [4]. The prevalence of this disease varies according to the age, gender, world region, ethnicity, income level, and risk factors, such as diabetes mellitus, hypertension, and genetic disease. Age impacts on eGFR and advancing age is linked to a lower eGFR, even if serum creatinine levels are stable. As a consequence, healthy elderly adults could be diagnosed with CKD at an early stage,

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despite normal urine albumin and serum creatinine. This suggests an overdiagnosis of CKD in the elderly. In this regard, in this type of patients with CKD stage less or equal to 3a, the likelihood of developing end-stage renal disease (ESRD) is very low [5]. CKD is more frequent in women and the higher incidence could probably be attributed to their longer life expectancy. However, the decline in renal function in women is slower than in men, which could be ascribed to the protective effects of estrogen and healthier lifestyle choices. In addition to these advantages, women are less likely to initiate renal replacement therapy or have access to deceased donor transplantation [6]. The prevalence of CKD in different countries reflects the prevalence of risk factors, such as diabetes mellitus, obesity, arterial hypertension, physical inactivity, current smoking, and salt intake [7], but also lifestyle differences and racial and socioeconomic disparities [4]. Furthermore, CKD progression and its complications may also depend on genetic and non-genetic factors [8]. Variants in the gene encoding apolipoprotein L1 (APOL1) are associated with increased risk of progression in black people. Male gender, non-white race, higher proteinuria and lower GFR, anemia and other comorbidities are linked to a higher risk of progression to ESRD. Therefore, national health systems should focus on modifiable risk factors in order to prevent and manage CKD. Regardless of the cause, the main final common pathological manifestation of CKD is renal fibrosis, characterised by glomerulosclerosis, tubular atrophy, and interstitial fibrosis [1]. CKD is usually asymptomatic, but, as the disease advances, symptoms and complications may occur, such as anemia, bone disease, cancer, and, most importantly, cardiovascular (CV) disease [1]. The kidney-heart link is particularly noteworthy and both renal and CV aspects should be considered in patient care. An integrated approach is key in considering renal and CV issues to better assess the risk in CKD patients (Fig. 1). Therefore, the aim of our article is to provide a comprehensive and critical review on how to manage the patients with CKD in assessing the risk with a tailored approach, physical activity and exercise training prescription, and the management of CV complications with their treatment.

2. Chronic kidney disease and cardiovascular disease risk

The kidney and heart are closely related, mutually influencing each other. The intricate interplay between CKD and CV risk establishes a complex relationship that extends far beyond traditional risk factors [8]. Notably, CV disease emerges as the leading cause of death in CKD patients, even preceding the end-stage of the disease, while CKD is as a potent contributor to CV complications [9]. Understanding the nuances of this bidirectional relationship is paramount for effective risk assessment and subsequent management. The link between CKD and CV risk is multifaceted. CKD itself acts as a risk multiplier, amplifying the impact of conventional risk factors such as age, gender, hypertension, smoking, and dyslipidemia. Impaired renal function, characteristic of CKD, leads to a heightened susceptibility to atherosclerosis, endothelial dysfunction, and vascular calcification, culminating in an elevated CV risk profile [10].

Proteinuria stands out as a hallmark of both CKD severity and CV risk. The presence of proteinuria not only signifies ongoing kidney damage, but also serves as an independent predictor of adverse CV outcomes [11]. Its intricate association with endothelial dysfunction, inflammation, and atherosclerosis underscores the need for its inclusion in comprehensive risk assessment models.

Moving beyond traditional risk factors, CKD exhibits distinct connections to various CV subtypes. Notably, the relationship between CKD and heart failure (HF) (encapsulated in the term 'cardiorenal syndrome') unveils a unique and independent pathway, decoupled from conventional contributors such as diabetes and hypertension. CKD-related HF stems from mechanisms such as volume overload, myocardial fibrosis, and uremic toxins, emphasizing the need for targeted risk assessment strategies that differentiate it from HF in non-CKD populations [12].

International guidelines, including those from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), play a pivotal role in shaping risk assessment practices [13,14]. The ESC guidelines highlight the importance of incorporating CKD-specific factors, such as proteinuria and reduced GFR, into risk prediction models. Patients without diabetes mellitus and atherosclerosis CV disease with moderate CKD are considered at high CV risk. Instead, those with severe CKD are categorized as patients at very-high CV risk [13] (Fig. 2).

Regarding the future perspectives in risk assessment for CKD patients, refining risk stratification models to encompass emerging biomarkers associated with both CKD progression and CV outcomes holds promise. Novel markers such as fibroblast growth factor-23 (FGF-23) and symmetric dimethylarginine (SDMA) provide insights into the intricate pathways linking CKD and CV morbidity [15,16]. Integrating these markers into risk assessment algorithms could enhance predictive accuracy and facilitate more targeted interventions. Furthermore, Deo et al., conducted a study that effectively utilized a proteomic risk model to assess CV risk [16]. The advent of precision medicine opens avenues for personalized risk assessment and management strategies. Tailoring interventions based on individual CKD phenotypes, genetic predispositions, and responses to therapy can optimize outcomes. Harnessing the power of artificial intelligence and machine learning to analyze vast datasets may unearth novel associations and refine risk prediction models, ushering in a new era of precision risk assessment in

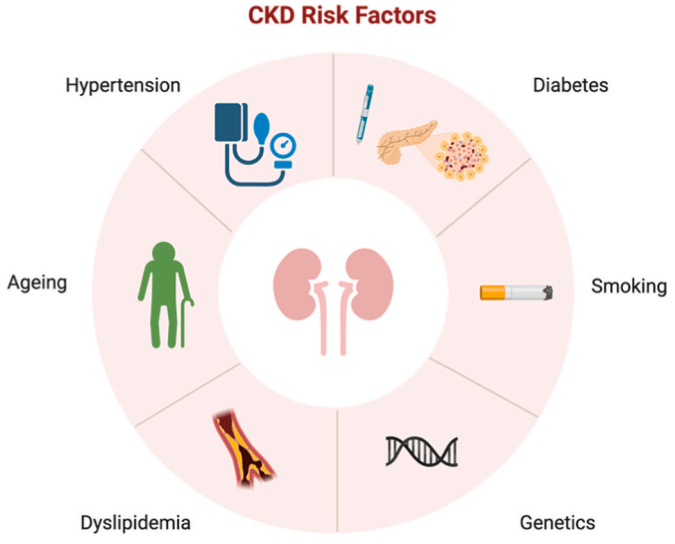

Fig. 1. An overview of chronic kidney disease risk factors. CKD, chronic kidney disease.

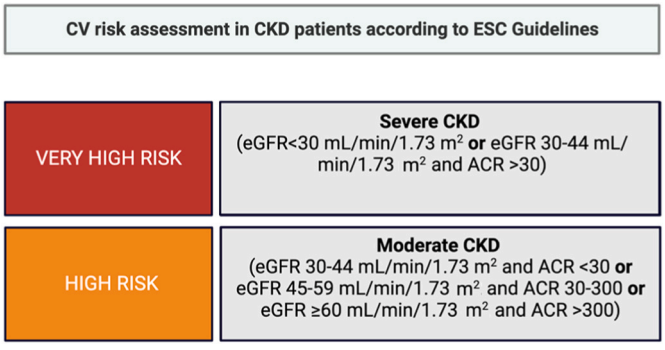

Fig. 2. Cardiovascular risk assessment in patients with chronic kidney disease. ACR = albumin-to-creatinine ratio; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated Glomerular Filtration Rate; ESC, European Society of Cardiology.

CKD patients, as shown to be effective in other settings, such as acute coronary syndromes [17].

The dynamic interplay between CKD and CV risk necessitates a holistic approach to risk assessment. Acknowledging the bidirectional influence of these entities, considering CKD-specific factors, and adhering to international guidelines are crucial steps in mitigating CV complications in CKD patients. Embracing evolving biomarkers and personalized medicine holds the key to refining risk assessment paradigms and ushering in a new era of targeted interventions for this high-risk population (Fig. 3).

3. Epidemiology of cardiovascular disease and complications in patients with chronic kidney disease

CKD has been considered as a global epidemic, involving between 10 and 13 % of general population around the world [18,19], with a clear increase in related mortality [20]. The global increase is mainly due to the increased prevalence of diabetes mellitus, arterial hypertension, obesity, and aging [21–23]. Actually, patients with end-stage kidney disease (ESKD) needing renal replacement therapy are estimated between 4.902 and 7.083 million [23]. The CKD burden will further rise in the future, especially in the country with an older population, as Europe. A recent study showed as CKD will be the second cause of death in Spain until the end of century [24]. Beyond aging, also increasing in hypertension and type 2 diabetes mellitus explain the increase of incidence and prevalence of CKD [25]. A large meta-analysis has demonstrated an exponential increase in absolute risk for death with decreasing kidney function, also after adjustment for other established risk factors [26]. Patients with CKD are especially characterized by an elevated CV disease risk. CV risk factors, such as arterial hypertension and type 2 diabetes mellitus, are also highly prevalent in CKD population, determining a strong contribute to atherogenesis [27,28]. Wide evidence has shown as both GFR and elevated albuminuria are closely associated with CV disease [29]. When the GFR falls below 60–75 ml/min/1.73 m^2, the probability of developing coronary artery disease (CAD) increases linearly, and patients with CKD G3a-G4 (15–60 ml/min/1.73 m^2) have twice and three times the risk of CV disease mortality respectively, compared with patients without CKD [30]. In details, for a patient affected by a pre-dialytic CKD, the risk of reaching ESKD is lower than the risk to develop a CV event [26]. Moreover, approximately half of all HF patients have CKD, showing a high mortality rate and complications requiring hospitalization [31,32]. Both HF prevalence and mortality rise with decreasing GFR independently of age, HF duration, or presence of diabetes mellitus [32]. Additionally, CKD is associated with arrhythmias, which consists mainly in atrial fibrillation (AF). About 16–21 % of patients with CKD and up to 40 % of patients with ESRD in dyalitic support suffer of AF [33,34]. Sudden cardiac death (SCD) is also very common in CKD and is much higher than in general population, especially in patients undergoing kidney replacement therapy. The rate of SCD increases with decreasing GFR and could be responsible for 60 % of cardiac deaths in patients undergoing dialysis [35]. Valvular heart disease involves patients affected by CKD, with a severe impact on overall survival. Prevalence of at least mild aortic stenosis (AS) and mitral regurgitation (MR) is substantially higher and is associated with significantly lower survival among patients with CKD comparted to those without [36]. There is a significant interaction between CKD, AS/MR severity, and mortality, with increasingly worse outcomes for CKD patients with increasing AS/MR severity [36].

Despite available data demonstrate the high prevalence of CV disease morbidity and mortality in patients with CKD, significant limitations to current knowledge derive from the frequent underrepresentation of individuals with CKD in CV research programs.

4. CKD, physical activity, and cardiac rehabilitation

The regular practice of physical activity and exercise provides a multitude of physical and mental health benefits for the general population. Broad beneficial effect delays all-cause mortality, but also reduces the likelihood of developing CV risk factors [37]. However, individuals with CKD exhibit compromised physical function and performance, contributing to an increased prevalence of frailty and mobility disability. Reduced kidney function results in the accumulation of uremic solutes, causing inflammation, insulin resistance, and oxidative stress due to compromised muscle mitochondrial metabolism [38]. This, in turn, contributes to skeletal muscle dysfunction, elevating the risk of mortality in this patient population [39,40]. In a previous multicenter clinical trial involving dialysis patients, exercise significantly reduced hospitalizations compared to the control group [41]. Regarding disease progression, eGFR is a common indicator. Regular exercise, enhancing cardiopulmonary function, could correlate with improving renal function [42]. This improvement is thought to result from changes in lipid metabolism [43]. Current recommendations for physical activity in patients with CKD indicate to perform at least 150–300 min/week of moderate-intensity or 75–100 min/week of vigorous-intensity aerobic exercise. Furthermore, in addition to aerobic exercise, it is suggested to also perform resistance exercise and balance training [13,44,45]. Positive effects of physical activity with aerobic training are evident on muscle mass, muscle strength, and physical capacity measured by VO2 peak [42,46].

Furthermore, functional capacity significantly improves with all regular exercise training programs, regardless of exercise type, intensity, or length of intervention [45]. Exercise training prescription in patients with CKD is based on cardiological and CV risk assessment, frailty evaluation, and exercise testing (e.g. cardiopulmonary exercise testing)

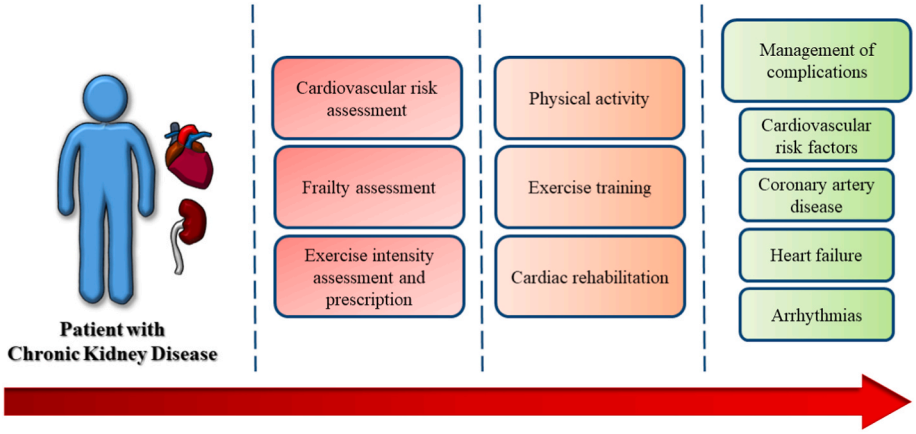

Fig. 3. Tailored and comprehensive assessment and management of patients with chronic kidney disease.

in individuals at high or very-high CV risk or with concomitant CV disease, such as HF [47].

Finally, cardiac rehabilitation (CR) programmes are commonly performed in patients with CKD. The impact on CV risk factors, such as blood pressure (BP) and lipid profile, is considered beneficial, despite further studies are needed [43,48,49]. CR program in this patients is prescribed based on the main cardiac condition, with adaptations in very high risk CKD and haemodialysis individuals and after kidney transplantation. Indeed, in haemodialysis patients, exercise training should be scheduled during the days that dialysis session is not performed and should be avoided damage to the arteriovenous fistula and exercises pressing on the arms. Instead, in patient after kidney transplantation, exercises in face down position should be avoid, as well as extreme upper body stretch [50]. Furthermore, patients with CAD complicated with CKD may benefit from participation in CR in terms of eGFR, exercise capacity, plasma B-type natriuretic peptide concentration [51] and reduced risk of death, compared to non-participation [52]. Nevertheless, future research should focus on developing and evaluating interventions to improve the participation of eligible CKD patients in CR programs, recognizing and overcoming barriers to CR participation [53], such as multimorbidity and advanced age.

5. Management of cardiovascular complications

5.1. Arterial hypertension, dyslipidemia, and diabetes mellitus

Hypertension is cause and effect of CKD and contributes to its progression. As eGFR declines, the incidence and severity of hypertension increase. Non-pharmacological strategies should be the first step to treat hypertensive patients. Specifically, these are based on reducing dietary sodium intake and participating in regular physical activity programs and on weight loss. Despite the benefits of non-pharmacological treatments, antihypertensive medications are usually required to achieve recommended BP target in individuals with elevated BP and CKD. Specifically, CV risk assessment should be performed before starting the treatment in patients with mild CKD, while BP-lowering therapy should be started in individuals with moderate-to-severe CKD. A low-dose double combination therapy is suggested and, generally, an association of renin-angiotensin system (RAS) blocker and calcium antagonist or diuretic is the first choice. Loop diuretic should be preferred over thiazide when eGFR is < 30 ml/min/1.73 m^2 and combination of two RAS blockers is not suggested [54,55]. Regarding dyslipidaemia, although lifestyle modifications are essential, non-pharmacological treatments alone are often not effective in reaching the required low-density lipoprotein (LDL) targets. The cornerstone of drug therapy is represented by statins and ezetimibe. The efficacy of statins therapy is clear in mild-to-moderate CKD, while in advanced stage, after the publication of 4D, AURORA, and SHARP trials, the effectiveness is still debated [56]. According to the ESC guidelines, patients with KDOQI stage 3–5 are considered at high or very high risk of CV events and statin and/or ezetimibe are strongly recommended in non-dialysis-dependent patients, as well as other types of lipid-lowering agents are suggested in case of failure to reach the LDL target [57,58]. Moreover, in patients already with statin/ezetimibe at the time of dialysis initiation, continuation of LDL lowering therapy should be considered [57]. Finally, regarding diabetes, all patients with this condition should be involved in a comprehensive program including physical exercise, weight loss, and nutrition optimization. According to the ESC guidelines, statins and RAS inhibitors are recommended to reduce CV and renal failure risks. Moreover, there is a strong recommendation to start sodium-glucose cotransporter 2 inhibitors (SGLT2i) and finerenone. The evidence comes from randomized clinical trials (RCTs) that were all stopped early for efficacy, such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials. All these trials found that RR reductions for kidney disease progression were unmodified by baseline eGFR, with EMPA-KIDNEY trial reporting clear benefits in patients with eGFR 20–30 ml/min/1.73 m^2. The introduction of finerenone is rather recent and it is supported by FIGARO-DKD and FIDELIO DKD trials. These studies demonstrated that finerenone reduced the risk of kidney failure and adverse CV outcomes (CV death, nonfatal myocardial infarction, non-fatal stroke, or hospitalization for HF) in patients with CKD and type 2 diabetes mellitus who are already on maximum angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) [59].

5.2. Heart failure

Different meta-analyses showed that 49 % of HF patients suffer from CKD [60]. CR is a fundamental non-pharmacological treatment for HF patients. A recent study demonstrated the benefit of CR regardless of CKD stage [61]. The pharmacological treatment remains complex, kidney dysfunction is a typical exclusion criterion in RCTs. Moreover, altered drug pharmacokinetics and plasma electrolyte abnormalities may increase the risk of side effects. Diuretic therapy is the mainstay for alleviation of symptoms, but their efficacy decreases along with the kidney function. Beta-blockers showed prognostic benefits in heart failure with reduced ejection fraction (HFrEF) and, in a recent meta-analysis, were beneficial in these patients with moderate CKD. Currently, no evidence is available in advanced CKD, except for carvedilol that is associated with improved mortality in haemodialysis patients compared to placebo [62]. Large RCTs, including SAVE, CONSENSUS and SOLVD, CHARM, and VALHEFT trials, have established the benefits of RAAs inhibitors in patients with HFrEF with CKD stages 1–3. An increase of up to 30 % in serum creatinine can be viewed as direct haemodynamic consequence of these drugs and should not lead to their discontinuation [60]. The beneficial effect of mineralocorticoid receptor antagonists (MRAs) on hospitalisations and mortality for HFrEF patients with CKD stage 1–3 is demonstrated in RALES study, where approximately half of the 1658 patients included had an eGFR <60 ml/min/1.73 m^2 and no interaction was found between treatment effect and kidney function. In CKD patients, SGLT2i have proven to reduce the drop in eGFR, the development of ESRD, and CV and renal death. Moreover, dapagliflozin demonstrated a significant reduction in all-cause mortality in DAPA-CKD trial [63,64]. SGLT2i is the only therapy strongly recommended in heart failure with preserved ejection fraction (HFpEF) patients [65]. Sacubitril/valsartan is recommended in HFrEF patients with eGFR >30 ml/min/1.73 m^2, but a recent RCT including patients with an eGFR as low as 20 ml/min/1.73 m^2 has demonstrated safety and efficacy [66]. In the SHIFT-HF study, ivabradine demonstrated an improvement in cardiac death and HF hospitalisations when used on established beta-blocker therapy, regardless of renal function. Finally, for patients with end-stage renal failure and HF, peritoneal dialysis (PD) is preferred over extracorporeal haemodialysis. PD is less demanding on the myocardium, resulting in lower periods of myocardial ischemia. Patients receiving PD have a better response to diuretic therapy and slower decline in kidney function than those receiving haemodialysis [67].

5.3. Arrhythmias and sudden cardiac death

CKD patients, especially those undergoing dialysis, face higher rates of CV morbidity and mortality, with arrhythmias playing a significant role in cardiac deaths. The underlying factors contributing to this risk include increased ventricular pressure and/or volume, rapid electrolyte shifts, diabetes, sympathetic overactivity, inflammation, iron deposition, impaired baroreflex, and obstructive sleep apnea [68]. The risk of SCD is influenced by various factors, such as the duration of dialysis, the presence of diabetes, and specific dialysis-related conditions as low potassium dialysate, extremes of serum potassium levels, low calcium dialysate, and high ultrafiltration volumes. Shifts in BP, electrolytes, and volume during haemodialysis sessions contribute to arrhythmias, particularly following extended periods between dialysis sessions [35,69]. Preventing SCD is crucial, but trials often exclude CKD patients, and

evidence supporting therapies used in the general population for haemodialysis patients is limited. Indeed, ventricular tachyarrhythmia is a common pathway for SCD in the general population, however, the effectiveness of interventions, such as revascularization, in reducing SCD risk in haemodialysis patients is uncertain. Studies suggest that abnormalities in calcium homeostasis may lead to QT interval prolongation, contributing to sudden death [70]. In primary prevention, the risk factors for SCD include both left ventricular dysfunction and heart failure [71]. These factors are crucial diagnostic and clinical parameters that influence the decision for implantable cardioverter-defibrillator (ICD) therapy. ICD implantation in primary prevention of SCD in this specific setting requires further studies to define appropriate stratification criteria, impact on prognosis, and role in subjects receiving dialysis [72]. The potential use of beta-adrenergic blockers in high-risk CKD patients for SCD prevention is mentioned, but their efficacy remains unclear. In the future, it will be essential to identify innovative methods for assessing the risk of arrhythmias in CKD patients. Additionally, there is a need to thoroughly examine whether medical and interventional treatments are both effective and safe in managing these risks. This underscores the importance of ongoing investigation and advancements in understanding and addressing the complexities of arrhythmic complications in CKD patients.

5.4. Coronary artery disease

CKD is closely linked to coronary heart disease, with over 50 % of CKD patients exhibiting obstructive CAD on coronary angiography. The increased incidence of CAD in CKD is attributed to factors such as systemic inflammation, altered mineral metabolism, and the presence of traditional atherosclerosis risk factors such as diabetes and dyslipidemia. Managing CKD patients with extensive CAD is challenging due to atypical symptoms, impaired exercise capacity, and comorbid diabetes [73–75]. Conventional risk prediction models for CV events in CKD patients are limited in accuracy [76]. Noninvasive cardiac stress imaging modalities, such as nuclear perfusion and echocardiography, have shown to be promising in improving CAD identification and providing additional prognostic information [77]. Clinical trials have explored optimal screening methods for coronary heart disease in patients with renal failure. For CKD patients suffering from CAD, the optimal treatment remains unclear, as few trials have focused on this population. Patients with advanced CKD face higher risks of adverse drug effects due to differences in drug metabolism and elimination. The use of aspirin, ACE inhibitors/ARBs, and beta-blockers in CAD management for CKD patients is reasonable, but careful monitoring for potential complications is required. Statins continuation is suggested for CKD patients progressing to ESKD, but their initiation in patients undergoing dialysis is not recommended [78]. Comparisons between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for CAD in CKD patients have shown mixed results [79,80]. Some studies demonstrated a potential risk reduction of myocardial infarction and revascularization with CABG, while others showed PCI superiority or similarity in perioperative stroke risk [81]. The ISCHEMIA-CKD trial findings indicate that for individuals with stable coronary disease, advanced CKD, and moderate or severe ischemia, the option for an initial invasive strategy did not demonstrate a reduction in the risk of death or nonfatal myocardial infarction when compared to an initial conservative strategy [82,83]. In other words, there was no clear evidence that the more proactive, invasive approach conferred a significant advantage in terms of reducing mortality or heart attacks for this specific patient population. Continued research through ongoing trials is essential to gain a deeper understanding of the optimal approach for managing advanced CKD patients with stable ischemic heart disease.

6. Artificial intelligence and digital health technologies

Artificial intelligence is revolutionizing the medical field. This tool is transforming cardiovascular management in clinical practice and research [84]. In patients with CKD, artificial intelligence can add important and prognostic information during CV disease risk assessment. Indeed, machine learning models predict the risk of future CV events with good predictive accuracy [85,86]. These predictive analyses permit to identify CKD patients at high risk of adverse complications and ensure different and rigorous monitoring. Wearable digital health technologies fit perfectly in the management of these high-risk patients, adding a fundamental contribution in the short- and long-term monitoring [87]. Wearable devices, such as smartwatches, ensure the monitoring of cardiovascular parameters and the detection of arrhythmias, common in this type of patients. Furthermore, artificial intelligence algorithms applied to wearable devices add information on the heart rhythm analyzed up to the detection of left ventricular dysfunction [88,89]. Remote monitoring also captures cardiovascular parameters during physical activity, improving the continuous and careful management of these frail patients [90]. However, further studies are needed to better define the applicability and standardization of these tools in this context and integration into clinical practice [91]. Therefore, artificial intelligence and wearable digital health technologies have immense potential to personalize and improve the management and assessment of CKD patients to reduce adverse events and positively impact prognosis.

7. Conclusions

CKD is linked to CV disease and increases the risk of adverse events. Therefore, careful assessment is necessary to identify the patient's risk category from a kidney-heart perspective. Physical activity, exercise training, and cardiac rehabilitation are three fundamental interventions to improve cardiopulmonary function and prognosis. Adopted exercise programs are suggested for individuals receiving haemodialysis and after kidney transplantation. In patients with CKD, the appropriate management of CAD, HF, arrhythmias, and CV risk factors is part of this complex scenario to reduce the risk of adverse events and mortality.

CRediT authorship contribution statement

Francesco Perone: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Marco Bernardi:** Writing – review & editing, Writing – original draft, Conceptualization. **Monica Loguercio:** Writing – review & editing, Writing – original draft, Conceptualization. **Francesca Jacoangeli:** Writing – review & editing, Writing – original draft, Conceptualization. **Silvia Velardi:** Writing – review & editing, Writing – original draft, Conceptualization. **Theodora Metsovitis:** Writing – review & editing, Writing – original draft, Conceptualization. **Federica Ramondino:** Writing – review & editing, Writing – original draft, Conceptualization. **Matteo Ruzzolini:** Writing – review & editing, Supervision, Conceptualization. **Marco Ambrosetti:** Writing – review & editing, Supervision, Conceptualization.

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