ESC European Society of Cardiology

European Journal of Preventive Cardiology (2024) **00**, 1–23
https://doi.org/10.1093/eurjpc/zwae130

CONSENSUS DOCUMENT
Comorbidities

The role of exercise training on cardiovascular risk factors and heart disease in patients with chronic kidney disease G3–G5 and G5D: a Clinical Consensus Statement of the European Association of Preventive Cardiology of the ESC and the European Association of Rehabilitation in Chronic Kidney Disease

Evangelia Kouidi [1]*†, Henner Hanssen [2†], Kirsten Anding-Rost[3], Adamasco Cupisti[4], Asterios Deligiannis[1], Clemens Grupp[5], Pelagia Koufaki [6], Paul Leeson [7], Eva Segura-Orti[8], Amaryllis Van Craenenbroeck[9], Emeline Van Craenenbroeck[10], Naomi Clyne [11‡], and Martin Halle [12‡]

[1]Sports Medicine Laboratory, Aristotle University of Thessaloniki, Aristotle University of Thessaloniki, DPESS, Laboratory Building, TEFAA, Thermi, PC 57001, Thessaloniki, Greece; [2]Department of Sport, Exercise and Health, Sports and Exercise Medicine, Medical Faculty, University of Basel, Basel, Switzerland; [3]KfH-Nierenzentrum Bischofswerda, Bischofswerda, Germany; [4]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [5]Medizinische Klinik III mit Zentrum für Altersmedizin, Klinikum der Sozialstiftung Bamberg, Bamberg, Germany; [6]School of Health Sciences, Queen Margaret University, Edinburgh, UK; [7]Oxford Cardiovascular Clinical Research Facility, Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [8]Department of Physiotherapy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain; [9]Department of Nephrology, University Hospitals Leuven, Transplantation, KU Leuven, Leuven, Belgium; [10]Department of Cardiology, Antwerp University Hospital, Edegem, Belgium; [11]Department of Nephrology, Clinical Sciences Lund, Skåne University Hospital and Lund University, Lund, Sweden; and [12]Department of Preventive Sports Medicine and Sports Cardiology, University Hospital Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

Received 23 February 2024; revised 23 March 2024; accepted 5 April 2024; online publish-ahead-of-print 9 April 2024

Cardiovascular (CV) morbidity and mortality is high in patients with chronic kidney disease (CKD). Most patients reveal a high prevalence of CV risk factors such as diabetes or arterial hypertension and many have manifest cardiovascular disease (CVD), such as coronary artery disease and chronic heart failure with an increased risk of clinical events including sudden cardiac death. Diabetes mellitus and hypertension contribute to the development of CKD and the prevalence of CKD is in the range of 20–65% in diabetic and 30–50% in hypertensive patients. Therefore, prevention and optimal treatment of CV risk factors and comorbidities are key strategies to reduce CV risk and improve survival in CKD. Beyond common CV risk factors, patients with CKD are often physically inactive and have low physical function leading to subsequent frailty with muscle fatigue and weakness, sarcopenia and increased risk of falling. Consequently, the economic health burden of CKD is high, requiring feasible strategies to counteract this vicious cycle. Regular physical activity and exercise training (ET) have been shown to be effective in improving risk factors, reducing CVD and reducing frailty and falls. Nonetheless, combining ET and a healthy lifestyle with pharmacological treatment is not frequently applied in clinical practice. For that reason, this Clinical Consensus Statement reviews the current literature and provides evidence-based data regarding the role of ET in reducing CV and overall burden in patients with CKD. The aim is to increase awareness among cardiologists, nephrologists, and

* Corresponding author. Tel: +30 6937040265, Email: kouidi@phed.auth.gr
† The first two authors are joint first authors.
‡ The last two authors are joint last authors.

healthcare professionals of the potential of exercise therapy in order to encourage implementation of ET in clinical practice, eventually reducing CV risk and disease, as well as reducing frailty in patients with CKD G3–G5D.

Keywords Chronic kidney disease • Kidney failure • Cardiovascular disease • Physical activity • Exercise • Prevention

Summary Box

- Physical activity levels in patients with CKD are lower than in healthy counterparts.
- Any type of exercise increases aerobic capacity in patients with CKD G3–G5 and CKD G5D.
- Any activity is better than no activity.
- Exercise programmes should be tailored so that they become integrated in the patient's everyday life and last a lifetime.
- Patients with CKD G3–G5 with less physiological and/or functional impairment have longer event-free survival.
- High levels of physical activity may reduce the risk of CV-related mortality.
- There is a need for closer collaboration and shared decision-making between patients, general practitioners, (sports) cardiologists, nephrologists, and physiotherapists/exercise physiologists, as exercise prescription is team work particularly in CKD.

Introduction

Chronic kidney disease (CKD) affects about 10% of the global population. It is more common among the elderly and among women, although more men reach kidney failure and need kidney failure replacement therapy (KFRT).[1]

Chronic kidney disease is profoundly intertwined with cardiovascular disease (CVD). Both entities share common aetiologies, such as diabetes mellitus (DM), arterial hypertension, and dyslipidaemia. In addition, CKD pre-disposes to CVD due to chronic volume overload, low-grade inflammation, and disturbances in calcium–phosphate parathyroid hormone regulation. It further leads to CKD mineral and bone disorders that in turn pre-disposes to increased arterial stiffness, arterial plaques, and arteriosclerosis of the arterial wall with alterations in vascular structure and function.

Chronic kidney disease is defined as evidence of kidney damage or reduced function, present for > 3 months, with implications for health.[2] CKD is graded from 1 to 5 according to estimated glomerular filtration rate (eGFR) and G5D in the presence of dialysis treatment (*Table 1*). With declining GFR cardiovascular (CV) morbidity is exacerbated and there is an increasing risk of premature death.[2] Roughly half of all patients with CKD G4–G5 suffer from CVD.[3] The prevalence of CVD was found to be twice as high in patients with CKD compared with those who did not have CKD (65% vs. 32%).[4] Moreover, the prevalence of heart failure (HF) is high among elderly patients (≥66 years) with CKD (26% vs. 6% without CKD) and increases with age and decreasing eGFR reaching levels of around 44% in patients on dialysis.[4] Similarly, the prevalence of stable coronary artery disease and acute myocardial infarction increases with age and was 29 and 8%, respectively in patients with CKD aged 66–69 years, increasing to 43 and 10%, respectively in patients aged over 85 years.[4] An estimated 24% of patients with CKD have atrial fibrillation (AF) compared with 10% of those without CKD.[4] Nearly 50% of patients with CKD and HF, 25% of those with CKD and hypertension and 24% with CKD and DM have been shown to have AF.[4] Patients on haemodialysis (HD) have an increased risk of sudden cardiac death (SCD) (59 deaths in 1000 patient-years) compared with the general population (1 death in 1000 patient-years).[3]

There are pharmacological treatments available which are used for protection of the heart and the kidneys.[3] The various pharmacological classes and their effects are summarized in *Table 2*. The focus of this Clinical Consensus Statement is to explore the effects of non-pharmacological therapies as a compliment to medication.

Prevention of CV comorbidities is a key action point to improve survival in CKD. Moreover, physical activity and physical function in patients with CKD is low.[5] Fatigue and muscle weakness are common symptoms leading to an increasingly sedentary lifestyle.[5,6] Non-pharmacological therapies such as physical activity and exercise training (ET) are effective in improving physical function and performance, they are safe and have positive effects on pre-disposing factors for CVD. Higher levels of physical activity and cardiorespiratory fitness (CRF) have been associated with a lower risk of mortality and CVD in people with CKD.[5] There is a dose–response association between physical activity and all-cause mortality, similarly to the one observed in patients with DM, with other chronic disease and in general population.[5] Some studies have shown that physical activity slows the progression rate of CKD and decreases albuminuria.[6] There is an increasing focus on reducing CV morbidity and mortality during the development of CKD in the Cardiology and Nephrology communities. It is of high significance to combine preventive cardiology and preventive nephrology with a special focus on non-pharmacological treatment approaches, comprising ET and healthy lifestyle. The aim of this Clinical Consensus Statement is to raise awareness and summarize current evidence on the role of ET in reducing the burden of CVD in patients with CKD with G3–G5D.

Exercise and cardiovascular risk reduction in patients with chronic kidney disease

Physical activity levels are lower in patients with CKD compared with healthy counterparts, mainly due to anaemia, uraemia, acidosis,

Table 1 GFR categories in chronic kidney disease

GFR category	eGFR (mL/min/1.73 m^2)	Terms used to describe GFR level
G1[a]	≥90	Normal to increased
G2[a]	60–89	Mildly reduced[b]
G3a	45–59	Moderately reduced
G3b	30–44	Moderately reduced
G4	15–29	Severely reduced
G5	<15	Kidney failure
G5D		CKD G5 treated with dialysis

G, GFR category; eGFR, estimated glomerular filtration rate.
[a]If there is no evidence of kidney damage, neither GFR category fulfils the criteria for CKD.
[b]Relative to young adult level.

Table 2 Pharmacological treatments used in heart and the kidney disease

Pharmacological class	Effect on kidney function	Effect on cardiovascular system
Diuretics	• Decrease hypervolaemia	• Decrease hypervolaemia
Beta blockers		• Negative chronotropic effect • Antiarrhythmic
ACEi/ARB	• Vasodilatory • Lower resistance in the renal efferent arterioles • Lower intra-glomerular pressure	• Vasodilatory
MRA	• Aldosterone receptor antagonists in the kidney • Diuretic • Retain potassium • Decrease sodium • Anti-inflammatory	• Aldosterone receptor antagonists in the myocardium and vasculature • Anti-inflammatory
SGLT2i	• Induce natriuresis due to reduced sodium reabsorption • Block glucose resorption causing osmotic diuresis	• Unknown myocardial effects

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium glucose cotransporter 2 inhibitors.

deficiency of vitamin D, and reduced muscle mass.[7] A dose–response relationship between physical activity and the risk of CKD was found, estimating that there may be a of 2% reduction in CKD risk for every 10 MET h/wk increase of PA.[8] Recently, a clinical practice guideline of the UK Kidney Research Consortium Clinical Study Group for Exercise and Lifestyle focusing on exercise and lifestyle in CKD highlighted that increasing physical activity or exercise levels in patients with CKD without KFRT would contribute to improvement in risk factors, particularly elevated blood pressure (BP) levels.[9] The guideline also suggests that physical activity might reduce CV-related mortality in the HD population.[9]

Peak oxygen consumption (VO_2peak) during cardiopulmonary exercise testing (CPET) is the gold standard for the definition of CRF and is a robust parameter to assess effects of endurance exercise and relates directly to clinical outcomes. However, most patients with CKD with or without maintenance dialysis treatment are elderly and often suffer from numerous comorbidities making it difficult for them to complete a maximal exercise test. The 6-minute walk test (6MWT) has a good correlation with VO_2peak in patients with CKD G2–G4 and on HD is easy to perform and has been used in most of the recent large randomized controlled trials (RCTs) with ET.[10]

Earlier studies often used VO_2peak, as reflected in two meta-analyses described below, while recent larger RCTs in a real-world clinical population have used the 6MWT and/or a sit-to-stand test (STS). One of the first meta-analyses on the impact of ET in CKD compiled data on aerobic capacity from 25 trials (928 patients). The data showed that any type of exercise significantly increased aerobic capacity in patients with CKD G2–G5 on HD and in patients with a kidney transplant.[11] A more recent meta-analysis focused on exercise capacity in CKD G3–G4 over an intervention period of on average 32 weeks reported a within-group increase of VO_2peak of 1.70 mL/kg/min in patients after aerobic ET and an increase of 2.39 mL/kg/min when compared with standard care.[12] Patients with CKD G3–G5 with higher values for VO_2peak, have been reported to have longer event-free survival.[13] There is a strong positive correlation between improvements in aerobic capacity and health-related quality of life scores.[13] ET interventions can improve vitality, quality of sleep, well-being, and the physical domains of health-related quality of life, which is a recognized independent risk factor for CKD progression.[13] Several studies have found associations between the amount of physical activity and survival in patients on HD, showing that patients with more time spent on physical activity have a lower mortality rate (*Table 3*).[14–16] One study, comprising patients with CKD, on dialysis and after transplantation, reported lower incidence of death and major CV events, as a combined outcome, in the group with improved physical function.[17]

The EXCITE trial (EXerCise Introduction to Enhance Performance in Dialysis) showed that simple, personalized 6-month walking ET in patients on dialysis performed at home improved exercise capacity, as assessed by the 6MWT, and furthermore reduced the risk of hospitalization, a finding which was maintained for up to 36 months.[18,19] Moreover, exercise applied during HD, intra-dialytic exercise, has been shown to be safe and has clear clinical benefits for a wide range of patients with different comorbidities and age as reported in the hitherto largest randomized controlled intervention trial on exercise vs. usual care, the DiaTT (dialysis training therapy) trial, enrolling a real-world patient population. Data after 12 months of combined endurance and resistance intra-dialytic ET was safe and significantly improved physical function, as assessed by the 60-STS. Furthermore, hospital admissions and annual days spent in hospital were reduced.[20]

The RENEXC (RENal EXerCise) trial, the hitherto largest RCT in patients with CKD G3–G5 comprising a real-world patient population including the elderly and patients with multiple comorbidities who conducted self-administered training at home or at a gym, showed in a head-to-head comparison of resistance training compared with balance training both in combination with endurance training, that both groups improved the 6MWT after 12 months of ET as well as other aspects of physical function.[21] The AWARD trial showed that a 12-month programme of in-centre aerobic and resistance ET in patients with CKD G3b–G4 and a high level of medical comorbidity resulted in a significant improvement in the 6MWT after 6 and 12 months, VO_2peak increased after 6 months ET, but the increase was not sustained after 12 months.[22]

ET has been shown to be safe and effective in increasing CRF at CKD G2–G5 and all modalities of KFRT. Initial studies focused on fitter and younger patients, but recent large RCTs have shown effects on CRF, physical function and morbidity, measured as hospitalizations, in real-world patients with CKD, i.e. also in the elderly and those with multiple comorbidities.

Table 3 Longitudinal studies on the relationship between physical activity and all-cause mortality in patients on haemodialysis

First author, year (country of origin)	Sample characteristics, Total *n*, Time on HD, % male, Age	Method used	Results on physical activity (PA) levels	Results on mortality risk
Hishii, 2019 (Japan)[14]	*n* = 71 patients HD vintage: 88.2 ± 87.7 months 39 men, 32 women, Age: 72.1 ± 11.7 years	Tri-accelerometer Follow-up: 5 years	• SB (%) 74.0 ± 13.6 • LPA (%) 24.4 ± 12.6 • MVPA (%) 1.8 ± 2.4	28.2% died during the observation period. The survival rate of the short-SB group (under the median SB value) was significantly higher than that of the long-SB group (over the median SB) HR=2.83 (1.11–7.32), *P* = 0.028 for the total days, 2.98 (1.21–8.03), *P* = 0.016 for the haemodialysis days, and 2.79 (1.13–7.49), *P* = 0.024 for the non-haemodialysis days
Matsuzawa, 2012 (Japan)[15]	*n* = 202 patients HD vintage: 40.0 (25th, 75th percentiles, 16.8, 119.3) months 48% male Age: 64 (25th, 75th percentiles, 57, 72) years	Uniaxial accelerometer for 7 days Follow-up: 7 years	PA time (min/d) <10 *n* = 8 (8.9%) ≤10 and <30 *n* = 44 (21.8%) ≤30 and <50 *n* = 65 (32.1%) ≤50 and <70 *n* = 30 (14.9%) ≤70 and <90 *n* = 24 (11.9%) ≥90 *n* = 21 (10.4%) Median (25th, 75th percentiles) PA time (min/d): 42.7 (22.8, 65.8) • Number of steps: 3925 (2287, 6244)	HR of physical activity time was reduced per 10 min/d [HR = 0.72 (0.62–0.85) *P* < 0.001] Greater physical activity time conferred a significant survival benefit (HR = 0.78 [0.66–0.92] *P* = 0.002)
Tentori, 2010 (USA)[16]	*n* = 20,920 patients HD vintage: 3.6 (5.2) years 58.2% male Age: 60.7 ± 14.8 years	Self-administered questionnaire on physical exercise frequency Follow-up: 1.75 years	• 47.4% (*n* = 9921): exercise at least once a week = regular exercisers • 8.5% (*n* = 1823): exercise less than once/week • 43.9% (*n* = 9176): never exercise	Mortality risk was lower: • among regular exercisers [HR = 0.73 (0.69–0.78); *P* < 0.0001] • at facilities with more regular exercisers [HR = 0.92 (0.89–0.94); *P* < 0.0001 for an additional 10% of facility regular exercisers] Greater exercise frequency was associated with longer survival when treated as an ordered variable [HR = 0.90 (0.88–0.92), *P* < 0.0001]

HD, haemodialysis; PA, physical activity; SB, sedentary behaviour, ≤1.5 metabolic equivalents (METs); LPA, light intensity physical activity, 1.6–2.9 METs; MVPA, moderate-to-vigorous intensity physical activity, ≥3.0 METs; HR: hazard ratio.

Exercise and coronary artery disease in patients with chronic kidney disease

Chronic kidney disease is associated with a dramatically reduced life expectancy of up to 25 years[3] with an exponential increase in absolute mortality risk when kidney function declines. CVD is a major contributor to this reduced life expectancy.[23] A patient with kidney disease is more likely to die from CVD than to reach kidney failure.[3] CKD is bi-directionally associated with hypertension and diabetes,[24,25] so that treatment of these risks both reduces deterioration in kidney function and prevents CVD.

Albuminuria is an important risk marker in these patients.[26] In addition, kidney dysfunction is associated with an abnormal lipid profile characterized as hypertriglyceridaemia and reduced HDL cholesterol.[27] Typically, CVD in patients with kidney disease is further complicated by excessive vascular calcification and increased inflammation. Coronary and large artery calcification is accompanied by peripheral valvular calcification and dysfunction.[28,29] The combination of vascular stiffening, traditional CV risks and kidney-associated changes in fluid status pre-dispose to HF both with reduced (HFrEF) and preserved ejection fraction (HFpEF). This myocardial disease is further exacerbated by metabolic disturbance and fibrosis.[3] Management of CV risk in patients with CKD requires traditional risk factor management such as BP and blood glucose control, particularly targeted at intervention of the renin–angiotensin–aldosterone system (RAAS) axis.[23] Research is ongoing into optimal interventions for novel risk factors such as calcification, inflammation, and myocardial fibrosis.[30,31] Understanding the extent to which lifestyle behaviours such as exercise changes are of benefit for CV risk reduction is of key importance for patient management. ET does not worsen proteinuria in patients with CKD stages 3–5, while high-intensity exercise may reduce proteinuria.[32] Decreasing BP and improving inflammation and endothelial function are the most important factors affecting albuminuria and these benefits can be achieved by ET in patients with CKD.[32] The RENEXC trial showed that a combined strength and aerobic training programme significantly reduced albuminuria in patients with CKD G3–G5.[21]

Effects of exercise training and cardiovascular disease reduction in chronic kidney disease patients with coronary artery disease

There are few reports which have studied the effect of ET on some non-traditional CVD risk factors in patients with CKD, such as inflammatory and pro-oxidative status, endothelial dysfunction, arterial stiffness, and left ventricular hypertrophy (LVH). Markers of inflammation and of oxidative stress have been shown to be decreased after 6 months of intra-dialytic ET,[33] with some reports showing no anti-inflammatory effect of exercise in patients on HD.[34] In a sub-study of the RENEXC trial 12 months of ET in patients with CKD G3–G5 had no effect on some anti-inflammatory markers, nor on pro-calcific or anti-calcific markers; however, lipoprotein (a) decreased significantly after ET.[35] The DiaTT study evaluated the impact of combined endurance and resistance intra-dialytic ET on events related to ischaemic heart disease and reported no effect after 12 months.[20] *Table 4* presents the RCT of ET and CV risk factors in patients with CKD G3–G5 and G5D. Despite evidence that ET has favourable effects on chronic inflammation and metabolic markers, the small number of patients included in the studies and the non-unequivocal findings make it difficult to draw any definite conclusions about the effects of exercise on non-traditional CVD risk factors in patients with CKD.[36]

Exercise and traditional cardiovascular risk factors in patients with chronic kidney disease

Hypertension in chronic kidney disease

Development of hypertension and CKD represent a bidirectional interdependency and vicious cycle. Hypertension is a leading cause of CKD through its deleterious effects on the renal microvasculature, and CKD drives the development of hypertension, by increasing sympathetic tone, activating the RAAS and contributing to systemic endothelial dysfunction. The prevalence of hypertension in patients with CKD is high and considered to be in the range of 60% for systolic and 30% for diastolic BP (defined as daytime ambulatory SBP ≥130 and DBP ≥80 mmHg).[44] Worsening of BP control in patients with CKD is linked to disease progression and increasing disease severity,[45] as well as increased CV morbidity and mortality.[26] Thus, tight control of BP in patients with CKD is of utmost importance to lower the health hazard and socioeconomic burden of CKD.

Blood pressure control and antihypertensive therapy

The 2023 ESH Guidelines for the management of arterial hypertension recommend a target BP for patients with hypertension and CKD at 130–139 mmHg systolic and 70–79 mmHg diastolic for all age groups.[46] However, for both non-diabetic and diabetic patients with albuminuria >30 mg/g a BP target of <130 systolic and <80 mmHg diastolic is suggested if well-tolerated.[46] The 2021 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for the management of BP in CKD, however, suggested reduction to systolic BP levels below 120 mmHg based on the results of a subgroup analysis of the Systolic BP Intervention Trial (Sprint).[47,48] Yet the optimal BP target in patients with CKD and albuminuria is still subject to controversy.[49]

Lifestyle advice is part of first-line antihypertensive treatment independent of the grade of hypertension and associated CV risk.[46,47] It is important to take into account that some anti-hypertensive medications provide additional BP-independent reno-protection, which may justify earlier initiation of drug treatment.[46] Managing hypertension in patients on HD, who often have a volume-sensitive BP elevation, and after kidney transplantation with some immunosuppressive medication inducing higher BP, remains a challenging task.

Effects of exercise training on blood pressure in patients with chronic kidney disease

A recent Consensus Document has discussed individualized exercise treatment depending on the initial BP level, although people with CKD were excluded.[50] There are four systematic reviews and meta-analyses that reported on the effects of ET on BP in patients with CKD G3–G5.[12,51–53] Data from 9 RCTs that included 463 participants reported that primarily aerobic exercise of light-to-moderate intensity, delivered mostly 3 times/week over a period of 6–52 weeks, resulted in a significant standardized mean difference in non-ambulatory SBP of −5.61 mmHg (95% CI: − 8.99 to − 2.23 mmHg) in favour of ET. The corresponding mean difference in DBP was −2.87 mmHg (95% CI: − 3.65 to − 2.08 mmHg).[52] In another systematic review, a significant standardized mean difference in SBP (−10.94 mmHg, 95% CI −15.83, −6.05) and DBP (−6.21 mmHg, 95% CI −10.93, −1.49) was reported between 16 and 26 weeks of aerobic training (based on 4 trials and

Table 4 Randomized controlled trials of exercise training and cardiovascular risk factors in patients with chronic kidney disease G3–G5 and G5D

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Anding-Rost, 2023 (Germany)[20]	CKD 5D *n* = 917 61.1% male Age: 65.9 ± 14.4 I, *n* = 446 HD vintage: 3.8 (0.2–39.9) years C, *n* = 471 HD vintage: 4.1 (0.2–42.6) years	I: Intra-dialytic supervised exercise programme during the first 2 h of HD and health literacy counselling C: Usual care	AT using a bed-cycle ergometer and RT in bed with elastic bands, exercise balls and dumbbells (8 exercises, two 1-min sets each)	12 months Assessments: Baseline 3 months 6 months 12 months	AT: HR-orientated training 12–13 RPE Borg Scale RT: 12–13 RPE Borg Scale	3/week	60 min (30 min AT and 30 min RT)	0→12 months: STS60: ↑ within I and ↓ within C and TUG and 6MWD : ↑ within I and in C:≈ Grip strength: I: ≈ C SF-36: PCS:↑ within I MCS: I:≈ C	Adherence: I: 88.1% of the offered exercise sessions Mortality, hospitalization and serious adverse events: I: ≈ C
Weiner, 2023 (USA)[22]	CKD G3b–G4 eGFR 33.3 ± 10.5 mL/min/1.73 m^2 *n* = 99 I, *n* = 49 69% male Age: 67.9 ± 7.7 C, *n* = 50 80% male Age: 68.1 ± 8.8	I: In-centre supervised exercise training (6 months) 1 of 3 weekly sessions home-based maintenance phase (6 months) C: Group health education	AT + RT AT: Walking light jogging, stationary cycling RT: Upper and lower extremity exercises C: Education on topics: healthy diet, CKD, diabetes and BP management	12 months Assessments: Baseline 6 months 12 months	AT:50%-60% →70–80% of HR reserve RT: 15–16 RPE Borg Scale	AT: 3/week RT: 2/week after AT C: Weekly (first 6 months) Monthly (the rest 6 months)	AT:20→40 RT: 10	0→6months: VO_2peak: ↑ within I 6MWD: ↑ within I TUG: ↑ within I SPPB: I ≈ C 6→12 months VO_2peak: I ≈ C 6MWD: ↑ within I TUG: ↑ within I SPPB: I ≈ C Risk Factors and Obesity: I ≈ C	Adherence: I: 0–6 months: 59.5% 6–12 months: 48.9% Adverse events I ≈ C Rate of adverse events (per 100 patient-months) I = 11.9 C = 12.6

Continued

Table 4 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Mallamaci, 2022 (Italy)[19]	CKD 5D *n* = 227 I, *n* = 104 64% male Age: 63 ± 13 C, *n* = 123 68% male Age:64 ± 14	I: Home-based walking exercise programme supervised by a central rehabilitation team C: Usual care	Walking sessions during the day off dialysis at pre-fixed cadence	6 months Assessments: Baseline 6 months 18 months 36 months	Training speed (1.4–2.8 km/h) 1–14 weeks 56–120 Steps/min Work/rest time 2:1 (5 times)–5:1 (2 times) 15–24 weeks 60–120 steps/min Work/rest time 5:1 (2 times)–10:1 (once)	3/week on the non-dialysis days	2 sessions of 10 min	0→ 36 months: Mortality: I ≈ C Hospitalization: 29% lower risk (HR, 0.71; 95% CI, 0.50 to 1.00; *P* = 0.05) in I vs. C In I with high adherence (>60% of sessions) 45% lower risk for hospitalization (HR, 0.55; 95% CI, 0.35–0.87; *P* = 0.01) vs. C	Adherence: I: >60% of prescribed sessions: 55 pts and <60%: 49 pts
Sprick, 2022 (USA)[37]	CKD G3–G4 *n* = 48 I, *n* = 26 76.9% male eGFR 44 ± 2 Age: 65 ± 1 C, *n* = 22- 81.8% male eGFR 47 ± 3 Age: 64 ± 2	I: Supervised AT exercise programme C: Stretching and balance	I AT: 'Spin' exercise on a stationary bicycle (short bouts of high intensity interval ET) C: Static and dynamic balance and low-intensity core strengthening exercises	3 months Assessments: Baseline 3 months	I 50–85% HR reserve C: <50% of HR reserve	I and C: 3/week	I and C: 20→45	0→3 months VO_2max: I ≈ C Endothelial function: RHI: ↑ within I Peak systolic BP during exercise: ↓ within I	Adherence: I completed 86 ± 2% and C: 89 ± 2% of the sessions

Continued

Table 4 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Sovatzidis, 2020 (Greece)[33]	CKD 5D $n = 20$ I, $n = 10$ 80% male HD vintage (months) 88.8 ± 9.9 Age: 52.8 ± 17.1 C, $n = 10$ 90% male HD vintage (months) 89.7 ± 10.1 Age: 53 ± 7.6	I: Supervised intra-dialytic cardiovascular training 60 min after the initiation of the HD session C: Abstained from exercise training during HD sessions	I: Bedside cycling—every month increase in the external resistance and duration of the ET	6 months Assessments: Baseline 6 months	11–13 RPE Borg Scale	3/week	Self-selected time (depending on each participant's tolerance)	0→6 months Body mass (kg) and body fat (%): ↓ within I VO_2peak, NSRI, STS60, handgrip strength and SF-36: ↑ within I Hs-CPR, TBARS, PC: ↓ within I GSH and GSH/GSSG ratio: ↑ within I TAC and CAT: ↑ within I	NR
Zhou, 2020 (Sweden)[35]	CKD G3–G5 $n = 112$ I, $n = 53$ 72% male mGFR 23 ± 9 Age: 67 ± 14 C, $n = 59$- 64% male mGFR 22 ± 7 Age: 66.3 ± 13	Individualized ET provided by a physiotherapist Self-administered at home or at gym I: AT±RT C:AT±balance	AT: Walking, jogging, cycling I RT: 4–6 exercises 2–3 sets of 10 reps C: Balance: 4–6 exercises 2–3 sets of 10 reps	12 months Assessments: Baseline 4 months 8 months 12 months	AT: RPE 13–15 Borg Scale I; RT: 13–17 RPE Borg Scale C: Balance: 13–17 RPE Borg Scale	3–5 sessions per week	I and C: Total 150 min per week AT 2X30 min RT and balance 3X30	0→12 months mGFR:↓ within I and C AAC score: ↑within I and C Lipoprotein (a): ↓ within I and C	Adherence 4 months I: 84% C: 89% 8 months: I: 70% C: 76% 12 months: I: 62% C: 68% No adverse event

Continued

Table 4 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Kirkman, 2019 (USA)[38]	CKD G3–G5 *n* = 36 eGFR 44 ± 2 Age: 58 ± 2 I, *n* = 15 80% male eGFR 45 ± 13 Age: 55 ± 13 C, *n* = 16- 62.5% male eGFR 41 ± 12 Age: 62 ± 9	I: Supervised AT at the University C: Routine care	AT: Cycling, walking, jogging or elliptical Patient's choice kept constant during the study	3 months Assessments: Baseline 3 months	60–85% of HR reserve 12–16 RPE Borge Scale	3/week	As tolerated →45 min	0→3 months VO_2peak: ↑ within I vs. C Microvascular function: ↑ within I Brachial artery FMD:↑ within I PWV, Aix:: I ≈ C	No adverse event
Oliveira e Silva, 2019 (Brazil)[39]	CKD: 5D N: 30 50% male Age: 58 ± 16.3 I, *n* = 15 46.7% male HD vintage (months) 26.0 ± 14.58 Age: 50 ± 17.2 C, *n* = 15 53.3% male HD vintage (months) 37.0 ± 31.1 Age: 58 ± 15.0	I: Intra-dialytic exercise programme within the first 2 h of HD C: Without training intervention	AT: cycling using cycloergometre adapted to the HD chairs	4 months Assessments: Baseline 4 months	65–75% of HRmax 13 RPE Borg Scale	3/week	30 min without interruption	0→4 months VO_2max: I ≈ C Aldosterone: ↓ within I CRP: I ≈, ↑ within C FMD: ↑ within I	NR

Continued

Table 4 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Cooke, 2018 (Canada)[40]	CKD 5D *n* = 20 70% male Age: 55.4 ± 16.2 I, *n* = 10 70% male Kt/V: 1.4 ± 0.3 Age: 58.2 ± 17.2 C, *n* = 10 70% male Kt/V: 1.5 ± 0.3 Age: 52.5 ± 15.4	I: Intra-dialytic supervised pedalling C: Usual haemodialysis	Pedalling for the amount of time to reach fatigue (16 RPE Borg Scale = hard)	4 months Assessments: baseline 4 months 8 months (4 months detraining)	12–16 RPE Borg Scale	3/week	Individualized according to participants' tolerance	0→4 months cfPWV:↓ within I AIx75: ≈I ↑ within C HR rest: ↓ within I 4→8 months detraining cfPWV, AIx75 and HR: I ≈	I: Compliance: 60% (IQR 42–79) Total ET time was 18.5 h (IQR 10.5–28.5) No adverse event
Greenwood, 2015 (UK)[41]	CKD G3–G4 *n* = 18 I, *n* = 8 75% male $eGFR_{cr}$ 36.6 ± 10.1 Age: 53.8 ± 13.5 C, *n* = 10- 90% male $eGFR_{cr}$ 46.5 ± 20.6 Age: 53.3 ± 12.9	I: Gymnasium-setting in a community hospital (twice supervised) and once at home 0 C: Usual care	I: AT +RT AT: stationary cycling RT: 1–2 sets ×10 reps→3 sets × 8–10 reps of upper and lower-body muscle groups →Theraband free weights	12 months Assessments: Baseline 6 months 12 months	AT: 80&% HR reserve RT: 80% 1-RM	3/week	Two 20 min sessions and →one 40 min session	0→12 months eGFRcr:↑ within I vs. ↓ within C VO_2peak:↑ within I vs. ↓ within C PWV:↓ within I vs. ↑ within C BMI and waist girth: ↓ within I	I; adherence: 79.2 ± 13.2% No adverse event

Continued

Table 4 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Van Craenenbroeck, 2015 (Belgium)[42]	CKD G3–G4 $n = 40$ I, $n = 19$ 58% male eGFR 37.5 ± 13.23 Age: 51.5 ± 11.8 C, $n = 21$- 52% male eGFR 39.6 ± 12.9 Age: 54.7 ± 14.1	I: Home-based intermittent AT and supervised at hospital: 3 sessions the first 2 weeks/ next 2 weeks 1 session C: Standard therapy	AT: cycling using magnetically braked home exercise bikes and HR transmitters	3 months Assessments: Baseline 3 months	90% of HR at the anaerobic threshold	4 daily sessions/ week	Total: 40 min/day (4 sessions ×10 min)	0→3 months VO_2peak: ↑ within I SF-36: Cognitive function, sleep, energy ↑ within I vs. C Hs-CRP, FMD, cfPWV, AIx75, circulating EPCs and OPCs: I ≈ C	I: Adherence: 90% Completed 95% of the sessions
Koh, 2010 (Australia)[43]	CKD: 5D N: 46 63% male Age: 51.9 ± 12.8 I_1, $n = 15$ 67% male HD vintage (months) 32.1 ± 26.7 Age: 52.3 ± 10.9 I_2, $n = 15$ 73% male HD vintage (months) 37.0 ± 31.1 Age: 52.1 ± 13.6 C, $n = 16$ 50% male HD vintage (months) 25.8 ± 22.2 Age: 51.3 ± 14.4	I_1: Intra-dialytic supervised exercise programme within the first 2 h of HD I_2: Home-based unsupervised exercise programme C: Usual care	I_1: AT using a cycle ergometer I_2: Walking	6 months Assessments: Baseline 6 months	I_1: 12–13 RPE Borg Scale monitored using HR I_2: 12–13 RPE Borg Scale	I_1 and I_2: 3/ week	I_1: 15 min→30 min by week 12→45 min by week 24 I_2: 15 min→→45 min by week 24	0→6 months: 6MWD, TUG, grip strength: $I_1 \approx I_2 \approx C$ PA levels: ↑ within I_1, I2 ≈ C Aortic and peripheral PWV, AIx75: $I_1 \approx I_2 \approx C$ SF36:$I_1 \approx I_2 \approx C$	Adherence: I_1: 75 ± 19% I_2: 71 ± 13% No adverse event

I, intervention group; C, comparator group; ↑, significant increase; ↓, significant decrease; ≈, no difference; CKD, chronic kidney disease; HD, haemodialysis; ET, exercise training; AT, aerobic training alone; RT, resistance training, NR, not reported; 1RM, one-repetition maximum; NSRI, North Staffordshire Royal Infirmary walk test, STS-60: sit-to-stand test; 6MWD, 6-minute walking distance; TUG, timed up and go test; SPPB, short physical performance battery; HR, heart rate; HRmax, maximal heart rate; BP, blood pressure; RPE, rate of perceived exertion—Borg Scale; VO_2peak, peak oxygen consumption; SF36, Short Form Survey; PCS, physical health component summary score; MCS, mental health component summary score; hs-CPR, high-sensitivity-CPR; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GSH, reduced glutathione; GSSG, oxidized glutathione; TAC, total antioxidant capacity; CAT, catalase activity; cfPWV, carotid femoral pulse wave velocity; Aix 75, augmentation index (corrected for a HR of 75 b/min); FMD, flow-mediated dilation; OPC, osteogenic progenitor cell; EPC, endothelial progenitor cell; AAC, abdominal aortic calcification; RHI, reactive hyperaemia index.

79 participants), but not during the first 16 weeks or between 26 and 52 weeks of ET.[51]

Combined aerobic and resistance training regimes resulted in no significant differences in either SBP or DBP, based on 3 studies and 204 participants [SBP: −4.06 mmHg (95% CI −9.31 to 1.18); DBP: −5.4 mmHg (95% CI: −10.09 to 0.02)].[53] Another meta-analysis reported no significant standardized mean difference.[12] However, none of the studies included in the aforementioned meta-analyses were designed or powered with BP as primary outcome and all of them had a moderate to serious risk of bias. Forest plot analysis suggested that significant standardized mean differences were mainly driven by large changes in single studies included in the meta-analysis.

There are also three3 systematic reviews and meta-analyses that combined data on the impact of exercise on BP in patients on HD[54–56] and one on peritoneal dialysis.[57] Aerobic intra-dialytic exercise (based on 9 trials and 305 participants) resulted in a significant reduction of systolic BP of −10.07 mmHg, (95% CI −16.35 to −3.78). No significant changes in DBP were noted. Combined aerobic and resistance training, based on 2 trials and 76 people, resulted in significant reduction in diastolic BP of −5.76 mmHg (95% CI: −8.83, −2.70) but no changes in SBP.[56] Similar conclusions were reported previously,[55] but could not be confirmed by others.[54] The lack of significance for the combination of aerobic and resistance training may be due to the low number of patients.

Diabetic nephropathy in patients with chronic kidney disease

Diabetic nephropathy (DN) is responsible for approximately one-third to half of all cases on KFRT.[58] It is the most common micro-vascular complication of DM.[59] The main pathophysiological mechanisms underlying DN are oxidative stress, the accumulation of advanced glycosylated end products and extracellular matrix, and activation of the RAAS.[59]

Treatment comprises dietary restrictions, optimizing BP and lipid status as well as anti-diabetic drug therapy. Already after a short-term intensive weight reduction intervention in patients with advanced DN, improvements in markers of glomerular filtration and risk factors for CKD progression were observed.[60] Blood sugar levels are advised to be adjusted aiming at HbA_{1c} levels between 6.5 and 8.0%, since it has been shown that both, higher and lower levels, are negatively correlated with DN.[61] Personalized HbA1c targets 6.5–8.0% (48–64 mmol/mol) are recommended, with a target <7.0% (<53 mmol/mol) to reduce micro-vascular complications.[62] With the progression of DN, drug options for type 2 (T2) DM decrease: at eGFR < 30 mL/min/1.73 m^2, only a few agents are approved, such as inhibitors of dipeptidyl peptidase 4, glinides, and glucagon-like peptide-1 receptor agonists. Moreover, treatment with RAS inhibitors and/or SGLT2 inhibitors, which are recommended to manage CVD risk or hyperglycaemia, has been shown to slow the decline in eGFR.[62]

Effects of exercise training on glycaemic control and diabetic nephropathy

Low-to-moderate intensity aerobic exercise seems to exert reno-protective effects in patients with T1DM and T2DM improving insulin sensitivity, microalbuminuria, and lipid levels.[59] A recent study in patients with DM has shown that moderate activity (at least 2 times/week to every day) is associated with significantly lower risk of kidney outcomes (doubling of serum creatinine or KFRT) and significantly lower incidence of new micro- and macro-albuminuria compared with lower exercise levels.[63] Results are less clear regarding the impact of high-intensity exercise on progression of kidney disease in DM. Patients with T1DM who practiced high-intensity exercise showed lower risk of progression to microalbuminuria and incidence of DN in comparison with patients who performed low and moderate intensity exercise.[59] Combined ET of moderate-to-high intensity (50–80% of heart rate reserve) for 12 weeks in patients with T2DM with CKD G2 and G3 increased post-exercise eGFR. More than 40% of patients with CKD G3 improved to G2 after the intervention.[64] Beneficial effects of resistance exercise on the course of DN in DM have to date not been convincingly demonstrated.[59] This is mainly due to the lack of clinical studies examining the effects of resistance ET on the metabolic (i.e. reactive oxygen species production and signalling, activation of the P2X7 receptor and nuclear factor erythroid 2-related factor 2) and haemodynamic (i.e. ECM protein deposition and fibrosis reductions) pathways that lead to DN progression.[59]

Another meta-analysis showed that physical activity in DM was associated with increased eGFR, decreased albuminuria and a lower risk of kidney failure, indicating that physical activity is effective in improving DN and slowing its progression. However, the incidence of DN was only reduced in T1DM not in T2DM.[63] The positive association between physical activity and kidney outcome has been shown in a meta-analysis in patients with and without DM.[65] However, data suggest that the benefit of physical activity was greater in patients with DM compared with patients without DM.[63] The mechanisms underlying the beneficial effects of ET on DN involve improvement of glycaemic control, BP, multiple lipoprotein abnormalities, and endothelial function.[66] However, more high-quality RCT are required on this topic. Clinical practice exercise guidelines for patients with CKD with DM including information about type and intensity of recommended PA are needed.[66]

Vascular dysfunction and atherosclerosis in patients with chronic kidney disease

Vascular calcification is common in patients with CKD. Reported prevalence is as high as 65% in patients on HD and approximately 60% in patients on peritoneal dialysis and in CKD G3–G4.[67] The condition occurs at a younger age and progresses faster in patients with CKD than in people with normal kidney function.[68] The high prevalence of traditional CV risk factors, as well as risk factors related to kidney failure such as chronic inflammation, dysregulated mineral homeostasis, uremic toxins, oxidative stress, and low levels of calcification inhibitors are some of the pro-calcific stimuli in CKD.[69,70] Moreover, endothelial dysfunction occurs early in the course of CKD and represents a functional yet reversible impairment of the intimal layer.[71] Both conditions are associated with increased morbidity and mortality.[67]

Effects of exercise training on vascular dysfunction and atherosclerosis in patients with chronic kidney disease

A sub-study of the RENEXC trial studied the effects of 12 months of aerobic combined with either resistance or balance ET on abdominal aortic calcification in patients with CKD G3–G5 not on KFRT and reported a progression of abdominal aortic calcification in both groups.[35]

The effects of ET on pulse wave velocity (PWV), as an estimate of central large artery stiffness, are contradictory. A decrease in PWV by a mean of 2.3 m/s was reported in patients with CKD not on KFRT after a 1-year combined aerobic and resistance anaerobic ET.[41] In patients on HD, intra-dialytic aerobic ET was found to reduce arterial stiffness.[40,72] However, no change in the aortic PWV was observed in patients on HD who participated in intra-dialytic cycle ergometre ET or home-based walking ET or usual care.[43] These results were confirmed by an RCT including patients with CKD G3–G4 who participated in 3 months of home-based aerobic ET, which showed no changes of carotid–femoral PWV.[42]

Endothelial dysfunction is an attractive target and vascular biomarker for the prevention and treatment of CKD-related disease and is reversible by exercise. Indeed, the pleiotropic effects of ET have been found

to improve endothelial function in several patient groups with chronic conditions. Twelve weeks of aerobic ET improved microvascular function by 4.6%, as assessed by the skin blood flow response to local heating measured by laser-Doppler flowmetry coupled with micro-dialysis, without affecting central arterial haemodynamics and arterial stiffness in patients with an eGFR <60 mL/min/1.73 m^2 and without overt CV disease.[38] On the contrary, flow-mediated dilation of the brachial artery did not change significantly following 3 months of home-based aerobic ET in patients with CKD G3–G4.[42] In patients on HD, 4 months of intra-dialytic aerobic ET (3 times per week) significantly improved the flow-mediated dilatation by 32.4% and reduced left ventricular (LV) mass index by 5.8%, without the increase in C-reactive protein serum levels that occurred in the control group (by 25%).[39] Recently, an improvement in reactive hyperaemia index has been reported, a measure of micro-vascular function, after 12 weeks of aerobic ET in patients with CKD G3–G4.[37] Retinal micro-vascular function has been linked with all-cause and CV mortality in patients on HD;[73] however, there are to date no ET trials studying retinal vessel health as an outcome in patients with CKD.

Cardiac morphology and heart failure in patients with chronic kidney disease

Three scenarios connect CKD and HF: First, CKD causes cardiac dysfunction and remodelling (type IV cardiorenal syndrome); second, cardiac dysfunction and remodelling cause kidney failure (type II cardiorenal syndrome); third, common mechanisms underlie heart and kidney failure, such as systemic inflammation, endothelial dysfunction, and oxidative stress. Irrespective of the mechanism, the co-existence of HF and kidney dysfunction is detrimental on clinical outcomes. The association between CKD and mortality is even more critical in patients with HF with HFpEF than in patients with HFrEF.[74] In HFpEF, kidney dysfunction is not only a prevalent comorbidity but also leads to a more detrimental cardiac phenotype. Patients with HFpEF and CKD present with more pronounced LVH, impaired left atrial function, and right ventricular dysfunction. Furthermore, venous congestion may contribute to the progression of CKD in HFpEF, inducing a vicious circle.[75]

Effects of exercise training on cardiac morphology and heart failure

Exercise-based cardiac rehabilitation in HFrEF is associated with improved cardiac function, attenuation of ventricular remodelling and a reduction in hospitalizations.[76] Therefore, these programmes are recommended according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.[77] In patients with HFrEF (LVEF <40%), ET has been shown to reverse LV remodelling, with favourable effects on ejection fraction, stroke volume, and end-diastolic and end-systolic diameters, with the most convincing benefits occurring with long-term (≥6 months) training.[78] Diastolic function, measured by *E*/é ratio, also improved in HFrEF, suggesting improved myocardial relaxation.[79] In patients with HFpEF (LVEF ≥ 50%), an early study has shown that a 3-month aerobic and resistance ET can improve CRF and LV diastolic functional capacity.[80] However, the same research group recently reported that in older patients with severe diastolic dysfunction even a year of ET did not result in significant changes in LV anatomy and function despite improvement of CRF.[81]

Many symptomatic patients with HF in exercise intervention trials also suffered from CKD; however, a description of kidney function in these RCTs or a dedicated subgroup analysis based on GFR category is missing. There are not many references on the impact of exercise on cardiac function in patients on maintenance dialysis with HF (*Table 5*). In patients on HD 6 months of ET improved LV systolic function at rest.[84] Most of the patients had borderline LV hypertrophy and high output systolic dysfunction, while some had HF of Class II of NYHA. Moreover, a stress echo study detected enhanced cardiac performance during acute supine exercise.[84] In the CYCLE-HD trial, 6 months of structured, progressive intra-dialytic cycling led to a clinically relevant reduction in LV mass and was associated with beneficial LV remodelling.[82] Another study, with intra-dialytic ET in patients with marginally affected EF, reported an improvement in LVEF and diastolic function, decreased systolic pulmonary artery pressure and right ventricular size with no alterations in LVH.[83] In patients with maintained cardiac function, implementing intra-dialytic ET increased LV diastolic diameter and EF without LV mass changes.[85] These adaptations may support a strengthening of the Frank and Starling mechanism. In contrast, another study demonstrated a reduction of LVH following intra-dialytic ET, concurrently with a decrease in aldosterone levels, concluding that aldosterone blockade might decrease LV mass in patients on HD.[39] Other mechanisms responsible for exercise-related improvement of cardiac function in patients on maintenance dialysis are restoration of the cardiac autonomic nervous system (CANS) balance, improvement in arterial compliance and reduction in cardiac stunning.[36,86] Moreover, non-cardiac benefits of ET, such as reduced oxidative stress and inflammation, improved neurohormonal control, release of micro-RNAs from contracting muscle and enhanced cardiorespiratory and skeletal muscle function, contribute to a lower progression of the HF syndrome in patients on maintenance dialysis.[36,42,87]

The ET prescriptions and the contraindications for patients on maintenance dialysis with cardiac dysfunction are comparable to those of patients with HF. Intra-dialytic exercise has negligible side effects, in particular when the training is performed during the first 2 h of a standard dialysis procedure. However, if ultra-filtration volumes are high inducing a risk of intra-dialytic hypotension with an acute reduction of cardiac output, exercise should be postponed until the ultra-filtration volumes have stabilized to acceptable levels.

Arrhythmias and sudden cardiac death in patients with chronic kidney disease

A significant proportion of CV mortality in patients on maintenance dialysis is a result of SCD.[3] Sudden cardiac death is mainly caused by ventricular arrhythmias such as ventricular tachycardia or tachyarrhythmia, torsade de pointes, ventricular fibrillation, and bradyarrhythmia.[88] The rate of SCD is 59 deaths per 1000 patient-years in patients on maintenance dialysis vs. 1 death per 1000 patient-years in the general population.[89] In patients on maintenance dialysis, the rate of SCD is disproportionately high compared with the incidence of coronary heart disease. Dialysis itself is a risk factor for SCD with the highest risk within the first 12 h after dialysis and after a long dialysis interval.[3] Potential mechanisms include insufficient dialysis dose, arrhythmias due to volume overload/depletion, sudden electrolyte shifts during and after dialysis, in particular of potassium and calcium.[3] Compared with peritoneal dialysis, the rate of SCD is 50% higher in patients on HD 3 months after dialysis initiation, although these rates reach parity after 2 years on maintenance dialysis. It seems that over time dialysis factors become more important than specific ones associated with dialysis modality.[90]

To date, non-invasive strategies such as assessment of heart rate variability (HRV), late potentials, QT dispersion, or T wave alternans failed to adequately predict SCD in patients on dialysis.[3] Studies with different drug therapies such as antiarrhythmic agents including beta blockers, calcium channel blockers, and inhibitors of the RAAS suggested that patients on maintenance dialysis might not derive the same benefits as patients with normal kidney function.[88] In most studies with implantable cardioverter-defibrillators (ICDs) patients with CKD were excluded.[3,88] A meta-analysis showed that the value of ICD implantation in this group has been questioned.[90] Despite the small number of patients on maintenance dialysis in clinical studies, 2015 ESC Guidelines for the management of patients with ventricular

Table 5 Randomized controlled trials of exercise training and cardiac morphology and function in patients on haemodialysis

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results—effectiveness outcomes	Adherence and adverse events
			Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Graham-Brown, 2021 (UK)[82]	CKD: 5D N: 101 I *n* = 51 63% male HD vintage (years): 1.2 (0.6, 2.5) Age: 55.1 ± 15.2 C *n* = 50 78% male HD vintage (years): 1.2 (0.4, 2.5) Age: 58.9 ± 14	I: Supervised progressive intra-dialytic exercise programme C: Standard HD therapy without ET	I: Cycling on specially adapted and calibrated cycle ergometers	6months Assessments: Baseline 6 months	12–14 RPE Borg Scale adjusting resistance. (RPE: 12.4 ± 2 for Month 1; RPE 12.7 ± 1.9 for Month 6) Power: (17.7 ± 13.2 W for Month 1; 18.8 ± 9.5 for Month 6)	3/week	30 min (41.1 ± 16.2 min for Month 1; 37.7 ± 14.6 min for Month 6)	0→6 months LVM and LVMI: ↓ within I vs. C LVM/LVEDV: ↓ within I vs. C LVEF: ↑ within I vs. C Native T1 times (septal and non-septal T1): ↓ within I vs. C Aortic PWV ↓ within I vs. C	Adherence: I: Completed 71.7% of the sessions (76.7% for Month 1, 61.4% for Month 6) Adverse events: I: 37 and C; 14 none exercise-related
Oliveira e Silva, 2019 (Brazil)[39]	CKD: 5D N: 30 50% male Age: 58 ± 16.3 I *n* = 15 46.7% male HD vintage (months) 26.0 ± 14.58 Age: 50 ± 17.2 C *n* = 15 53.3% male HD vintage (months) 37.0 ± 31.1 Age: 58 ± 15.0	I: Intra-dialytic exercise programme within the first 2 h of HD C: Without training intervention	AT: cycling using cycloergometer adapted to the HD chairs	4 months Assessments: Baseline 4 months	65–75% of HRmax 13 RPE Borge Scale	3/week	30 min without interruption	0→4 months VO_2max: I ≈ C Aldosterone: ↓ within I LV IVSd: ↓ within I LV PWd: ↓ within I LVMI: ↓ within I	NR

Continued

Table 5 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, eGFR (mL/min/1.73 m^2), total *N*, *n* per group, % male, age (y)	Intervention	Prescribed exercise training programme Setting type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)	Results—effectiveness outcomes	Adherence and adverse events
Momeni, 2014 (Iran)[83]	CKD: 5D N: 40 75% male Age: 43.1 ± 10.5 I *n* = 20 C *n* = 20	I: Intra-dialytic exercise programme C: without ET intervention	I: cycling using Minibike equipment	3 months Assessments: Baseline 3 months	NR	3/week	30 min	**0→3 months** LVEF: ↑within I vs. C sPAP: ↓within I RV size:↓within I VTI MV:↓within I MVPG min: ↑within I	NR
Deligiannis, 1999 (Greece) [84]	CKD: 5D N: 38 I_1 *n* = 16 68.8% male HD vintage (months) 78 ± 62 Age: 46.4 ± 13.9 I_2 *n* = 10 80% male HD vintage (months) 62.0 ± 37 Age: 51.4 ± 12.5 C_1 *n* = 12 33.3% male HD vintage (months) 79 ± 86 Age: 50.2 ± 7.9 C_2 *n* = 15 44.4% male Healthy sedentary Age: 46.9 ± 6.4	I_1: outpatient supervised exercise programme on the non-dialysis days I_2: Home-based exercise programme C_1: Usual care C_2: Untrained	I_1 AT + RT (3–6 months) + team games (younger), swimming (older) (4–6 months) Intermittent AT, calisthenics, steps, flexibility stretching RT: Low-weight exercises I2: Cycling using cycloergometer, flexibility and muscular extension exercises	6 months Assessments: Baseline 6 months	I_1: 60–70% of HRmax I2: 50–60% of HRmax	I_1: 3/week I_2: at least 5/week	I_1: 90 min I_2: 30 min	0→6 months HR rest, BP rest: ↓ within I_1 HRmax:↑ within I_1 VO_{2max}: ↑ within I_1 and I_2 LVIDd:↑ within I_1 LVMI:↑ within I_1 and I_2 Stress echo: At sub-maximal effort: LVESVI: ↓within I_1 and I_2 LVEF: ↑within I1 and I_2 SVI: ↑within I1 and I_2 COI:↑within I1 and I_2	No cardiovascular adverse event

I, intervention group; C, comparator group; ↑, significant increase; ↓, significant decrease; ≈, no difference; CKD, chronic kidney disease; HD, haemodialysis; BP, blood pressure; ET, exercise training; AT, aerobic training alone; RT, resistance training; NR, not reported; HR, heart rate; HRmax, maximal heart rate; RPE, rate of perceived exertion—Borg Scale; VO_2peak or max, peak or maximal oxygen consumption; LV, left ventricle; RV, right ventricle; IVSd, intra-ventricular septum in diastole; PWd, posterior wall in diastole; LVMI, left ventricular mass index; RHI, reactive hyperaemia index; LVIDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESVI, left ventricular end-systolic volume index; COI, cardiac output index; SVI, stroke volume index; PWV, peak wave velocity; sPAP, systolic pulmonary pressure; VTI MV, velocity time integral mitral valve inflow; MVPG, mitral valve pressure gradient.

Table 6 Randomized controlled trials of exercise training and cardiac autonomic function and the incidence of arrhythmias in patients with chronic kidney disease G3–G5 and G5D

First author, year (country of origin)	Sample characteristics CKD stage, total N, eGFR (mL/min/1.73 m^2), n per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting Type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Michou 2023 (Greece)[93]	CKD: 5D N: 28 I $n = 15$ 66.7% male HD vintage (years) 6.53 ± 5.7 Age: 62.06 ± 6.34 C $n = 13$ 53.8% male HD vintage (years) 4.7 ± 3.17 Age: 63.3 ± 8.5	I: home-based individualizedAT+RT on the non-dialysis days C: usual care	AT: walking or cycling on a stationary cycle. RT: 6 exercises in 2 sets of 8–10 reps adding rubber bands, balls and dumbbells progressively	6 months Assessments Baseline 6 months	50–70% VO_2peak	3/week	60–90 min (AT: 15→40 min)	**0→6 months** VO_2peak: ↑ within I vs. C HbA1c: ↓within I vs. C FPG, TC, TG, LDL: ↓ within I HDL:↑ within I vs. C SDNN: ↑ within I vs. C rMSSD, pNN50: ↑ within I vs. C LF: ↓within I vs. C HF: ↑ within I vs. C TS ↑ within I vs. C	**Adherence:** I: completed 95 ± 2% of the sessions. No adverse event
Huang 2021 (Taiwan)[94]	CKD: 5D N: 83 I $n = 40$ 72.5% male Age: 53.7 ± 10.04 C $n = 43$ 65.1% male Age: 61.19 ± 10.2	I: Breathing-based leg ET lied on the bed 2 h after HD C: usual care	I: leg lifts, quadriceps femoris contraction, knee extension followed by 5 abdominal breaths	12 weeks Assessments Week 4, Week 8, Week 12	Low-intensity (HR and BP monitored)	3/week	15 min	**0→12 weeks** fatigue score ↓ within I Short - term HRV indices I≈C	Attrition rate: 3.5%

Continued

Table 6 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, total N, eGFR (mL/min/1.73 m^2), n per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting Type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Huppertz 2020 (Australia)[95]	CKD G3–G4 *n* = 113 54.4% male eGFR: 39.4 ± 8.6 Age: 60.4 ± 9.3 I: *n* = 56 56.1% male eGFR 38.6 ± 8.4 Age: 58.8 ± 9.7 C *n* = 57 53.6% male eGFR 47=0.2 ± 8.8 Age: 62.1 ± 8.6	I lifestyle intervention: Gym-based supervised ET followed by 10-month home-based ET 4 weeks group behaviour modification programme (focused on behaviour change and sustainable diet for weight loss)	Gym-based: individualized AT+RT AT: treadmill, stationary bike, or rowing ergometer, and whole-body RT with machines and free weights. Home-based: individualized RT using Thera-Bands and a Swiss ball	12 months (2 months gym-based and 10 months home-based) Assessments Baseline 12 months	11–13 RPE Borg Scale	2 gym-based sessions/ week	Total 150 min/ week (2 sessions ×20–30 min AT)	0→12 months VO_2peak: ↑ within I vs. C HRrest:↓ within I Systolic BP rest: ↓ within I BPpeak: ↓ within I HR reserve: ↓ within I HRV indices I≈C	Adherence: I attended 70% of the gym-based ET sessions and 5 additional visits (range, 0–10) during the home-based ET
Kouidi, 2010 (Greece)[96]	CKD: 5D *N*: 54 I *n* = 24 58.3% male HD vintage (years) 6.1 ± 4.6 Age: 46.3 ± 11.2 C *n* = 29 55.2% male HD vintage (years) 6.3 ± 4.9 Age: 45.8 ± 10.9	I: Intra-dialytic supervised AT+RT, during the first 2 h of HD sessions C: Usual care	AT: Intra-dialytic cycling using bed bicycles, followed by RT: 2 sets of exercises for lower limbs 8–13 reps → adding therabands and weights Progressively ↑ workload	1 year Assessments Baseline 1 year	11–13 RPE Borg Scale 50–70% VO_2peak	3/week	60–90 min (AT: 30→60 min + RT 20 min)	0→1 year VO_2peak: ↑ within I vs. C BDI, HADS: ↓within I vs. C SDNN: ↑ within I vs. C rMSSD, pNN50: ↑ within I vs. C LF/HF: ↑ within I vs. C	Adherence: I: completed 82% (68–92%) of the sessions. No adverse event

Continued

Table 6 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, total N, eGFR (mL/min/1.73 m^2), n per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting Type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Kouidi, 2009 (Greece)[97]	CKD: 5D N: 59 I $n = 30$ 60% male HD vintage (years) 6.3 ± 3.7 Age: 54.6 ± 8.9 C $n = 29$ 55.2% male HD vintage (years) 6.2 ± 3.9 Age: 53.2 ± 6.1	I: intra-dialytic supervised AT+RT, adjusted periodically to increase performance during the first 2 h of HD sessions C: Usual care	AT: intra-dialytic cycling using bed bicycles, followed by RT: isotonic, isometric and flexibility exercises 10 reps →3 sets x15 reps, adding therabands and weights. Progressively increased workload	10 months Assessments Baseline 10 months	AT+RT: 13 RPE Borg Scale HR< 60–70% HRmax	3/week	90 min (warm up 10 min, AT: 40min, RT: 30 min, cool-down 10 min)	**0→10 months** VO_2peak: ↑ within I vs. C LVEF: ↑ within I vs. C 24-h HR: ↓ within I vs. C SDNN: ↑ within I vs. C LF/HF ↑ within I vs. C Total score of risk factors: ↓within I vs. C	**Adherence:** I: completed 88.3% of the sessions. No adverse event
Petraki, 2008 (Greece)[98]	CKD: 5D N: 43 I $n = 22$ 68.2% male HD vintage (months) 76.32 ± 7.0 Age: 50.05 ± 13.2 C_1 $n = 21$ 81% male HD vintage (months) 72.8 ± 5.3 Age: 50.52 ± 14.4 C_2 $n = 20$ 75% male Healthy sedentary Age: 48.1 ± 9.2	I: Intra-dialytic supervised AT+RT, adjusted periodically to increase performance during the first 2 h of HD sessions C1: Sedentary C2: Sedentary	AT: intra-dialytic cycling using bed bikes, followed by RT: isotonic, isometric and flexibility exercises, adding therabands and weights. Progressively increased workload	7 months Assessments Baseline 7 months	AT: passive cycling (1 week) →active cycling 13 RPE Borg Scale	3 /week	90 min (AT: 30min→ 60 min, RT: 30 min)	**0→7 months** VO_2peak: ↑ within I vs. C_1 BRS: ↑ within I vs. C_1 BEI: ↑ within I vs. C_1 Event count ↑ within I vs. C_1 Ramp count: ↑ within I vs. C_1 I: ↓ indices vs. C_2	No adverse event

Continued

Table 6 *Continued*

First author, year (country of origin)	Sample characteristics CKD stage, total N, eGFR (mL/min/1.73 m^2), n per group, % male, age (y)	Intervention	Prescribed exercise training programme					Results – Effectiveness outcomes	Adherence and Adverse events
			Setting Type	Total duration (months) and assessment points	Intensity	Frequency (x/week)	Duration of ET session (min)		
Deligiannis, 1999 (Greece)[86]	CKD: 5D N: 60 53.3% male Age: 48 ± 12 I *n* = 30 56.7% male HD vintage (years) 6.3 ± 3.0 Age: 48 ± 12 C_1 *n* = 30 50% male HD vintage (years) 6.2 ± 3.6 Age: 48 ± 11 C_2 *n* = 30 53.3% male Healthy sedentary Age: 49 ± 11	I: Outpatient supervised AT+RT exercise programme on the non-dialysis days, adjusted periodically to increase performance C1: Sedentary C2: Sedentary	I AT: cycling, walking, calisthenics, steps, Swimming or ball games RT: Low-weight exercises, stretching	6 months Assessments Baseline 6 months	60–70% HRmax	3–4/week	90 min (50 min AT + 20 min RT)	0→6 months VO_2max:↑ within I vs. C_1 HRV index: ↑ within I vs. C_1 SDNN:↑ within I vs. C_1 Arrhythmias-Lown class>II: ↓ within I vs. C_1	No adverse event

I, intervention group; C, comparator group; ↑, significant increase; ↓, significant decrease; ≈, no difference; CKD, chronic kidney disease; HD, haemodialysis; ET, exercise training; AT, aerobic training alone, RT, resistance training, NR, not reported; HR, heart rate; HRmax, maximal heart rate; BP, blood pressure; RPE, rate of perceived exertion—Borg Scale; VO_2peak, peak or maximal oxygen consumption; 6MWD, 6-minute walking distance; LVEF, left ventricular ejection fraction; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; HbA1c, glycated haemoglobin; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; HRV, heart rate variability; BRS, arterial baroreflex sensitivity; BEI, baroreflex effectiveness index; SDNN, standard deviation of RR intervals; rMSSD, root mean square of successive differences between normal heartbeats; pNN50, the number of pairs of successive NN (R–R) intervals that differ by >50 ms; LF, low frequency; HF, high frequency; TS, turbulence slope.

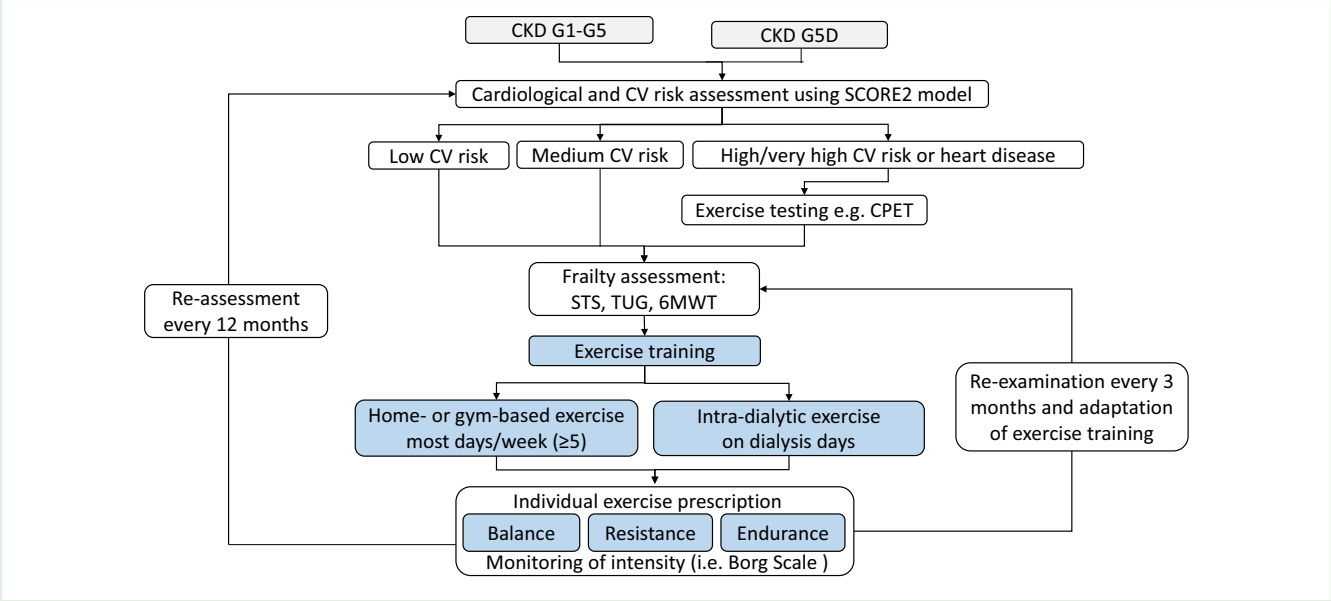

Figure 1 Algorithm for exercise prescription in patients with chronic kidney disease and kidney failure treated by dialysis. CKD, chronic kidney disease; CV, cardiovascular risk; CPET, cardiopulmonary exercise testing; STS, sit-to-stand test; TUG, timed up and go test; 6MWT, 6-minute walk test.

arrhythmias and the prevention of SCD and a current review article from the European Dialysis Working Group of ERA recommend primary prophylactic ICD implantation if the EF is ≤35%.[88,91]

Effects of exercise training on cardiac autonomic function and arrhythmias

With the progression of CKD, an increase in cardiac autonomic dysfunction has been observed, which contributes to an increased CVD risk and CV mortality.[92] Among patients with CKD sympathetic overactivity, vagal withdrawal, and sympathovagal imbalance are common, increasing the risk of cardiac arrhythmias.[92] Endurance training has been proposed as a non-pharmacological approach to improve cardiac autonomic function (*Table 6*).

In patients with CKD G3–G4, 12 months of lifestyle intervention including regular moderate intensity ET and behaviour modification classes did not affect cardiac autonomic function as assessed by short-term HRV analysis.[95] Acute intra-dialytic exercise did not affect CANS activity in HD, as assessed by pupillometry and HRV parameters.[99] Similarly, studies implementing 12 weeks of intra-dialytic aerobic ET of low-to-moderate intensity did not detect any significant influence of exercise on short-term HRV indices.[94,100]

On the other hand, longer exercise interventions, either intra-dialytic or out-of-clinic and at home on non-dialysis days, lasting on average 6–10 months, were found to improve cardiac autonomic function, as assessed by long-term HRV or arterial baroreflex sensitivity.[86,93,97,98] Long-term regular ET led to a significant increase in cardiac vagal activity and a decrease in sympathetic activity and sympathovagal balance,[96] even in diabetic patients on HD.[93] Moreover, the results of these studies indicated that the exercise interventions that cause a marked improvement in patients' CRF can also provide significant improvement in CANS activity, mainly due to favourable neurohormonal adaptations, such as decreased catecholamine levels at rest and during sub-maximal exercise and suppression of angiotensin II levels.[101,102] Additionally, ET was found to improve endothelial function leading to increased nitric oxide bioavailability and sympathovagal balance.[103] These results have a high clinical significance since patients with increased HRV indices showed lower incidence of cardiac arrhythmias.[86,97]

Research gaps and conclusions

There is limited evidence on how to best prescribe exercise treatment and ensure safety precautions for patients with CKD and concomitant risk factors and comorbidities. Clinicians usually follow the recommendations given for cardiac patients and tailor exercise prescription according to each patient's functional capacity and degree of frailty.

KDIGO 2021 on the management of BP recommends moderate-intensity physical activity for a cumulative duration of at least 150 min per week or to a level compatible with their CV and physical tolerance.[47] However, it is advisable that patients with chronic diseases walk about 7000–10 000 steps per day, the daily step count in patients with CKD is found to be <5000 steps.[104] In clinical practice, many patients are elderly and frail, have multiple comorbidities, are severely deconditioned and are not able to achieve the exercise targets proposed. Recently, studies have focused on the effectiveness of simple, self-administered home-based ET programmes on CV health.[19,21,93] Apart from the type of exercise, equal benefits on physical function could be obtained from short-duration ET.[105] The DiaTT trial including a large real-world HD population reveals the benefits of intra-dialytic exercise. Aside from profound improvements on physical function assessed by STS test, timed up and go test, and 6MWT, annual hospitalization rate was halved and quality of life in certain categories improved.[20] These findings together with the results from exercise on non-dialysis days in the EXCITE trial and self-administered home- or gym-based exercise in the RENEXC trial show the overall clinical beneficial opportunities of exercise in patients with CKD G5D and with CKD G3–G5, even with low exercise doses.[18,19,21] On the other hand, there are studies implementing high-intensity interval training both in patients with CKD G3–G4[106] and with CKD G5D,[107] indicating that it is feasible and safe in clinically stable CKD patients.

Table 7 Physical activity/exercise training advice for adults with CKD[108,109]

All patients with CKD should generally reduce sedentary time daily and engage in at least light activity throughout the day and should stay as active as their abilities and health condition allow
Patients with CKD are advised to strive for at least 150–300 min a week of moderate- intensity or 75–150 min a week of vigorous-intensity endurance exercise, or an equivalent combination
In addition to endurance exercise, patients with CKD should include resistance exercise and balance training on most days of the week
In patients on haemodialysis, it is advisable that intra-dialytic exercise training programmes combine endurance and resistance exercises
It is advisable that frailty assessment is performed in all patients with CKD annually
Cardiological evaluation should be performed annually to assess cardiovascular risk
Exercise testing, e.g. CPET, may be advisable in patients at high cardiovascular risk or with cardiovascular disease, e.g. heart failure for exercise intensity prescription
Rehabilitation exercise groups are advisable to increase adherence to exercise programmes
All available measures to increase adherence to exercise are advisable, such as group or individual education, behaviour-change techniques, wearable activity sensors, telemedicine
Patients with CKD and concomitant cardiovascular disease are advised to exercise according to heart failure, coronary heart disease, or peripheral artery disease ESC guidelines

CKD, chronic kidney disease.

KDIGO 2021 recommends considering CRF status, physical limitations, cognitive function, and risk of falls when deciding on the type and intensity of ET in the individual patient with CKD.[47] According to the 2020 ESC Guidelines on sports cardiology and exercise in patients with CVD, the form and intensity of physical activity and ET should be considered and modified as necessary on the individual level.[108] Thus, assessment of physical function is important to detect patients functional limitations and needs as well as to ensure patients' safety during exercise (*Figure 1*). Considering that patients with CKD have a high prevalence of CAD and often a plethora of CV risk factors, it is important that the patient's nephrologist performs a clinical evaluation and a physiotherapist or exercise physiologist tests the patient before prescribing personalized ET. An exercise test provides important information for risk stratification (*Figure 1*). Simple field tests as the 6MWT and STS tests are useful in clinical practice for prescribing and monitoring ET.[13] Self-monitoring exercise intensity by using the Borg Scale of rating of perceived exertion enables both the patient and the physiotherapist to adjust the intensity of the prescription and maintain a level of adequate exertion which is both safe and effective.[105]

Some evidence suggests that regular ET may have added value for reduction of overall CV risk and mortality in patients with CKD. Clinicians and healthcare professionals should encourage patients with CKD to be active and participate in individualized ET programmes. Selection of ET modalities and prescription of optimal individualized training programmes is essential but also challenging. Key elements of why and how to principally apply exercise treatment in CKD, based on the evidence presented in this document, are summarized in the Summary Box. Until more data on individualized exercise prescription and associated improvement of CV outcome in patients with CKD are available, the principles of exercise prescription in CKD should be orientated towards recommendations of current ESC guidelines on CVD prevention[109] and exercise in patients with CVD,[108] even though not CKD-specific but taking into account the specific multi-morbidity and potential frailty of these patients (*Table 7*). Exercise should be prescribed based on shared decision-making and on the perception that even a small increase in physical activity levels and physical function can have a clinically relevant impact on the improvement of CV outcome in patients with CKD.

Author contribution

All authors contributed to the writing, design, and review of the manuscript.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: none declared.

Data availability

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. *Nephrol Dial Transplant* 2019;**34**:1803–1805.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
3. Jankowski J, Floege J, Fliser D, Bohm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation* 2021;**143**:1157–1172.
4. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bragg-Gresham J, Balkrishnan R, *et al.* US renal data system 2018 annual data report: chapter 4: cardiovascular disease in patients with CKD. *Am J Kidney Dis* 2019;**73**:S79–S98.
5. Martins P, Marques E, Leal D, Ferreira A, Wilund K, Viana J. Association between physical activity and mortality in end-stage kidney disease: a systematic review of observational studies. *BMC Nephrol* 2021;**22**:227.
6. Clyne N, Anding-Rost K. Exercise training in chronic kidney disease—effects, expectations and adherence. *Clin Kidney J* 2021;**14**:ii3–ii14.
7. Segura-Orti E, Gordon PL, Doyle JW, Johansen KL. Correlates of physical functioning and performance across the spectrum of kidney function. *Clin Nurs Res* 2018;**27**:579–596.
8. Zhu Y, Bu Y, Zhang G, Ding S, Zhai D, Wan Z, *et al.* Association of physical activity with chronic kidney disease: a systematic review and dose–response meta-analysis. *Aging (Albany NY)* 2020;**12**:19221–19232.
9. Baker LA, March DS, Wilkinson TJ, Billany RE, Bishop NC, Castle EM, *et al.* Clinical practice guideline exercise and lifestyle in chronic kidney disease. *BMC Nephrol* 2022;**23**.
10. Ross R, Murthy J, Wollak I, Jackson A. The six minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulm Med* 2010;**10**:31.
11. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2011;**10**:CD003236.
12. Wyngaert KV, Van Craenenbroeck AH, Van Biesen W, Dhondt A, Tanghe A, Van Ginckel A, *et al.* The effects of aerobic exercise on eGFR, blood pressure and VO_2peak in patients with chronic kidney disease stages 3–4: a systematic review and meta-analysis. *PLoS One* 2018;**13**:e0203662.
13. Segura-Orti E, Koufaki P, Kouidi E. Bridging the gap from research to practice for enhanced health-related quality of life in people with chronic kidney disease. *Clin Kidney J* 2021;**14**:ii34–ii42.
14. Hishii S, Miyatake N, Nishi H, Katayama A, Ujike K, Koumoto K, *et al.* Relationship between sedentary behavior and all-cause mortality in Japanese chronic haemodialysis patients: a prospective cohort study. *Acta Med Okayama* 2019;**73**:419–425.

15. Matsuzawa R, Matsunaga A, Wang G, Kutsuna T, Ishii A, Abe Y, *et al.* Habitual physical activity measured by accelerometer and survival in maintenance haemodialysis patients. *Clin J Am Soc Nephrol* 2012;**7**:2010–2016.
16. Tentori F, Elder SJ, Thumma J, Pisoni RL, Bommer J, Fissell RB, *et al.* Physical exercise among participants in the dialysis outcomes and practice patterns study (DOPPS): correlates and associated outcomes. *Nephrol Dial Transplant* 2010;**25**:3050–3062.
17. Greenwood S, Castle E, Lindup H, Mayes J, Waite I, Grant D, *et al.* Mortality and morbidity following exercise-based renal rehabilitation in patients with chronic kidney disease: the effect of programme completion and change in exercise capacity. *Nephrol Dial Transplant* 2019;**34**:618–625.
18. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, *et al.* Exercise in patients on dialysis: a multicenter, randomized clinical trial. *J Am Soc Nephrol* 2017;**28**:1259–1268.
19. Mallamaci F, D'Arrigo G, Tripepi G, Lamberti N, Torino C, Manfredini F, *et al.* Long-Term effect of physical exercise on the risk for hospitalization and death in dialysis patients. A post-trial long-term observational study. *Clin J Am Soc Nephrol* 2022;**17**:1176–1182.
20. Anding-Rost K, von Gersdorff G, von Korn P, Ihorst G, Josef A, Kaufmann M, *et al.* Exercise during haemodialysis in patients with chronic kidney failure. *NEJM Evidence* 2023;**2**:EVIDoa2300057.
21. Hellberg M, Höglund P, Svensson P, Clyne N. Randomized controlled trial of exercise in chronic kidney disease—the RENEXC study. *Kidney Int Rep* 2019;**4**:963–976.
22. Weiner DE, Liu CK, Miao S, Fielding R, Katzel L, Giffuni J, *et al.* Effect of long-term exercise training on physical performance and cardiorespiratory function in adults with CKD: a randomized controlled trial. *Am J Kidney Dis* 2023;**81**:59–66.
23. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;**32**:S112–S119.
24. Ortiz A, Covic A, Fliser D, Fouque D, Goldsmith D, Kanbay M, *et al.*; Board of the E-mWGoERAE. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet* 2014;**383**:1831–1843.
25. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, *et al.* Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One* 2018;**13**:e0192895.
26. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, *et al.* Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–352.
27. Noels H, Lehrke M, Vanholder R, Jankowski J. Lipoproteins and fatty acids in chronic kidney disease: molecular and metabolic alterations. *Nat Rev Nephrol* 2021;**17**:528–542.
28. Guerin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 2000;**15**:1014–1021.
29. London GM, Pannier B, Marchais SJ, Guerin AP. Calcification of the aortic valve in the dialyzed patient. *J Am Soc Nephrol* 2000;**11**:778–783.
30. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 2018;**61**:2108–2117.
31. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, *et al.* Mineralocorticoid receptor antagonist tolerability study-diabetic nephropathy study G. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;**314**:884–894.
32. Yang L, Wu X, Wang Y, Wang C, Hu R, Wu Y. Effects of exercise training on proteinuria in adult patients with chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2020;**21**:172.
33. Sovatzidis A, Chatzinikolaou A, Fatouros IG, Panagoutsos S, Draganidis D, Nikolaidou E, *et al.* Intradialytic cardiovascular exercise training alters redox status, reduces inflammation and improves physical performance in patients with chronic kidney disease. *Antioxidants (Basel)* 2020;**9**:868.
34. Watson EL, Baker LA, Wilkinson TJ, Gould DW, Xenophontos S, Graham-Brown M, *et al.* Inflammation and physical dysfunction: responses to moderate intensity exercise in chronic kidney disease. *Nephrol Dial Transplant* 2022;**37**:860–868.
35. Zhou Y, Hellberg M, Hellmark T, Höglund P, Clyne N. Twelve months of exercise training did not halt abdominal aortic calcification in patients with CKD—a sub-study of RENEXC—a randomized controlled trial. *BMC Nephrol* 2020;**21**:233.
36. Bishop N, Burton J, Graham-Brown M, Stensel D, Viana J, Watson E. Exercise and chronic kidney disease: potential mechanisms underlying the physiological benefits. *Nat Rev Nephrol* 2023;**19**:244–256.
37. Sprick JD, Mammino K, Jeong J, DaCosta DR, Hu Y, Morison DG, *et al.* Aerobic exercise training improves endothelial function and attenuates blood pressure reactivity during maximal exercise in chronic kidney disease. *J Appl Physiol (1985)* 2022;**132**:785–793.
38. Kirkman DL, Ramick MG, Muth BJ, Stock JM, Pohlig RT, Townsend RT, *et al.* The effects of aerobic exercise on vascular function in non-dialysis chronic kidney disease: a randomized controlled trial. *Am J Physiol Renal Physiol* 2019;**316**:F898–F905.
39. Oliveira e Silva VR, Stringuetta Belik F, Hueb JC, de Souza Gonçalves R, Costa Teixeira Caramori J, *et al.* Aerobic exercise training and nontraditional cardiovascular risk factors in haemodialysis patients: results from a prospective randomized trial. *Cardiorenal Med* 2019;**9**:391–399.
40. Cooke AB, Ta V, Iqbal S, Gomez YH, Mavrakanas T, Barré P, *et al.* The impact of intradialytic pedaling exercise on arterial stiffness: a pilot randomized controlled trial in a haemodialysis population. *Am J Hypertens* 2018;**31**:458–466.
41. Greenwood SA, Koufaki P, Mercer TH, MacLaughlin HL, Rush R, Lindup H, *et al.* Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: a pilot randomized controlled trial. *Am J Kidney Dis* 2015;**65**:425–434.
42. Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, Vrints CJ, Conraads VM, Verpooten GA, *et al.* Effect of moderate aerobic exercise training on endothelial function and arterial stiffness in CKD stages 3–4: a randomized controlled trial. *Am J Kidney Dis* 2015;**66**:285–296.
43. Koh KP, Fassett RG, Sharman JE, Coombes JS, Williams AD. Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in haemodialysis patients: a randomized pilot study. *Am J Kidney Dis* 2010;**55**:88–99.
44. Agarwal R, Andersen MJ. Correlates of systolic hypertension in patients with chronic kidney disease. *Hypertension* 2005;**46**:514–520.
45. Bakris GL, Ritz E; World Kidney Day Steering Committee. The message for world kidney day 2009. Hypertension and kidney disease—a marriage that should be prevented. *J Hypertens* 2009;**27**:666–669.
46. Mancia G, Kreutz R, Brunstroom M, Burnier M, Grassi G, Januszewicz A, *et al.* 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens* 2023;**41**:1874–2071.
47. Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, *et al.* Kidney disease: improving global outcomes blood pressure work G. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;**99**:S1–S87.
48. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, *et al.* Effects of intensive BP control in CKD. *JASN* 2017;**28**:2812–2823.
49. Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, *et al.* Trial of intensive blood-pressure control in older patients with hypertension. *NEJM* 2021;**385**:1268–1279.
50. Hanssen H, Boardman H, Deiseroth A, Moholdt T, Simonenko M, Krankel N, *et al.* Personalized exercise prescription in the prevention and treatment of arterial hypertension: a consensus document from the European Association of Preventive Cardiology (EAPC) and the ESC council on hypertension. *Eur J Prev Cardiol* 2022;**29**:205–215.
51. Thompson S, Wiebe N, Padwal RS, Gyenes G, Headley SAE, Radhakrishnan J, *et al.* The effect of exercise on blood pressure in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2019;**14**:e0211032.
52. Zhang L, Wang Y, Xiong L, Luo Y, Huang Z, Yi B. Exercise therapy improves eGFR, and reduces blood pressure and BMI in non-dialysis CKD patients: evidence from a meta-analysis. *BMC Nephrol* 2019;**20**:398.
53. Wu X, Yang L, Wang Y, Wang C, Hu R, Wu Y. Effects of combined aerobic and resistance exercise on renal function in adult patients with chronic kidney disease: a systematic review and meta-analysis. *Clin Rehabil* 2020;**34**:851–865.
54. Young HML, March DS, Graham-Brown MPM, Jones AW, Curtis F, Grantham CS, *et al.* Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2018;**33**:1436–1445.
55. Pu J, Jiang Z, Wu W, Li L, Zhang L, Li Y, *et al.* Efficacy and safety of intradialytic exercise in haemodialysis patients: a systematic review and meta-analysis. *BMJ Open* 2019;**9**:e020633.
56. Ferrari F, Helal L, Dipp T, Soares D, Soldatelli Â, Mills AL, *et al.* Intradialytic training in patients with end-stage renal disease: a systematic review and meta-analysis of randomized clinical trials assessing the effects of five different training interventions. *J Nephrol* 2020;**33**:251–266.
57. Thangarasa T, Imtiaz R, Hiremath S, Zimmerman D. Physical activity in patients treated with peritoneal dialysis: a systematic review and meta-analysis. *Can J Kidney Health Dis* 2018;**5**:205435811877982.
58. Tuttle KR, Bakris GL, Bilous RW, Bilous RW, Chiang JL, de Boer IH, *et al.* Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;**37**:2864–2883.
59. Amaral LSB, Souza CS, Lima HN, Soares TJ. Influence of exercise training on diabetic kidney disease: a brief physiological approach. *Exp Biol Med (Maywood)* 2020;**245**:1142–1154.
60. Friedman AN, Chambers M, Kamendulis LM, Temmerman J. Short-term changes after a weight reduction intervention in advanced diabetic nephropathy. *Clin J Am Soc Nephrol* 2013;**8**:1892–1898.

61. Shurraw S, Hemmelgarn B, Lin M, Majumdar S, Klarenbach S, Manns B, *et al.* Alberta Kidney Disease Network. Association between glycaemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. *Arch Intern Med* 2011;**171**:1920–1927.
62. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, *et al.* 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;**44**:4043–4140.
63. Böhm M, Schumacher H, Werner C, Teo K, Lonn E, Mahfoud F, *et al.* Association between exercise frequency with renal and cardiovascular outcomes in diabetic and non-diabetic individuals at high cardiovascular risk. *Cardiovasc Diabetol* 2022;**21**:12.
64. Nylen ES, Gandhi SM, Kheirbek R, Kokkinos P. Enhanced fitness and renal function in type 2 diabetes. *Diabet Med* 2015;**32**:1342–1345.
65. Kelly JT, Su G, Zhang L, Qin X, Marshall S, González-Ortiz A, *et al.* Modifiable lifestyle factors for primary prevention of CKD: a systematic review and meta-analysis. *J Am Soc Nephrol* 2021;**32**:239–253.
66. Cai Z, Yang Y, Zhang J. Effects of physical activity on the progression of diabetic nephropathy: a meta-analysis. *Biosci Rep* 2021;**41**:BSR20203624.
67. Wang XR, Zhang JJ, Xu XX, Wu YG. Prevalence of coronary artery calcification and its association with mortality, cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. *Ren Fail* 2019;**41**:244–256.
68. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, *et al.* Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;**342**:1478–1483.
69. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2008;**19**:213–216.
70. Shroff R, Weaver DJ, Mitsnefes MM. Cardiovascular complications in children with chronic kidney disease. *Nat Rev Nephrol* 2011;**7**:642–649.
71. Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, Hoymans VY, Verpooten GA, Vrints CJ, *et al.* Impaired vascular function contributes to exercise intolerance in chronic kidney disease. *Nephrol Dial Transplant* 2016;**31**:2064–2072.
72. Mustata S, Chan C, Lai V, Miller JA. Impact of an exercise programme on arterial stiffness and insulin resistance in haemodialysis patients. *J Am Soc Nephrol* 2004;**15**:2713–2718.
73. Günthner R, Streese L, Angermann S, Lorenz G, Braunisch M, Matschkal J, *et al.* Mortality prediction of retinal vessel diameters and function in a long-term follow-up of haemodialysis patients. *Cardiovasc Res* 2022;**118**:3239–3249.
74. Brouwers FP, de Boer RA, van der Harst P, Voors A, Gansevoort R, Bakker S, *et al.* Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013;**34**:1424–1431.
75. Gori M, Senni M, Gupta DK, Charytan D, Kraigher-Krainer E, Pieske B, *et al.* Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J* 2014;**35**:3442–3451.
76. O'Connor CM, Whellan DJ, Lee KL, Keteyian S, Cooper L, Ellis S, *et al.* Efficacy and safety of exercise training in patients with chronic heart failure: hF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
77. McDonagh TA, Metra M, Adamo M, Gardner R, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
78. Tucker WJ, Beaudry RI, Liang Y, Clark A, Tomczak C, Nelson M, *et al.* Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. *Prog Cardiovasc Dis* 2019;**62**:163–171.
79. Pearson MJ, Mungovan SF, Smart NA. Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev* 2017;**22**:229–242.
80. Edelmann F, Gelbrich G, Düngen HD, Fröhling S, Wachter R, Stahrenberg R, *et al.* Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (exercise training in diastolic heart failure) pilot study. *J Am Coll Cardiol* 2011;**58**:1780–1791.
81. Mueller S, Winzer EB, Duvinage A, Gevaert A, Edelmann F, Haller B, *et al.* Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2021;**325**:542–551.
82. Graham-Brown M, March D, Young R, Highton P, Young H, Churchward D, *et al.* A randomized controlled trial to investigate the effects of intra-dialytic cycling on left ventricular mass. *Kidney Int* 2021;**99**:1478–1486.
83. Momeni A, Nematolahi A, Nasr M. Effect of intradialytic exercise on echocardiographic findings in haemodialysis patients. *Iranian J Kidney Disease* 2014;**8**:207–211.
84. Deligiannis A, Kouidi E, Tassoulas E, Gigis P, Tourkantonis A, Coats A. Cardiac effects of exercise rehabilitation in haemodialysis patients. *Int J Cardiol* 1999;**70**:253–266.
85. Guio BM, Gomes CP, da Costa FB, de Oliveira A, Duarte MT, Leite Júnior M. Beneficial effects of intradialytic cardiopulmonary rehabilitation. *J Bras Nefrol* 2017;**39**:275–282.
86. Deligiannis A, Kouidi E, Tourkantonis A. Effects of physical training on heart rate variability in patients on haemodialysis. *Am J Cardiol* 1999;**84**:197–202.
87. Deligiannis A, D'Alessandro C, Cupisti A. Exercise training in dialysis patients: impact on cardiovascular and skeletal muscle health. *Clin Kidney J* 2021;**14**:ii25–ii33.
88. Genovesi S, Boriani G, Covic A, Vernooij R, Combe C, Burlacu A, *et al.* Sudden cardiac death in dialysis patients: different causes and management strategies. *Nephrol Dial Transplant* 2021;**36**:396–405.
89. Green D, Roberts PR, New DI, Kalra PA. Sudden cardiac death in haemodialysis patients: an in-depth review. *Am J Kidney Dis* 2011;**57**:921–929.
90. Korantzopoulos P, Liu T, Li L, Goudevenos JA, Li G. Implantable cardioverter defibrillator therapy in chronic kidney disease: a meta-analysis. *Europace* 2009;**11**:1469–1475.
91. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al.* 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015;**17**:1601–1687.
92. Clyne N, Hellberg M, Kouidi E, Deligiannis A, Höglund P. Relationship between declining glomerular filtration rate and measures of cardiac and vascular autonomic neuropathy. *Nephrology (Carlton)* 2016;**21**:1047–1055.
93. Michou V, Liakopoulos V, Roumeliotis S, Roumeliotis A, Anifanti M, Tsamos G, *et al.* Effects of home-based exercise training on cardiac autonomic neuropathy and metabolic profile in diabetic haemodialysis patients. *Life* 2023;**13**:232.
94. Huang H-Y, Hung K-S, Yeh M-L, Chou H-L, Yeh AL, Liao T-Y. Breathing-based leg exercises during haemodialysis improve quality of life: a randomized controlled trial. *Clin Rehabil* 2021;**35**:1175–1184.
95. Huppertz N, Beetham K, Howden E, Leicht A, Isbel N, Coombes J. A 12-month lifestyle intervention does not improve cardiac autonomic function in patients with chronic kidney disease. *Auton Neurosci Basic Clin* 2020;**224**:102642.
96. Kouidi E, Karagiannis V, Grekas D, Iakovides A, Kaprinis G, Tourkantonis A, *et al.* Depression, heart rate variability, and exercise training in dialysis patients. *EJCPR* 2010;**17**:160–167.
97. Kouidi E, Grekas D, Deligiannis A. Effects of exercise training on noninvasive cardiac measures in patients undergoing long-term haemodialysis: a randomized controlled trial. *Am J Kidney Dis* 2009;**54**:511–521.
98. Petraki M, Kouidi E, Grekas D, Deligiannis A. Effects of exercise training during haemodialysis on cardiac baroreflex sensitivity. *Clin Nephrol* 2008;**70**:210–219.
99. Kaltsatou A, Hadjigeorgiou G, Grigoriou S, Karatzaferi C, Giannaki C, Lavdas E, *et al.* Cardiac autonomic function during intradialytic exercise training. *J Postgrad Med* 2019;**131**:539–545.
100. Morais M, Raimundo R, Oliveira F, de Abreu L, Bezerra I, Silva R, *et al.* Is aerobic exercise training during haemodialysis a reliable intervention for autonomic dysfunction in individuals with chronic kidney disease? A prospective longitudinal clinical trial. *J Multidisciplinary Healthcare* 2019;**12**:711–718.
101. Buch AN, Coote JH, Townend JN. Mortality, cardiac vagal control and physical training–what's the link? *Exp Physiol* 2002;**7**:423–435.
102. Besnier F, Labrunée M, Pathak A, Pavy-Le Traon A, Galès C, Sénard JM, *et al.* Exercise training-induced modification in autonomic nervous system: an update for cardiac patients. *Ann Phys Rehabil Med* 2017;**60**:27–35.
103. Pearson MJ, Smart NA. Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev* 2018;**23**:91–108.
104. Zhang F, Ren Y, Wang H, Bai Y, Huang L. Daily step counts in patients with chronic kidney disease: a systematic review and meta-analysis of observational studies. *Front Med (Lausanne)* 2022;**9**:842423.
105. Svensson P, Hellberg M, Zhou Y, Wisén A, Clyne N. The Borg scale is a sustainable method for prescribing and monitoring self-administered aerobic endurance exercise in patients with chronic kidney disease. *Eur J Physiother* 2023;**25**:265–273. DOI: 10.1080/21679169.2022.20862935
106. Beetham KS, Howden EJ, Fassett RG, Petersen A, Trewin AJ, Isbel NM, *et al.* High-intensity interval training in chronic kidney disease: a randomized pilot study. *Scand J Med Sci Sports* 2019;**29**:1197–1204.
107. Nilsson BB, Bunæs-Næss H, Edvardsen E, Stenehjem AE. High-intensity interval training in haemodialysis patients: a pilot randomised controlled trial. *BMJ Open Sport Exerc Med* 2019;**5**:e000617.
108. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, *et al.* 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96.
109. Visseren F, Mach F, Smulders Y, Carballo D, Koskinas K, Bäck M, *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol* 2022;**29**:5–115.