Comparison of the clinical parameters of paricalcitol and finerenone in slowing down the progression of chronic kidney disease

Mellis, Delia

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

DELIA MELLIS

COMPARISON OF THE CLINICAL PARAMETERS OF PARICALCITOL AND FINERENONE IN SLOWING DOWN THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Diploma Thesis

Academic year:

2023/2024

Mentor:

Prof. Dr. med. Johannes Brachmann

COBURG, September 2024

TABLE OF CONTENT

1. INTRODUCTION…….……...…...1
1.1 THE KIDNEY – THE ORGAN…….2
1.1.1 ANATOMY…….2
1.1.2 HISTOLOGY……..2
1.1.3 PHYSIOLOGY……...……3
1.1.4 SYMPTOMS……..4
1.1.5 DIAGNOSIS……...4
1.2 RENAL INSUFFICIENCY……...6
1.2.1 DEFINITION……..6
1.2.2 ACUTE RENAL FAILURE……6
1.2.3 CHRONIC RENAL FAILURE……...8
1.2.4 CLASSIFICATION OF CHRONIC RENAL FAILURE……8
1.2.5 EPIDEMIOLOGY……..9
1.2.6 MORTALITY IN DIALYSIS PATIENTS…….10
1.2.7 PATHOGENESIS…….12
1.2.8 PATHOPHYSIOLOGY……13
1.2.9 SYMPTOMS……14
1.2.10 DIAGNOSIS……...15
1.2.11 TREATMENT…….16
1.2.12 RENAL REPLACEMENT THERAPY……..17
1.2.13 COMPLICATIONS……18
1.3 INFLAMMATION……..19
1.3.1 DEFINITION……19
1.3.2 RELEVANCE OF INFLAMMATION IN DIALYSIS PATIENTS……...20
1.3.3 URINARY MARKER OF INFLAMMATION…….21
1.3.4 CALCIFICATION……21
1.4 PARICALCITOL…….24
1.4.1 MECHANISM OF ACTION……24
1.4.2 VITAMIN D AND CHRONIC KIDNEY DISEASE…….25
1.5 FINERENONE……25
1.5.1 MECHANISM OF ACTION……25

2. OBJECTIVES……...27
2.1 AIM OF THE STUDY…….28
2.2 HYPOTHESIS…….28
3. PATIENTS AND METHODS……29
3.1 STUDY DESIGN AND ETHICAL APPROVAL……30
3.2 SEARCH CRITERIA……..30
3.3 ELIGIBILITY CRITERIA……...31
3.4 DATA EXTRACTION…….32
3.5 METHODOLOGICAL QUALITY ASSESSMENT……...32
4. RESULTS……..34
4.1 STUDY CHARACTERISTICS……...35
4.2 SUMMARY OF INCLUDED STUDIES…….38
4.3 METHODOLOGICAL ASSESMENT……44
4.4 OUTCOME ANALYSIS…….45
5. DISCUSSION……...54
6. CONCLUSION…….59
7. REFERENCES……..61
8. SUMMARY……..68
9. CROATIAN SUMMARY…….70

ACKNOWLEDGEMENT

I would like to express my gratitude and appreciation to my mentor Prof. Dr. med. Brachmann, who encouraged me with this thesis with supporting advice. Thank you also to Dr. Patrick Biggar, who has supported me not only in this diploma thesis, but throughout six years of medical school.

Furthermore, I would like to thank my parents for their support and encouragement throughout medical school. You were always there for the good and bad times.

Special thanks go to my friends Margarete Will, Linda Heinrich and Teresa Sappelt, who have supported me in one way or another to write this diploma thesis.

To my dearest friends of medical school – Thank you so much for supporting me with your time, patience, and faith every day of med school. Together, we went beyond and above of what we thought we could do.

LIST OF ABBREVIATIONS

ACEi	–	angiotensin converting enzyme inhibitors
ADQI	–	acute dialysis quality initiative
AKIN	–	acute kidney injury network
ARB	–	angiotensin receptor blocker
ARR	–	absolute risk reduction
CKD	–	chronic kidney disease
CT	–	computer tomography
DMT2	–	diabetes mellitus type 2
EGFR	–	estimated glomerular filtration rate
GFR	–	glomerular filtration rate
HbA1c	–	glycated hemoglobin
KDa	–	kilo Dalton
KDIGO	–	kidney disease improving global outcomes
KDOQI	–	kidney disease outcome quality initiative
MRT	–	magnet resonant tomography
RAAS	–	renin angiotensin aldosterone system
RCT	–	randomized controlled trial
RRR	–	relative risk reduction
UACR	–	urinary albumin creatinine ratio

1. INTRODUCTION

1.1 THE KIDNEY – THE ORGAN

1.1.1 ANATOMY

The kidneys are paired and lie in the retroperitoneal space at the level between the 12th thoracic and the third lumbar vertebrae. Their weight is each about 150 grams and their size is about 10-12 cm long and 5-6 cm wide (1).

The arterial blood supply into the renal hilum via the left and right renal arteries originates directly from the abdominal aorta at the level of the first lumbar vertebra. In the kidneys, they divide further into segmental, interlobar, arcuate, cortical radiate arteries and afferent arterioles leading to the glomerular capillaries. From there, they develop into the venous system with afferent veins, vasa recta and peritubular capillaries, cortical radiate, arcuate, interlobar and renal veins, which drain into the inferior vena cava (1).

The kidneys are innervated by the renal plexus with sympathetic and parasympathetic fibers, which originate from the celiac plexus (1).

1.1.2 HISTOLOGY

Macroscopically, the kidneys are bean shaped and have a brown reddish, fibrous capsule. In a frontal cut, they have a renal cortex in the outer lining and the medulla in the center. The medulla contains 5-7 renal pyramids divided by the renal columns. The tip of each pyramid is a renal papilla, draining primary urine into the minor and major calyces and finally into the renal pelvis, which is the beginning of the ureter (2).

Microscopically, the renal cortex and outer medulla contain the nephrons, which are the functional units of the kidneys. Every kidney has about 1-1.5 million nephrons (3). The nephron consists of the glomerulus, a bundle of about thirty capillaries, which is supplied by the afferent arteriole and drained by the efferent arteriole (2). The glomerulus is surrounded by the Bowman´s capsule, which has an outer, parietal layer and an inner, visceral layer. The parietal layer consists of squamous cells. The visceral layer consists of podocytes, which ultrafiltrate the primary urine into the tubular system (2). The filtration barrier consists of three layers, the endothelium of the glomerulus for blood cells, the glomerular basement membrane for molecules larger than 70 000 Daltons, such as proteins or albumin, and the podocytes (2). The tubular system is divided into the proximal convoluted tubule, the intermediate part, also called the loop of Henle with a thin descending and thick ascending part, the distal convoluted tubule and the collecting tubule (2). The collecting tubules drain in larger papillary ducts into the renal

papilla, where the urine is further transported (2). The juxtaglomerular apparatus is situated between the renal corpuscle with the afferent and efferent arteriole and the distal convoluted tubule. It has three components: the granular cells, the macula densa and the mesangium extraglomerular cells. The granular cells are close to the afferent arteriole and contain renin. The macula densa is situated on the wall of the distal convoluted tubule. The mesangium extraglomerular cells are between the described cells and are connected to the mesangium intraglomerular cells (2).

1.1.3 PHYSIOLOGY

The kidneys have multiple essential functions, for which they need a high blood flow. Their minute blood volume is about 1200 ml, which is equal to 20% of the cardiac output (3). The renal function involves the homeostasis of water and electrolytes, such as sodium, potassium, calcium, chloride, and magnesium (3). Furthermore, the kidneys excrete substances, such as urea, uric acid and creatinine. The kidneys reabsorb nutrients, such as glucose and amino acids. They regulate the homeostasis of acids and bases by excreting or reabsorbing hydrogen, hydrogen carbonate and bicarbonate (3). Another important function is the synthesis of hormones and enzymes. Erythropoietin is important for the activation of the erythropoiesis. Renin regulates the blood pressure via RAAS and will be explained in detail in the section about GFR. The final hydroxylation of cholecalciferol to active vitamin D also takes place in the kidneys (4).

Each function is assigned to a specific part of the nephron. In the glomerulus, the primary urine is ultra filtrated from the capillaries. The glomerulus is lined by three layers. The endothelial layer retains blood cells within the capillary (3). The glomerular basement membrane has tightly packed, negatively charged proteins, which retain plasma molecules larger than >50-400 kDa and negatively charged proteins such as albumin. Therefore, the ultrafiltrate is normally almost free of protein (3). The podocytes cover the negatively charged glycocalyx and filters molecules up to 5 nm. Molecules with a smaller size of 5 kDa are freely filtered, including glucose, amino acids, peptides, inulin, urea, uric acid and creatinine (3). The primary urine is drained into the tubular system. In the proximal convoluted tubule and thick descending part approximately about 60% of water and salts and almost all glucose and amino acids are reabsorbed (3). The loop of Henle has a high osmotic pressure for the concentration of the primary urine. In the thick ascending tubule, Na^+-K^+-$2Cl^-$symporters are active, which support urine concentration (3). The distal tubule returns adjacent to the glomerulus as the

juxtaglomerular apparatus, which gives precise feedback and regulates the filtration rate in the glomerulus. The filtration rate is down regulated by constriction of the afferent arteriole if the sodium concentration or the flow rate is too high (3). The collecting tubule is regulated by the hormones aldosterone and ADH regarding urine concentration and water excretion. Aquaporin-2 is a water channel, which becomes active under the influence of ADH, thus enabling intense water reabsorption (3). Aldosterone increases the reabsorption of sodium and secretion of potassium and hydrogen (4).

The GFR is the flow rate of filtered fluid in milliliters per minute. The normal GFR is about 120 ml/min. The filtration rate depends on the hydrostatic pressure in the glomerulus, the surface area and the water permeability (3). The capillary pressure needs to be constant, therefore, the kidneys exercise autoregulation of the capillary blood pressure. This compensates blood pressure ranges between 80-180 mmHg (3) by two mechanisms: The Bayliss effect is a myogenic reaction of the smooth muscle cells of the walls of the afferent arterioles and interlobular arteries. With increasing intravascular pressure, slow calcium channels open mechanically and lead to a preglomerular vasoconstriction and vice versa (3). The second mechanism is the tubuloglomerular feedback. If the sodium chloride concentration rises within the ascending part of the loop of Henle, the macula densa cells in the juxtaglomerular apparatus initiate preglomerular vasoconstriction (3). If the blood pressure falls below 80 mmHg, renin is released by the granular cells in the juxtaglomerular apparatus to activate the RAAS. Renin activates angiotensin II, which induces global vasoconstriction to increase systemic blood pressure and vasoconstriction of the efferent arterioles to increase pressure in the glomerulus, therefore, leading to a higher GRF (3). If the blood pressure is chronically elevated, pressure diuresis results (4), which can damage the glomeruli and consequently the renal function.

1.1.4 SYMPTOMS

A first symptom of renal failure to the patient may be a disturbance of miction. Oliguria, anuria and polyuria may indicate acute or chronic kidney failure (4). Another important symptom may be noticeable oedema, especially at the extremities or eye lids (4).

1.1.5 DIAGNOSIS

A valid diagnosis starts with an anamnesis, where a clinician asks the patient about miction, flank pain, oedema, fever and headache. A clinical examination includes the evaluation of the vital signs, oedema, skin colorit, dermal sensitivity regarding polyneuropathy, kidney palpitation pain, transabdominal auscultation of the renal arteries (4).

A blood analysis gives additional information about creatinine, urea and inflammatory markers. Serum creatinine is subject to several factors as it is a metabolite of muscle mass and is excreted and secreted by the glomeruli. Urea is a metabolite of proteins and can be reabsorbed. Inflammatory markers are not specific to the kidneys, but are relevant for the evaluation, if an inflammatory process is active in the patient (4).

Urine analysis can be taken from a sample of spontaneous urine or from collected urine, meaning spontaneous urination in a specified 24-hour collection period or from a catheter. Firstly, color and clearness are evaluated macroscopically. Bright urine indicates a strong diuresis, dark urine can indicate dehydration or acute renal failure. Red urine is a sign of haematuria or may be caused by drugs or food. If leukocytes are in the urine, it appears cloudy. A urine stick gives further information, if erythrocytes, leukocytes, glucose, or proteins are excreted in the urine (4). Macro- or microhematuria, glycosuria or proteinuria indicate renal damage (4). Proteinuria can be categorized into prerenal, glomerular, tubular, glomerutubular and postrenal. The glomerular proteinuria is characterized by permeability for proteins larger than 60 kDa and may be divided into selective proteinuria when only albumin is excreted, or nonselective proteinuria, when e.g. additionally IgG is secreted (4). A urine stick gives information about the pH of the urine, specific weight, bilirubin, and ketone bodies (4).

Functional diagnostics includes the evaluation of the clearance. The unit of clearance is in milliliters per minute and indicates, how much blood plasma volume is filtered. The GFR is a marker for renal function and is equal to the clearance of freely filtered substances (4). The pressure within the Bowmans capsule is maintained constant and the glomerular capillary pressure is autoregulated by the afferent and efferent arteriole (3). This has the strongest influence on the GFR. If the GFR is reduced, this can be caused by a lower glomerular capillary pressure because of hypovolemia or hypotension, by higher hydrostatic pressure in the Bowmans capsule in case of urinary congestion or when the filtration is reduced by reduced permeability caused by structural damage in diabetes or amyloidosis. A higher GFR can be caused vice versa by hypervolemia, hypertension, or fever (4).

The options for medical imaging of the kidneys includes sonography, x-ray, CT and MRT with or without contrast agents. Sonography is the first imaging method due to its availability, low costs, and no radiation exposure. A clinician can evaluate renal size, blood flow and ureter dilation (4). An x-ray of the kidneys may be performed without contrast agents to detect urolithiasis. In chronic urolithiasis or congenital ureter anomalies, an x-ray or CT may

be performed with and without additional iodine contrast agent to detect obstructions and their causes (4). CT and MRT are used if a tumor is suspected. The MRT is more appropriate due to its better imaging of soft tissue than a CT. A radio nuclear contrast agent may be used with a scintigraphy gamma camera to assess the clearance of each kidney individually (4).

Invasive diagnostics include a biopsy of the kidneys if a nephrotic syndrome is suspected or if there is idiopathic acute renal failure (4).

1.2 RENAL INSUFFICIENCY

1.2.1 DEFINITION

Renal insufficiency can be divided into acute renal failure and chronic renal insufficiency.

Acute renal failure is the sudden decrease in renal function and the corresponding GFR. This results in a sudden increase in serum levels of urea and creatinine, ultimately leading to dysfunction of salt and water homeostasis (5).

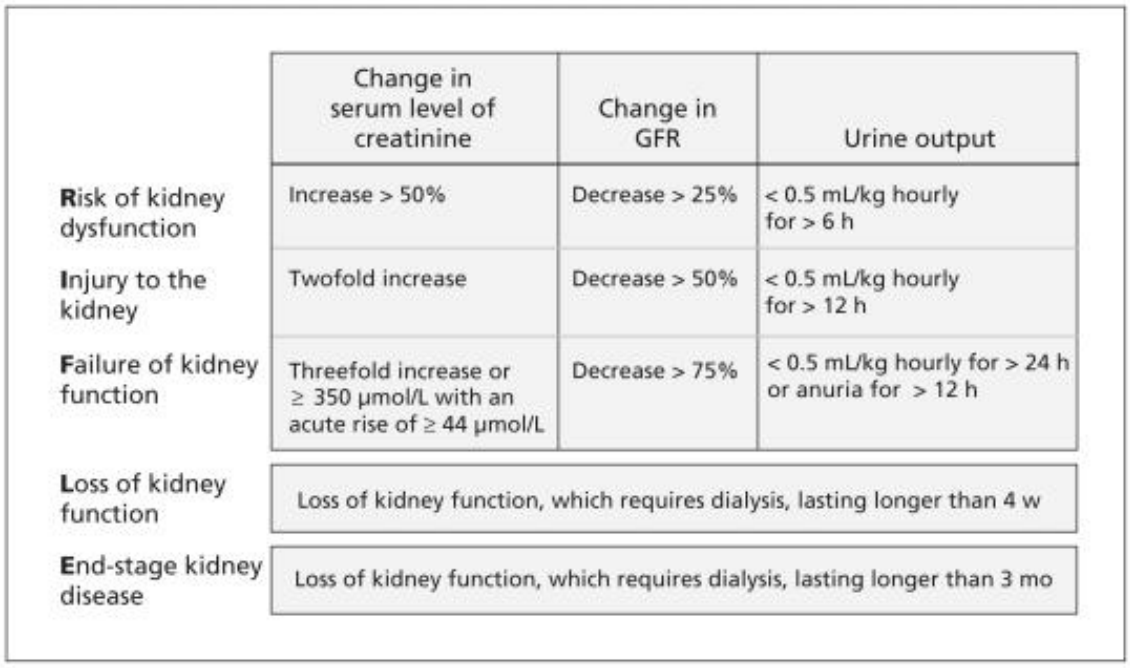
Chronic renal failure is an irreversible and persistent decline of glomerular, tubular and endocrine renal function persisting over 3 months. The insufficiency is progressive and ultimately resulting in renal replacement therapy, such as dialysis or renal transplantation (6).

1.2.2 ACUTE RENAL FAILURE

The traditional definition of acute renal failure is vague, as there are no specific time frames in hours or days for “sudden” or “rapid”. The severity of acute renal failure may correlate with the rapidity of onset (5).

The serum concentration of urea may vary, as it depends on drug therapy, amount of protein intake, gastrointestinal hemorrhage and critical illness. The serum concentration of creatinine depends on the muscle mass, which varies with age, sex, amount of muscles and creatinine generation. Therefore, creatinine cannot give an acute estimate of the true GFR and lags behind changes in the GFR. If a patient is on dialysis, creatinine is removed from the blood. All in all, this makes creatinine a rather unreliable marker for the GRF (5).

Historically, there was no universal definition of acute kidney disease. The RIFLE classification (Figure 1) for acute renal failure was developed in 2000 by the Acute Dialysis Quality Initiative ADQI as a guideline for treatment and prevention. It includes the grade of injury as risk of kidney dysfunction, injury to the kidney, extent of kidney failure as measured in changes in creatinine levels, GFR and urine output, and, furthermore, the development of loss of kidney function and end-stage kidney disease. This together forms the acronym RIFLE



	Change in serum level of creatinine	Change in GFR	Urine output
Risk of kidney dysfunction	Increase > 50%	Decrease > 25%	< 0.5 mL/kg hourly for > 6 h
Injury to the kidney	Twofold increase	Decrease > 50%	< 0.5 mL/kg hourly for > 12 h
Failure of kidney function	Threefold increase or ≥ 350 µmol/L with an acute rise of ≥ 44 µmol/L	Decrease > 75%	< 0.5 mL/kg hourly for > 24 h or anuria for > 12 h
Loss of kidney function	Loss of kidney function, which requires dialysis, lasting longer than 4 w		
End-stage kidney disease	Loss of kidney function, which requires dialysis, lasting longer than 3 mo		

(5).

Figure 1. RIFLE classification (h = hours, w = weeks, mo = months)

Source: Hilton R. Defining acute renal failure. CMAJ. 2011;183:1167-9.

The RIFLE classification has several weaknesses: Outpatients with acute renal dysfunction may present without baseline values for their individual renal function, which the RIFLE classification heavily depends on as visible in Figure 1. Quick changes in serum creatinine are also problematic, as they do not correlate immediately with an actual change in GFR. The assignment to the group of changes of creatinine and urine output into the same group may be arbitrary, as serum creatinine is a more precise predictor of mortality than urine output. In this case, it is important to use the less favorable RIFLE level (5).

In 2005, modifications were made to the RIFLE criteria by AKIN. The term “acute kidney injury” was introduced to include the whole spectrum of renal dysfunction, from minor

changes to dialysis (Figure 2). “Abrupt” was defined as within 48 hours for reduced renal function with increase of creatinine level in total or in percent or reduction of urine output to categorize acute renal injury into three stages and for following the clinical course (5).

	Change in serum level of creatinine	Urine output
Stage 1	Increase of ≥ 26.4 µmol/L or 150%–200% from baseline	< 0.5 mL/kg hourly for > 6 h
Stage 2	Increase > 200%–300% from baseline	< 0.5 mL/kg hourly for > 12 h
Stage 3	Increase > 300% from baseline or ≥ 354 µmol/L with an acute increase of ≥ 44 µmol/L	< 0.3 mL/kg hourly for > 24 h or anuria for > 12 h

Figure 2. Staging scheme for acute kidney injury

Source: Hilton R. Defining acute renal failure. CMAJ. 2011;183:1167-9.

This improves the shortcomings of the RIFLE classification, as no previous baseline measurements are needed, however, the classification requires 48 hours, and two samples. Urinary tract obstruction must be excluded, as urine output remains as one criterium. The outcomes of the RIFLE criteria loss, i.e. end-stage kidney disease, were removed from the AKIN system but remain as consequences of the renal injury (5).

1.2.3 CHRONIC RENAL FAILURE

The definition of chronic renal failure applies if kidney damage or decreased kidney function persists over three months, independent of the cause. Kidney damage can be established via imaging, biopsy, clinical markers or urinary sediment alterations, referring to pathologic changes in the native or transplanted kidney. Clinical markers are increased albuminuria, specifically an albumin-creatinine ratio ACR >30 mg/g, and a decrease in kidney function measured in reduced GFR or eGFR (7).

1.2.4 CLASSIFICATION OF CHRONIC RENAL FAILURE

Renal damage can be classified according to the KDIGO classification from 2012 (Figure 3), reviewed from the 2002 classification by KDOQI. It subdivides the eGFR into six categories and the albuminuria into three categories, including ACR. This classification

suggests details about the severity of the CKD rather than pathologic abnormalities, which could be seen in imaging diagnostics or renal biopsy (6). The KDIGO classification is a particularly useful tool to identify prognostic indications related to renal dysfunction and albuminuria. The downside is a possible overdiagnosis regarding the elderly population (6).

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	⩾90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

Figure 3. Prognosis of CKD by eGFR and albuminuria categories

Source: Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int. 2014;85:49-61.

1.2.5 EPIDEMIOLOGY

Early and moderate CKD is asymptomatic. It is estimated that the prevalence of CKD in the general population is around 10-14%. Albuminuria A2 and GFR below 60 ml/min/1.73 m² have a prevalence of 3-7% in the general population (6). Data from 2013 suggest an incidence of 10 new diagnosed patients per 100000 persons every year in western Europe (4).

Non-modifiable risk factors for developing CKD are age, male gender, non-white ethnicity and genetic factors. Especially the elderly population has a high probability for CKD, also called community CKD, as the rate of GFR on average declines by 0.75 to 1 ml/min/year

above the age of 40 to 50 years (6). However, cardiovascular events in this population seem to have a higher mortality than CKD itself. Younger patients with hereditary or acquired nephropathy, also called referred CKD as they are treated by a nephrologist and not the primary care physician, have a faster decline in GFR (6). In diabetic nephropathy this ranges around 10ml/min/year (6).

Modifiable risk factors for CKD are systemic hypertension, proteinuria and metabolic factors. As described in the next section, systemic hypertension is one of the main causes of end stage renal disease. It increases the pressure in the glomerular capillary beds and contributes to glomerulosclerosis. 24-hour or night-time blood pressure measurements, especially of the systolic blood pressure, apparently correspond to the progression of CKD (6). Decreasing proteinuria can also be a sign of progressing CKD, but an increase of proteinuria usually correlates with the progression of CKD (8).

Therefore, KDOQI guidelines suggest screening in high-risk patients over 65 years with hypertension or DMT2. Screening comprises urine analysis, UACR and a blood sample for serum creatinine and eGFR (6).

1.2.6 MORTALITY IN DIALYSIS PATIENTS

The mortality of dialysis patients has improved over the last years, but it is still seven times higher in dialysis patients over 65 years of age or older than in the general population. The mortality rate is up to 20% per year in dialysis patients (9).

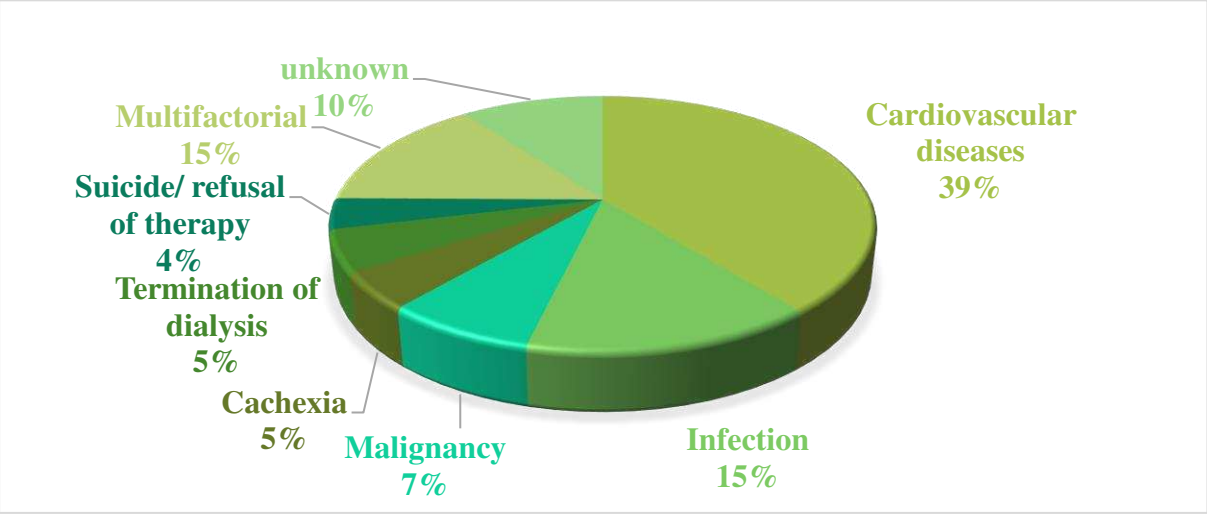


Figure 4. Reasons for mortality in dialysis patients

Source: Fey H. Effekte von Paricalcitol auf Inflammation und Kalzifikationsregulation bei Hämodialysepatienten. Würzburg, Germany: Universität Würzburg; 2013.

As visible in Figure 4, cardiovascular events account for over 30% of deaths in the general population (10). Therefore, it is not surprising, that dialysis patients with their propensity to vessel calcification suffer from cardiovascular events at significantly higher rates with 39% of cardiovascular disease as cause of death, in particular, coronary artery disease and myocardial infarction, congestive heart insufficiency, cerebrovascular diseases, stroke, atrial fibrillation and sudden cardiac death (9). Risk factors for cardiovascular events are arterial hypertension and DMT2, which have a high prevalence with 75% and 50% in dialysis patients. The common treatment with statins in patients with cardiovascular disease does not seem to benefit dialysis patients (9). Even though smoking may have a negative effect on the CKD, it surprisingly does not seem to influence cardiovascular mortality (9). The age of a dialysis patient has a huge impact on cardiovascular mortality as is shown in Figure 5. In young dialysis patients between 25-35 years, their risk of dying from a cardiovascular event is 500 times higher than in the general population at the same age. Even elderly dialysis patients of over 85 years have a risk of five times compared to their age group in the general population (9).

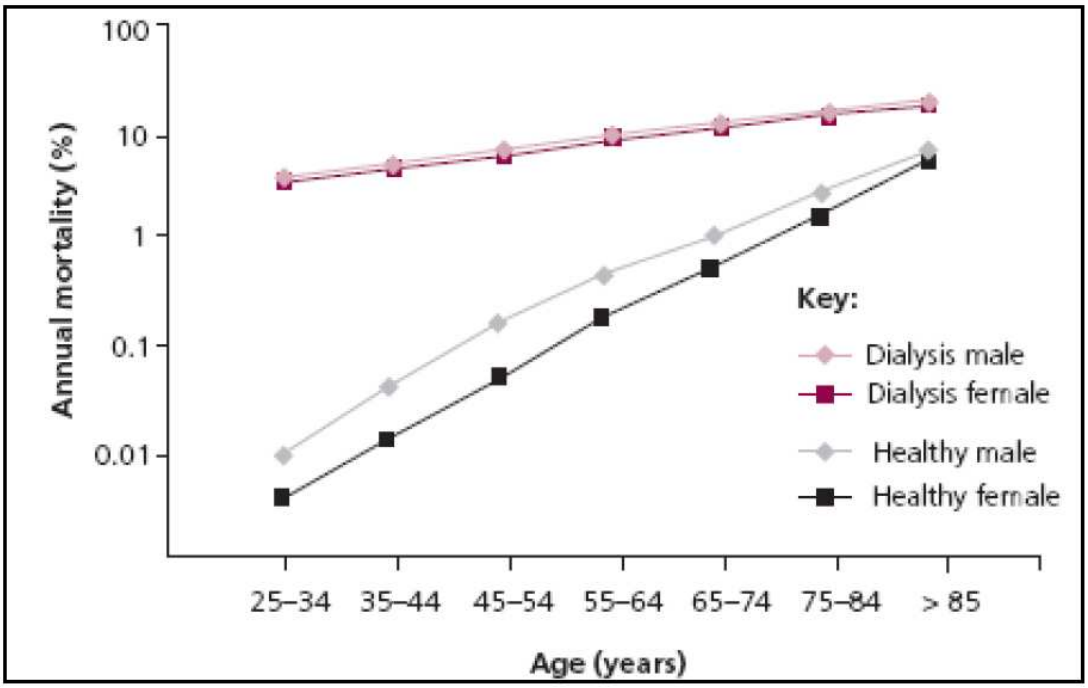


Figure 5. Age dependent cardiovascular mortality in dialysis patients

Source: Fey H. Effekte von Paricalcitol auf Inflammation und Kalzifikationsregulation bei Hämodialysepatienten. Würzburg, Germany: Universität Würzburg; 2013.

The gender appears to have a minor role in dialysis patients compared to cardiovascular patients only, where males are at higher mortality risk (9). Albuminuria is a significant independent risk factor for cardiovascular mortality in connection with chronic renal insufficiency. Atherosclerosis as a risk factor for cardiovascular mortality is accelerated by acute phase proteins produced in chronic systemic inflammation. Extraosseous calcification caused by the disturbance of the calcium phosphate homeostasis because of a secondary hyperparathyroidism, also appears to influence the cardiovascular system negatively (9). Additionally, cardiovascular events are influenced by renal anemia and left ventricular hypertrophy and dysfunction. However, correction of anemia to normal hemoglobin levels apparently increases cardiovascular mortality especially by increasing the risk for strokes (9). Left ventricular hypertrophy can be detected in approximately 70% of dialysis patients, which is probably caused by several accompanying symptoms such as arterial hypertension, fluid volume and RAAS system disbalance, renal anemia, atherosclerosis, oxidative stress and inflammation with growth factor and fibrose factor stimulation (9). Also, the duration and frequency and therefore the dialysis quality have an influence on mortality. Risk factors for cardiovascular events in the general population and dialysis patients are partially similar and partially different, depending on the etiology of cardiovascular damage (9).

1.2.7 PATHOGENESIS

Predisposing diseases for CKD are most commonly DMT2 with 30-50% followed by hypertension with 27.2%. Other primary diseases are primary glomerulonephritis (8.2%), diabetes mellitus type 1 (3.9%), chronic tubulointestinal nephritis (3.6%), hereditary or cystic diseases (3.1%), secondary glomerulonephritis or vasculitis (2.1%), plasma cell dyscrasias or neoplasm (2.1%) and sickle cell nephropathy (<1%) (11).

The etiology can be divided into prerenal, intrinsic renal and postrenal processes (Figure 6). Prerenal disease processes describe a decreased renal perfusion pressure. This may be caused by e.g. chronic heart failure or liver cirrhosis leading to progressive renal insufficiency (6). Intrinsic causes are divided into 1. renal vascular diseases, for example in nephrosclerosis or renal artery stenosis from atherosclerotic (12) or inflammatory changes, 2. glomerular disease with nephritic (microscopic hematuria, sometimes proteinuria) or nephrotic (proteinuria >3.5 gm per 24 h) cause (13) and 3. tubular and interstitial disease as the most common, e.g. polycystic kidney disease (6). Postrenal diseases are caused by chronic obstruction, which may be caused by hyperplasia of the prostate, nephrolithiasis, or an obstructive tumor (6).

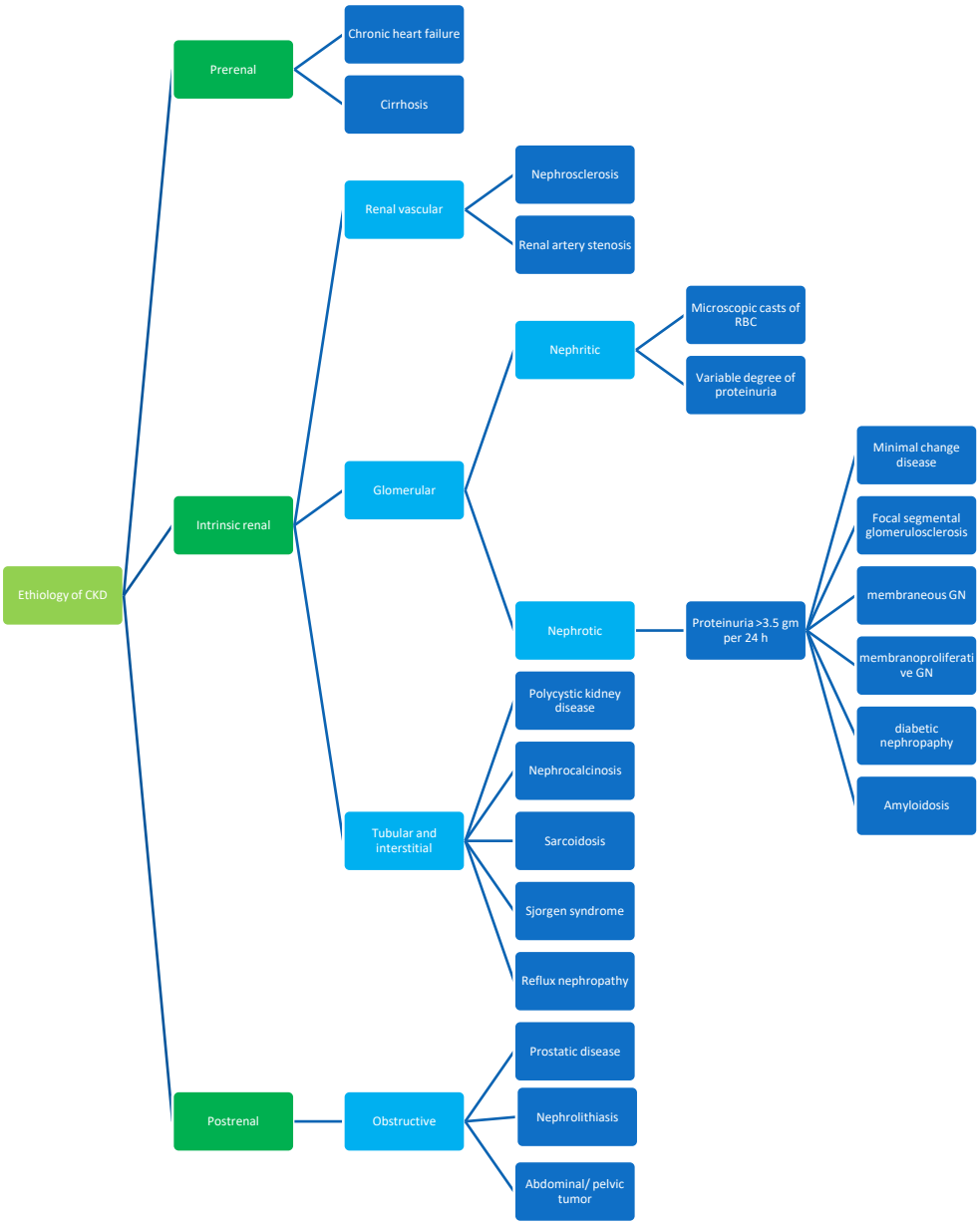


Figure 6. Etiology of CKD

Source: Vaidya SR, Aeddula NR. Chronic Kidney Disease [Internet]. StatPearls: StatPearls Publishing; 2022 [Updated 2022 Oct 24; cited 2024 Feb 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535404/

1.2.8 PATHOPHYSIOLOGY

In renal insufficiency, progression is caused by loss of renal functional units, the nephrons. As nephrons sclerose, increasing hemodynamic load is redistributed to the remaining nephrons, leading to a hyper perfusion and hyperfiltration. The consequence is damage to the remaining capillary endothelium and increased permeability for proteins due to loss of

regulatory functions (4). Proteinuria stimulates the release of growth factors and the proliferation of mesangial cells, leading to more fibrosing nephrons. This leads histologically to focal segmental glomerulosclerosis (14).

1.2.9 SYMPTOMS

At an early stage, CKD is usually asymptomatic. Initial symptoms can be polyuria and nycturia because of decreased renal concentration capacity. First symptoms usually occur only when the creatinine clearance falls below 50 ml/min (4).

Uremic symptoms appear as urea, uric acid and creatinine accumulate. Gastrointestinal symptoms manifest in form of loss of appetite, nausea, vomiting and diarrhea. Peripheral polyneuropathy, muscle twitches, encephalopathy with headache and decreased mental concentration manifest as signs of damage to the nervous system. Pericarditis and pleuritis may occur. A bleeding tendency occurs due to thrombocytopenia and thrombocyte dysfunction. The patient may show renal anemia. Pruitus, Café-au-Lait spots due to uremic toxins and uremic foetor are also common symptoms in advanced renal failure. (4).

Hypervolemia is a direct result of the decreased GFR leading to sodium and water retention. This causes arterial hypertonia, peripheral oedema and pulmonary oedema. Hypertension may be intensified by activation of the RAAS system (4).

In renal insufficiency, as the kidneys are responsible for the electrolyte homeostasis, hyperkalemia, hyperphosphatemia and hypocalcemia occur. Hyperkalemia may be intensified by the decreased excretion of H+ ions, causing renal acidosis. Hypocalcemia triggers an increased release of PTH (4). Together with the decreased 1.25-(OH)2-vitamin D3 synthesis and the decreased excretion of phosphate, this leads to high turnover renal osteopenia, where fibroblasts and osteoclasts are stimulated to release calcium from the bone (Figure 7). Osteomalacia is a symptom of vitamin D deficiency, leading to a mineralization disturbance of the bone, leaving it uncalcified. This is worsened by aluminum containing phosphate binders for therapy, which were historically in widespread usage until the late 90ies. Renal osteopenia can lead to diffuse bone pain, spontaneous fractures, and muscle weakness (4). Symptoms only occur in 5-10% of patients, while 30% have radiologic evidence of renal osteopenia (4).

Another sign of renal failure is renal anemia, which is caused by the decreased synthesis of erythropoietin as a hormone, which stimulates red blood cell production synthesis. This is exacerbated by blood and iron loss on hemodialysis, fibrosis of the bone marrow and uremic

toxins, which shorten the lifetime of red blood cells. The patients may experience paleness, weakness, tiredness, and exertional dyspnea (4).

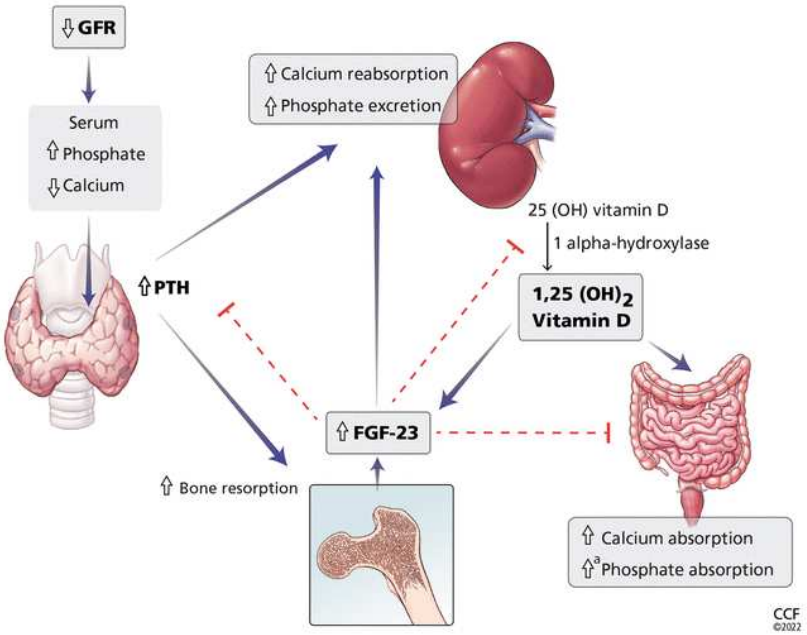


Figure 7. Calcium and phosphate metabolism in CKD

Source: Bartolomeo K, Tan XY, Fatica R. Extraosseous calcification in kidney disease. Cleve Clin J Med. 2022;89:81-90.

1.2.10 DIAGNOSIS

A first diagnosis in the general practitioner´s office can be made by screening including the patient's history regarding for example chronic hypertension, proteinuria, microhematuria and prostatic disease, left ventricular cardiac hypertrophy, multiple myeloma and systemic vasculitis. and actively inquiring for symptoms. In chronic renal insufficiency, the samples of blood and urine should be monitored regularly to determine any trends (6). In a blood sample, low serum calcium and high phosphorus levels with normal parathyroid hormone level may rather suggest acute kidney injury than CKD. If a high blood urea nitrogen over 140 mg/dl and serum creatinine over 13.5 mg/dl stand out in a blood sample, this suggests rather CKD than acute kidney injury (6). In CKD, electrolyte imbalance with hyperkalemia, hyperphosphatemia, hypocalcemia and vitamin D deficiency, high PTH and metabolic acidosis should make the physician suspicious. A urine sample with proteinuria, glycosuria and urine sediment may give hints as to the cause of the CKD (4).

Traditionally, proteinuria should be assessed with an early morning urine sample, to determine the degree of albuminuria, carefully considering, that other proteins might be excreted as well. However, the urine protein-creatinine ratio is now considered superior as the results are more robust due to mathematical adjustment for urine creatinine versus the inaccuracies involved in 24 hour collection sampling (6).

An indispensable tool in the diagnosis of CKD is imaging, beginning with an ultrasound examination. Typical for CKD are kidneys that are small with a narrowed and hyperechogenic cortex suggestive of renal atrophy and scarring. Cystic transformation may also imply chronic progress. Hydronephrosis of the kidneys are the hall mark of obstructive uropathy. The vascular flow should be determined with renal ultrasound Doppler, if renal artery stenosis is suspected (6). More invasive imaging is a low dose non-contrast CT scan for urolithiasis, because many renal stones are not visible on ultrasound. Renal angiography may reveal aneurysms and constrictions, suspicious of polyarteritis nodosa. Voiding cystoureterography should be used to confirm or exclude chronic vesicouretheral reflux as a cause of CKD (6).

Besides renal imaging, x-ray images of the bones may be helpful to rule out renal osteopenia. As mentioned earlier, this is often asymptomatic, but detectable by x-ray. In hypertensive patients, echocardiography may show cardiac hypertrophy of the left ventricle. Also, pericardial effusion due to uremia should be ruled out (4).

As a rule, treatable underlying causes should be investigated and treated along with the CKD (6).

1.2.11 TREATMENT

This section on treatment is divided into three subsections: a) therapy of the underlying disease, b) slowing down the progression of the disease and c) treatment of complications.

a) The general management includes adjusting drug doses to the eGFR for drugs like ACE inhibitors and DMT2 treatment. Nephrotoxic drugs such as aminoglycosides and NSAIDs should be replaced by non-toxic drugs. An arteriovenous fistula might be placed, if needed for dialysis. Other underlying diseases such as hypertension, glomerulonephritis and other systemic diseases should be treated (4).
b) The next step is to slow down the progression of CKD. Hypertension, proteinuria, metabolic acidosis, and hyperlipidemia should be at the center of attention (6). The target blood pressure should be at low normal levels about 130/80 mmHg and at

target proteinuria below 1 g/day. If the proteinuria is higher than this, then the blood pressure should be further lowered by adjusting it to 125/75 mmHg [4, p. 96]. ACEi such as ramipril or ARBs such as candesartan are nephroprotective by lowering the pressure in the glomerulus and, thus, reducing proteinuria. Protein restriction below 1 g/kg body weight is suggested to reduce metabolism induced hyperfiltration and proteinuria (4). To treat metabolic acidosis, bicarbonate supplementation can be beneficial (15). Smoking cessation is suggested by multiple studies to reduce the risk of developing nephrosclerosis (15).

c) The treatment of complications includes the treatment of secondary hyperparathyroidism by diet modification, phosphate binders, calcitriol for increased enteral calcium absorption and decreased PTH release. Albeit with tight control to prevent hyperphosphatemia, calcium sensitizers, e.g. cinacalcet, stimulating calcium sensor sensitivity in the parathyroid glands enabling more specific PTH secretion control than with vitamin D and, thus, delaying or averting the need for parathyroidectomy (4). Renal anemia can be controlled by administering erythropoietin, if hematocrit falls below 30% (4), considering approximately 40% for males and 36% for females as reference values in otherwise healthy adults (16). However, iron deficiency should be excluded or treated beforehand (4). By regular weighing, hyperhydration can be detected early and treated with salt and water intake restriction also with the support of loop diuretics such as furosemide, even with low eGFR (4). Sodium bicarbonate can treat metabolic acidosis (15). Hyperkalemia can be prevented by avoiding potassium sparring antidiuretics such as spironolactone and adjusting the diet (4). However, in an emergency, hemodialysis may be required (4).

1.2.12 RENAL REPLACEMENT THERAPY

If renal insufficiency progresses, this might be an indication for renal replacement therapy. Urgent indications in the presence of uremia include pericarditis or pleuritis, progressive uremic encephalopathy or neuropathy and bleeding diathesis (6). Other indications are resistant hypertension, resistant edema, metabolic disorders (6) including electrolyte imbalance such as hyperkalemia >6.5 mmol/l and metabolic acidosis with pH < 7.2 and BE < -10 mmol/l (4), persistent nausea and vomiting and evidence of malnutrition (6). Renal replacement therapy includes hemodialysis, continuous or intermittent peritoneal dialysis (17) and kidney transplantation additionally to conservative or palliative care (6). The treatment goal

is to eliminate uremic substances such as urea, uric acid, creatinine and many other uremic molecules not regularly measured in daily routine, and to maintain homeostasis of water, electrolytes and acid base homeostasis (4).

Hemodialysis is a common choice for about 85% of dialysis patients in Germany (4). As the most common form and for easy venous access, an arteriovenous fistula is created between the radial artery and the cephalic vein, typically a Cimino-Brescia-Shunt and is usable for permanent dialysis. Complications include infections, thrombosis, stenosis, or aneurysms (4). In an emergency, a central venous access in form of a Shaldon catheter can be placed, preferably in the jugular vein, whereas the subclavian vein should be avoided due to later complications of vessel puncture-stenosis (4). The principle of hemodialysis is the passive diffusion of particles below 25 kDa through a semipermeable membrane, where blood and the dialysate run in opposite directions. Also, water can be extracted in form of ultrafiltration. Urea, uric acid, creatinine and uremic toxins are extracted from the blood, while potassium and bicarbonate diffuse into the blood. Chronic intermittent dialysis takes place three times per week for 4-8 hours in a dialysis center or at home with various session durations and session frequencies (4). Hemofiltration is a further renal replacement procedure, where blood is filtered via hydrostatic pressure. Blood plasma is extracted with it all uremic substances and particles up to 35 kDa. After filtration, fluid and electrolytes are replaced by pure substrate infusion (4). Another option is peritoneal dialysis, where the peritoneum is used as the semipermeable membrane. The dialysis liquid with glucose but without potassium is inserted into the peritoneal cavity via a catheter. The fluid is replaced regularly during the day and/or night. Patients have less blood loss and are more independent but are more susceptible to peritoneal infection and loss of protein and glucose via the ultrafiltrate from the abdominal cavity (4).

Renal transplantation has a better general survival prognosis than hemodialysis. Patients are eligible, if they qualify for hemodialysis or peritoneal dialysis (6).

Conservative management is chosen for very frail patients with restricted life expectancy. The treatment is symptomatic and includes advanced care planning (6).

1.2.13 COMPLICATIONS

The ability to maintain fluid and electrolyte homeostasis on high sodium intake is lost in CKD. Therefore, the salt or sodium intake should be restricted to 2 g per day, as the KDIGO suggests (6). Hyperkalemia needs to be prevented in patients with oliguria, hypoaldosteronism and tissue break down. This can be achieved by restricting the potassium intake and careful

dosage of ACE inhibitors and nonselective beta-blockers (4,6); however, in persistent cases oral potassium binders may also be required. As a treatment for metabolic acidosis caused by retained H^+, supplementation with bicarbonate to achieve a serum bicarbonate target of 23 mmol/L is suggested to prevent osteopenia, increased protein catabolism and secondary hyperparathyroidism (6). Secondary hyperparathyroidism is a consequence of hypocalcemia and hyperphosphatemia, leading to renal osteodystrophy and predisposing to vessel calcification. This can be treated by phosphate binders (6) and calcitriol substitution for better enteral calcium reabsorption and decreased PTH synthesis (4). Volume expansion caused by CKD causes hypertension and edema, and in due course heart failure. Therefore, loop diuretics should be added to the antihypertensive therapy (6). Normocytic normochromic anemia due to inappropriately low erythropoietin levels (4) should be checked at least yearly in CKD 3, every half a year in CKD IV and V and every quarter of a year in dialysis patients (6). If the hemoglobin is below 10 g/dl and provided iron storage parameters are in an adequate range regarding the stage of CKD, erythropoietin stimulating agents should be considered (6).

In end stage renal disease, malnutrition due to anorexia and reduced protein intake is possible (4,6). Therefore, the diet should provide more than 30 Kcal/kg/day (6). Prolonged bleeding time can be caused by uremic impaired platelet function, which can manifest as active bleeding during surgery (4,6).

1.3 INFLAMMATION

1.3.1 DEFINITION

Inflammation is a medical term referring to a collection of symptoms. These cardinal symptoms were first described in Latin by Aulus Cornelius Celsus as *tumor* (edema, swelling), *rubor* (erythema, redness), *calor* (heat), *dolor* (pain) and *function laesa* (loss of function) (18,19). Inflammation is a response to harmful stimuli, such as damage to living tissue such as burns, radiation, frostbite, or necrosis due to lack of oxygen and defense mechanism against microbes and their toxins (18). Erythema is caused by blood vessel dilation triggered by histamine at the sight of injury. Localized warmth results from increased blood flow in the skin. Systemic inflammation can result in fever (18). Edema is a consequence of increased permeability of blood vessels and the transition of exudate and fluid into the damaged tissue. The resulting distortion of tissue leads to pain and loss of function. Proteins such as clotting factors, antibodies and leukocytes, specifically phagocytes, called neutrophils, and enzymes are present in the exudate. The leukocytes are guided by specific chemicals to the target region, a

mechanism called chemotaxis (18). Neutrophils release more proteins of the complement system, e.g. C3a and C5a, which trigger more vasoactive and chemotactic reactions. After 24-28 hours the neutrophils task is taken over by macrophages, which are a cellular hallmark in the change from an acute to chronic inflammation (18). The purpose of inflammation is to eliminate the harming agent and to heal the damaged tissue. Therefore, acute inflammation is beneficial, even though unpleasant as in an insect bite or a sore throat. If the regulatory mechanisms of inflammation are not effective or the causative agent cannot be eliminated, chronic inflammation can ensue causing harm and tissue destruction. Examples for this are allergies or autoimmune reactions (18).

Following acute inflammation, two outcomes are possible: healing and repair or suppuration and chronic inflammation. Healing and repair is the process of regeneration of damaged cells with the ability to proliferate. While this can be relatively easy in simple structures such as skin, complex structures cannot be replicated or can only be reconstructed abnormally resulting in permanent organ disease. In this case, a fibrous scar is formed by fibroblasts producing collagen and the damaged tissue is transformed into connective tissue with fine vascularization, called granulation tissue. The volume is often not fully replaced; therefore, an organ may seem smaller or distorted (18). Suppuration is the formation of pus. If the inflammation is difficult to eradicate, pus forms in a cavity surrounded by a membrane called abscess. Pus contains dead neutrophils, bacteria, debris, and exudate. Because of the limited accessibility for antibodies and antibiotics, surgical drainage is often needed. If acute inflammation progresses, healing cannot start, and the process may become chronic. The milestone of chronic inflammation is the persistent infiltration of especially macrophages, but also lymphocytes and plasma cells producing antibodies recruited by chemotactic factors into the affected tissue further inflicting tissue damage and functional impairment (18).

1.3.2 RELEVANCE OF INFLAMMATION IN DIALYSIS PATIENTS

In dialysis patients, chronic (micro-)inflammation is detectable in 32-55%. This is a very high prevalence (9). The markers generally used for the detection were acute phase proteins, specifically high sensitive C-reactive protein (hsCRP) and interleukin 6 (IL-6). Albumin and serum ferritin are also markers for inflammation, albeit with delayed kinetic characteristics (9). There are multiple causes of inflammation in renal insufficiency.

The concentrations of proinflammatory cytokines such as hsCRP and IL-6 vary depending on the GFR and are higher in advanced CKD, probably due to decreased elimination

or an increased synthesis due to uremia (9). In volume overload, more cytokines are systemically released, possibly due to bacterial translocation from the gut and endotoxin synthesis leading to a generalized immune answer with cytokines (9). In dialysis patients with malnutrition, a significant elevation of oxidants is measurable, which might be caused by more inflammatory cytokines. Oxidized LDL is a result of oxidative stress and might induce endothelial dysfunction. Other forms of oxidative stress are advanced glycation end products (AGE), which are proteins with added carbonyl groups. They increase in chronic renal insufficiency and are associated with inflammation and malnutrition (9). The situation of oxidative stress is worsened by the decreased concentration of antioxidants in the blood serum. This is partly due to a decreased intake and uptake of vitamin C and carotenoids due to potassium restriction. This could also be associated with cardiovascular events in dialysis patients. Low serum levels of vitamin C could also be connected to an increased number of cardiovascular events in dialysis patients (9). Uremia is a common complication of progressive renal insufficiency. Uremic toxins have a modulating effect on leukocytes by guanidine connections with pro- and anti-inflammatory effects leading to an increased immune response while also making patients more susceptible to infections. Dialysis patients have more periodontal infections and subclinical persistent infections (9). The continuous exposure of blood to the dialysis membrane leads to increased inflammatory parameters and bacterial contamination especially from the dialysate. Peritonitis, catheter infections and volume overload are a cause of inflammation in peritoneal dialysis patients (9). In patients with a non-resected renal transplant failure, chronic inflammation is common (9).

1.3.3 URINARY MARKER OF INFLAMMATION

Increasing fibrosis of the renal tubulointerstitial tissue is characteristic of chronic renal failure (20). The extension of fibrosis can be evaluated by invasive renal biopsy, which can, however, only give information about the momentary situation. Albuminuria is not a totally sufficient marker for tubulointerstitial fibrosis, because 50% of DMT2 patients show no or only a slight albuminuria (21). Possible measurements for investigation could be the new biomarker DKK3 (Dickkopf 3), which is an indicator for the progression on CKD, more specifically tubulointerstitial fibrosis. This is a more accurate biomarker than albuminuria, which can also be collected by urine sample and easily tested by ELISA. DDK3 measures the inflammation and damage within the renal tissue, whereas albuminuria measures the insufficiency of albumin reabsorption in the distal renal tubules (22). Few studies have been performed to investigate the

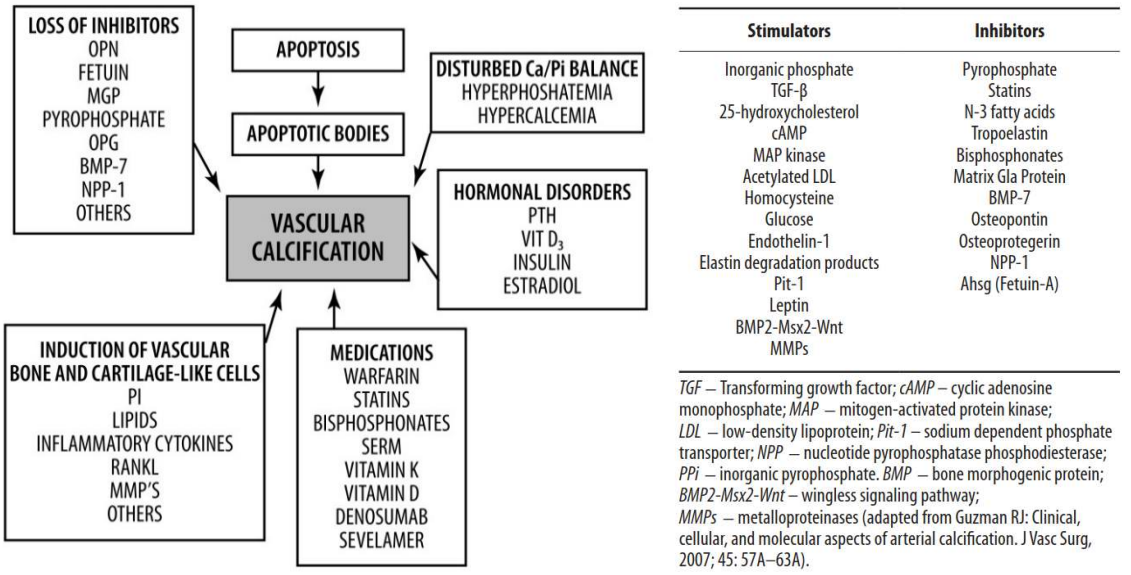
progression of CKD with DKK3, but so far none of these investigated finerenone and paricalcitol.

1.3.4 CALCIFICATION

Calcification of blood vessels is caused by an accumulation and deposition of calcium in the vessel wall, decreasing their elasticity and affecting hemodynamics of the vascular system. Consequences can be arterial hypertension, cardiac hypertrophy, ischemic heart disease and peripheral artery disease, which significantly increase mortality in patients over 60 years of age. This is a major problem in patients with end-stage renal disease, therefore, an optimal control of the serum calcium and phosphate is beneficial (23).

Arterial calcification is not only a process in advanced atherosclerosis, but also appears early in renal failure (24). The ascending aorta is made of elastic fibers, which stretch during the systole, storing energy, and contract during the diastole, releasing energy. Calcium deposits cause the loss of this elasticity, leading to systolic hypertension. This causes left ventricular myocardial hypertrophy resulting in higher myocardial oxygen demand, diastolic dysfunction, and valve incompetence. Calcification of the coronary arteries impedes coronary diastolic blood flow, potentially leading to unstable angina pectoris and myocardial infarction (23). Calcium depositions on the aortic valve lead to potentially lethal aortic stenosis (23). Studies reveal, that nearly 30% of Americans older than 45 years have calcium deposits in arterial walls (25). Classical risk factors are similar to those of atherosclerosis: hypertension, obesity, hypertriglyceridemia, increased low-density lipoproteins (LDL) and decreased high-density lipoproteins (HDL) (26). Renal failure and diabetes contribute significantly to calcium deposit accumulation in vessel walls (27). The probability of coronary incidents, organ damage, morbidity, and mortality in these patients are as high as in patients with advanced calcification of the aortal arch, even if classical risk factors, irrespectively of age, are reduced (28). In patients with CKD, but also with diabetes, intense calcium-phosphate accumulation is noticeable in the smooth muscle layer of the blood vessels. The pathogenesis (Figure 8) is osteogenic differentiation in the vascular smooth muscle cells stimulated by excess of phosphate and calcium via signaling pathways (29). Vascular insufficiency increases the risk of sudden cardiac death (30) and lower limb amputation (31). In arterioles smaller than 0.6 mm in diameter, a specific type of patchy calcification in the smooth muscle cells can develop, which is called calciphylaxis (23). Patients with CKD on warfarin are especially often affected.

Warfarin is associated with aortic stenosis and extreme vascular calcification, possibly by blocking the inhibitors of vascular calcification, such as fetuin-A, matrix gla protein, and bone morphogenic protein-2 (32). Fetuin-A levels are lower in hemodialysis patients, which are also associated with raised levels of CRP, increased calcium deposits and cardiovascular and general mortality (33). Together with age, serum calcium and PTH, fetuin-A is a good predictor of calcification progression (34). Vitamin D_3 also plays a significant role in the vascular calcification of the inner and muscular layer of blood vessels by changing the gene expression of more than 150 genes, influencing the cell cycle, reducing proliferation, differentiation, and apoptosis (35). Within physiological concentrations, vitamin D_3 affects myorelaxation and reduces endothelial thrombogenicity, increases fibrinolysis and inhibits inflammatory response (36). Outside of physiological concentrations, it activates metalloproteinases, especially MMP-2 and MMP-9. They heavily influence vascular remodeling (37). Besides vitamin D_3, PTH also plays a significant promoting role in the vascular calcification by inhibiting the synthesis and release of osteoprotegerin (OPG), which protects the bone (38).



Stimulators	Inhibitors
Inorganic phosphate	Pyrophosphate
TGF-β	Statins
25-hydroxycholesterol	N-3 fatty acids
cAMP	Tropoelastin
MAP kinase	Bisphosphonates
Acetylated LDL	Matrix Gla Protein
Homocysteine	BMP-7
Glucose	Osteopontin
Endothelin-1	Osteoprotegerin
Elastin degradation products	NPP-1
Pit-1	Ahsg (Fetuin-A)
Leptin	
BMP2-Msx2-Wnt	
MMPs	

TGF – Transforming growth factor; *cAMP* – cyclic adenosine monophosphate; *MAP* – mitogen-activated protein kinase; *LDL* – low-density lipoprotein; *Pit-1* – sodium dependent phosphate transporter; *NPP* – nucleotide pyrophosphatase phosphodiesterase; *PPi* – inorganic pyrophosphate. *BMP* – bone morphogenic protein; *BMP2-Msx2-Wnt* – wingless signaling pathway; *MMPs* – metalloproteinases (adapted from Guzman RJ: Clinical, cellular, and molecular aspects of arterial calcification. J Vasc Surg, 2007; 45: 57A–63A).

Figure 8. Pathogenesis of vascular calcification, source: (23)

Source: Karwowski W, Naumnik B, Szczepański M, Myśliwiec M. The mechanism of vascular calcification - a systematic review. Med Sci Monit. 2012;18:RA1-11.

1.4 PARICALCITOL

Paricalcitol, Zemplar® by brand name, is a synthetic vitamin D_2 analog. It is prescribed to patients with secondary hyperparathyroidism in CKD stages 3 to 5 (39,40). Paricalcitol should not be taken, if the patient has a vitamin D intoxication, hypercalcemia, or in combination with thiazide diuretics, antacids or phosphate binders and should be avoided in pregnancy and lactation (41).

Paricalcitol can be taken orally as capsules. The dosage depends on the iPTH value: if iPTH is <500 pg/ml, 1 µg once a day is recommended, if iPTH is >500 pg/ml, then 2 µg daily or 4 µg three times per week are recommended with dose adjustment according to iPTH, calcium and phosphate levels in serum. The half-life of paricalcitol is about 4-6 hours. It is metabolized by hepatic and non-hepatic enzymes, including CYP24 and excreted hepatobiliary (39).

1.4.1 MECHANISM OF ACTION

Paricalcitol is a synthetic, biologically active vitamin D analog selectively binding to the vitamin-D-receptor-activator (VDR). VDR upregulates the calcium sensitive receptors (CaSR) in the parathyroid gland, thus, reducing PTH release, synthesis and secretion, while supposedly only minimally influencing calcium and phosphate homeostasis. It actively promotes osteoblastic activity increasing the bone density and mineralization (41). Additionally, paricalcitol is able to decrease inflammation in the kidney by actively inhibiting the infiltration of T cells into injured tissue (42). All functions of vitamin D can be seen in Figure 9.

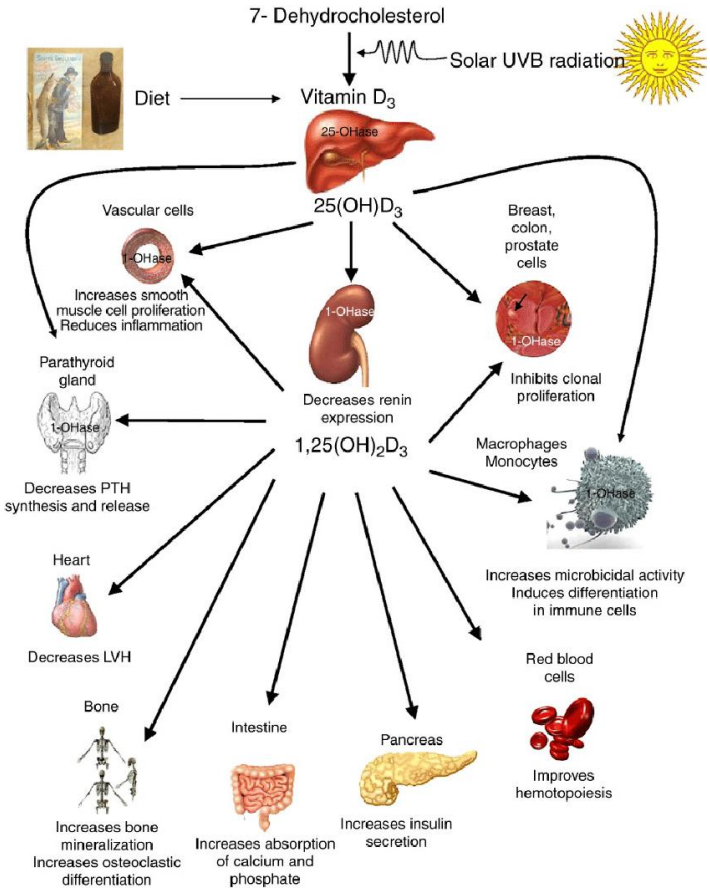


Figure 9. Vitamin D function

Source: Türkmen AS, Kalkan. Food Quality: Balancing Health and disease. Karaman, Turkey; Elsevier: 2018. 471-92 p.

1.4.2 VITAMIN D AND CHRONIC KIDNEY DISEASE

In the course of CKD, renal mass is decreases, leading to less availability of the converting enzyme for vitamin D synthesis. Furthermore, as GFR progressively declines, the delivery of the vitamin D precursor to the kidneys decreases. This leads to chronic hypovitaminosis D in CKD patients (9).

1.5 FINERENONE

Finerenone, or brand name Kerendia®, is a nonsteroidal mineralocorticoid receptor antagonist. It is indicated in adults with CKD with DMT2 to positively influence renal and cardiovascular adverse events (43,44). An additional indication in Europe is CKD in stage 3 and 4 with albuminuria associated with DMT2 (45).

Patients with low eGFR or prior hyperkalemia require close monitoring, because an increased risk of hyperkalemia has been observed in safety studies (46). Patients with severe

liver dysfunction should not take finerenone due to the changed CYP3A4 function, such patients were excluded from studies with finerenone. If there is medium or low liver dysfunction, close monitoring is advised. The same applies for any type of CYP3A4 modulating co-medication (46). Finerenone should also be avoided in pregnancy and lactation (46).

Finerenone is taken orally in form of a tablet. The recommended dosage is 20 mg, which is also the maximal recommended daily dosage. A top-up dosage from 10 to 20 mg may be recommended for patients with an eGFR below 60 ml/min/1.73m² or at risk of hyperkalemia (46). Regarding pharmacodynamics, finerenone has a moderate duration of action with a wide therapeutic window from 1.25 mg to 80 mg in clinical trials (45). Approximately 90% is metabolized in the liver by CYP3A4 enzyme without formation of active metabolites (45,43). Finerenone is eliminated via urine and feces (43). The half-life of 10 mg finerenone was measured with 17.4 hours in plasma and 12.3 hours in whole blood in 4 healthy men, while the terminal half-life is about 2-3 hours (45).

1.5.1 MECHANISM OF ACTION

As a non-steroidal selective mineralocorticoid receptor antagonist, finerenone selectively binds to mineralocorticoid receptors and, therefore, prohibits overactivation (Figure 10). Overactivation leads to increased RAAS activation, triggering increased fluid and sodium retention and increased blood pressure, which negatively influences hypertension, heart failure and CKD. By possibly positively influencing fibrosis and inflammation, finerenone apparently has a positive influence on fibrosis and inflammation in the kidney and heart (47).

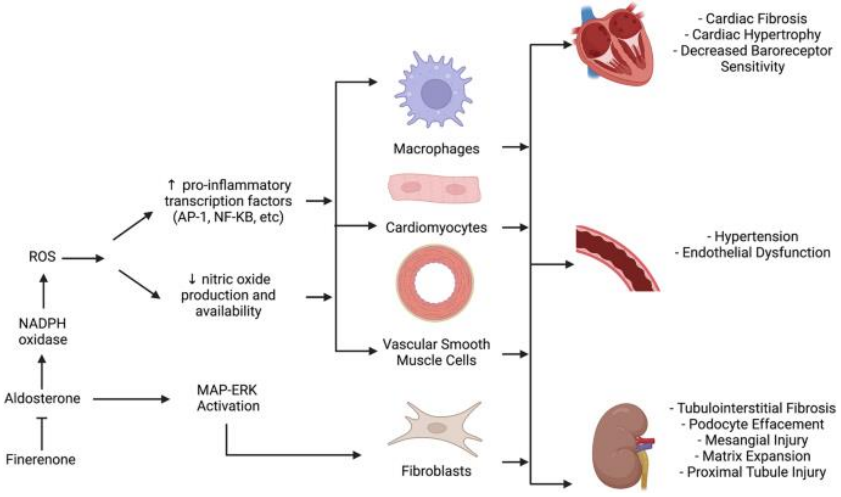


Figure 10. Pathologic mechanisms of aldosterone, Source: (48)

Source: Palanisamy S, Funes Hernandez M, Chang TI, Mahaffey KW. Cardiovascular and Renal Outcomes with Finerenone, a Selective Mineralocorticoid Receptor Antagonist. Cardiol Ther. 2022;11:337-354.

2. OBJECTIVES

2.1 AIM OF STUDY

The aim of this study was to investigate retrospectively the available data regarding proteinuria as a prognostic measure of the progression of CKD on paricalcitol medication considering the recent positive study results pertaining to finerenone. Furthermore, to compare the two different drugs paricalcitol and finerenone regarding their therapeutic effects on cardiovascular outcomes. Present data support the assumption of a causal association between proteinuria and improvement in cardiovascular prognosis, independent of the primary indication for paricalcitol of treatment of secondary hyperparathyroidism.

2.2 HYPOTHESIS

We propose that there will be different outcomes in the comparison of finerenone and paricalcitol in the following points of investigation:

1. Renal outcomes: We propose, there will be different outcomes for finerenone and paricalcitol for eGFR and UACR.
2. Cardiovascular outcomes: We propose, there will be different outcomes for finerenone and paricalcitol for myocardial infarction, stroke and death due to cardiovascular cause.
3. Death: We propose, there will be different outcomes for finerenone and paricalcitol for overall mortality.

3. PATIENTS AND METHODS

3.1 STUDY DESIGN AND ETHICAL APPROVAL

The study design of this diploma thesis is a meta-analysis including 7 studies. The design of the studies was prospective in three of three studies for finerenone and three prospective and one observational study for paricalcitol.

Based on §2 of the statues for the IRB of the Medical School REGIOMED Coburg, the committee decided, that there are no objections to the implementation of the research project.

3.2 SEARCH STRATEGY

The literature search was performed in accordance with the PRISMA guidelines (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (49). The search was conducted on July 16th 2024 by two independent investigators of the PubMed database. Investigators were the author of this thesis and an advanced medical student. To find comparable studies, the search key words for RCTs was:

1. Finerenone AND albuminuria
2. Paricalcitol AND albuminuria

The total search records were analysed for the eligibility criteria to identify the remaining articles first by title/abstract review and second by full text review (Table 1).

Table 1. PubMed search

Search key words	**Finerenone AND albuminuria**	**Paricalcitol AND albuminuria**
PubMed reports	60 results	47 results
Excluded if not RCT	43 excluded	37 excluded
Excluded after title/ abstract review	8 excluded	5 excluded
Excluded after full text review	7 excluded	4 excluded
Included RCTs	3 included	1 included
Additional literature	0 included	3 included

3.3 ELIGIBILITY CRITERIA

For the identification of the relevant studies for this meta-analysis the PICOT research question was analyzed. The following inclusion criteria were used during the literature search:

1. **Patient population**: All patients with CKD were over 18 years. To make the groups even more comparable, patient populations had DMT2 and were treated with RAAS inhibitors, such as ACEi or ARBs.
2. **Intervention**: The patients were treated with 10 mg or 20 mg of finerenone once daily for at least 24 weeks up to several years.
3. **Comparison**: The patients were treated with 1 µg or 2 µg paricalcitol once daily for at least 24 weeks. Each study had a control group with matching placebo.
4. **Outcome**: The outcome of interest is the change of eGFR, UACR and composite renal outcomes. Additionally, cardiovascular composite outcomes were analyzed.
5. **Study design**: All studies with exact eGFR and UACR levels were included. The studies covered different stages of CKD, which will be explained in the summary of studies. DMT2 was defined as an HbA1c above 6,5%. Studies with incomplete data or without outcomes of interest were excluded. Case reports, literature reviews, commentaries, editorials, conference abstracts and expert opinions were excluded.

The study “Effect of Paricalcitol on Left Ventricular Mass and Function in CKD” (Opera) was included, even though it did not provide completely comparable renal results. The study was included due to the mostly matching patient profile and providing insight into cardiovascular outcomes. There has been only little research for cardiovascular outcomes, because paricalcitol was initially developed for other indications.

The study “Principal Results of the VITamin D and OmegA-3 Trial and updated Meta-analyses of relevant vitamin D Trials” (Vital 2) by Manson did not meet all our criteria as he observed a cohort without CKD and DMT2. This study was intended to detect positive cardiovascular effects on a prophylactic basis. It was included in our analysis due to the large number of participants and the results of cardiovascular outcomes, which were not found in any other large study meeting the criteria.

One observational study of paricalcitol was additionally included. Even though it was not an RCT, it did have interesting insights confirming the results of the paricalcitol RCT of de Zeeuw and validating their measurements.

3.4 DATA EXTRACTION

After retrieval of study results, data synthesis was performed by one investigator, the author of this thesis, using Microsoft Excel spreadsheets. The extracted data from each study was the first author, publication year, study design, sample size, average age and gender of the patients, dose of finerenone or paricalcitol with duration of intervention and follow up. All available baseline measurements of UACR and eGFR were documented. Furthermore, available data about DMT2 were collected such as duration of diagnosis and HbA1c. Cardiovascular baseline and outcomes were documented such as blood pressure, history of hypertension, cardiovascular events and congestive heart failure and adverse effects, e.g. non-fatal myocardial infarction, non-fatal stroke and death due to cardiovascular cause. Overall mortality was also extracted if available.

3.5 METHODOLOGICAL QUALITY ASSESSMENT

Using the Downs and Black checklist (Table 2), two researchers independently assessed the methodological quality of the remaining 7 studies. The researchers were the author of this diploma thesis Delia Mellis, and another advanced medical school student, Linda Heinrich. Downs and Black is a validated evaluation scale assessing 28 points: reporting (11 points), external (3 points) and internal validity (7 points), internal validity-confounding (6 points) and power (1 point). Possible scores are between 0 and 28 points for RCTs and 0 to 21 for observational studies. The risk of bias was categorized into high (0-15), moderate (16-23) or low (>23) (50).To identify the level of agreement between investigators regarding risk of bias, Cohens kappa was calculated (51), which was calculated by using the formula $\kappa = P/G$, where P is the sum by the lower rating investigator and G is the sum by the higher rating investigator. The degree of agreement was classified as follows: slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), significant (0.61-0.80) and almost perfect (0.81-1.00). Statistical analyses showed that the investigators achieved an almost perfect rate of agreement with a factor of at least 0.84.

Table 2. Down and Black checklist results

Study	Reporting	External Validity	Internal Validity	Validity-Confounding	Power	Total Scores
Methodological assessment by Investigator 1 (Delia Mellis)						
Pitt *et al*., 2021	10	3	7	4	1	25
Agarwal *et al*., 2021	11	3	7	4	0	27
Bakris *et al*. 2023	11	3	7	5	1	27
De Zeeuw *et al*., 2010	10	3	7	4	1	25
Wang *et al*., 2013	10	2	7	5	1	25
Manson *et al*., 2020	9	2	6	5	0	22
Mendes *et al*., 2019	9	2	4 (of 5)	1 (of 2)	0	16 (of 21)
Methodological assessment by Investigator 2 (Linda Heinrich)						
Pitt *et al.*, 2021	11	3	7	5	1	27
Agarwal *et al.*, 2021	11	3	7	6	0	26
Bakris *et al.* 2023	11	3	7	5	1	27
De Zeeuw *et al.*, 2010	11	3	7	4	1	26
Wang *et al.*, 2013	9	3	7	5	1	26
Manson *et al.*, 2020	11	2	7	5	0	25
Mendes *et al.*, 2019	11	3	4 (of 5)	1 (of 2)	0	19 (of 21)
Total score of inter-investigator agreement						
	Invest. 1	**Invest. 2**	**Mean**	**Kappa Value**		
Pitt *et al.*, 2021	25	27	26	0.93		
Agarwal *et al.*, 2021	27	26	26.5	0.96		
Bakris *et al.* 2023	27	27	27	1.00		
De Zeeuw *et al.*, 2010	25	26	25.5	0.96		
Wang *et al.*, 2013	25	26	25.5	0.96		
Manson *et al.*, 2020	22	25	23.5	0.88		
Mendes *et al.*, 2019	16 (of 21)	19 (of 21)	17.5	0.84		

4. RESULTS

4.1 STUDY CHARACTERISTICS

The PubMed search for finerenone and paricalcitol and albuminuria resulted in 60 and 47 results.

For finerenone, out of 60 results, 43 results were excluded due to not being RCTs, another 7 were excluded after title and abstract review because of not matching intervention or target population. After full text review, another 7 articles were excluded due to missing relevant measurements leaving 3 RCTs for meta-analysis (Figure 11).

For paricalcitol, out of 47 results, 37 were excluded due to not being RCTs, 5 were excluded by title and abstract review due to not matching target population. After full text review, another 4 studies were excluded due to not containing data on relevant measurements. Following a literature search of excluded paricalcitol articles, three studies were included, even though they did not completely match the target population or being an RCT, because they provided insight into data, which were otherwise not able to be retrieved from matching populations (Figure 12).

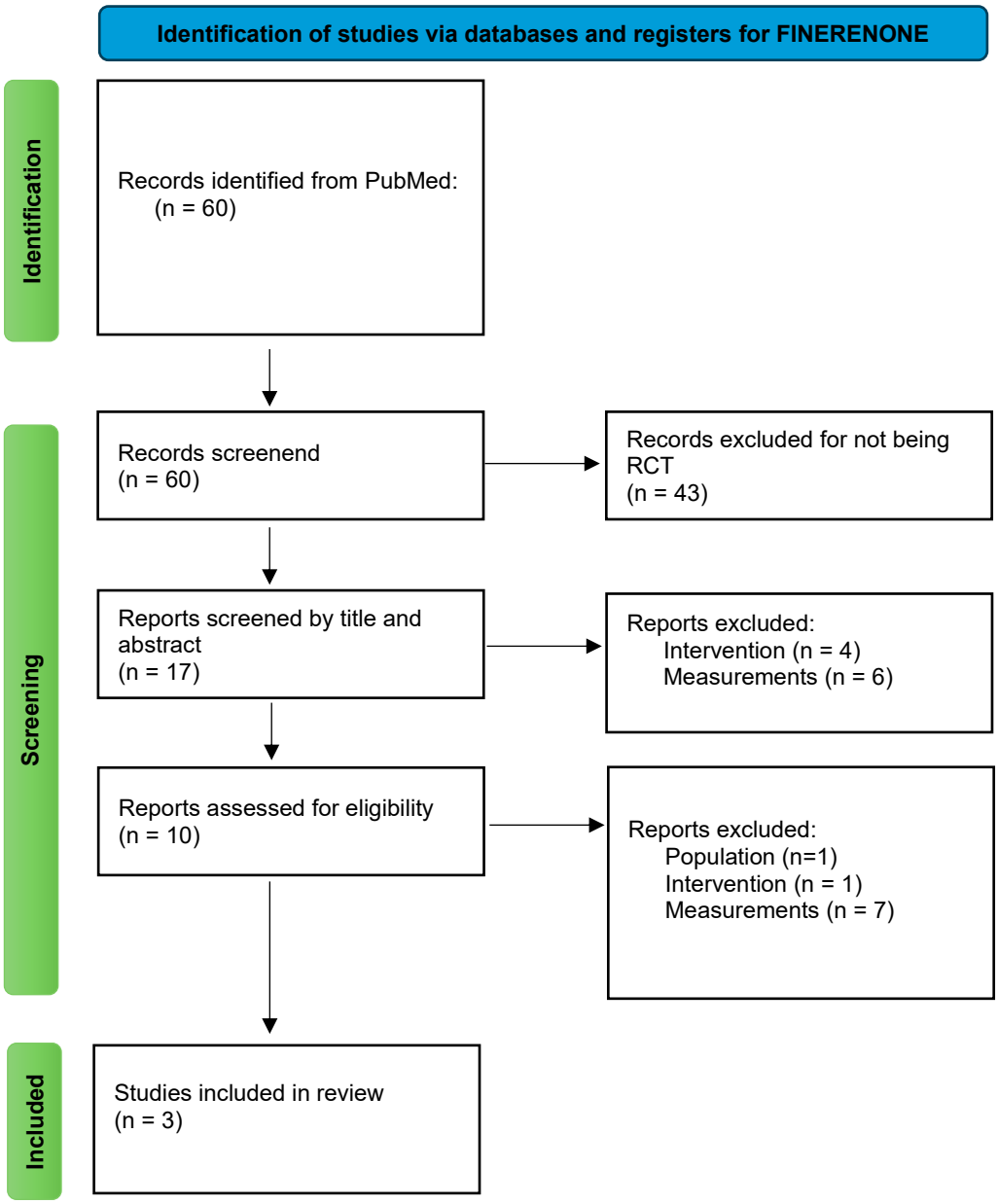


Figure 11. Prisma flowchart for finerenone

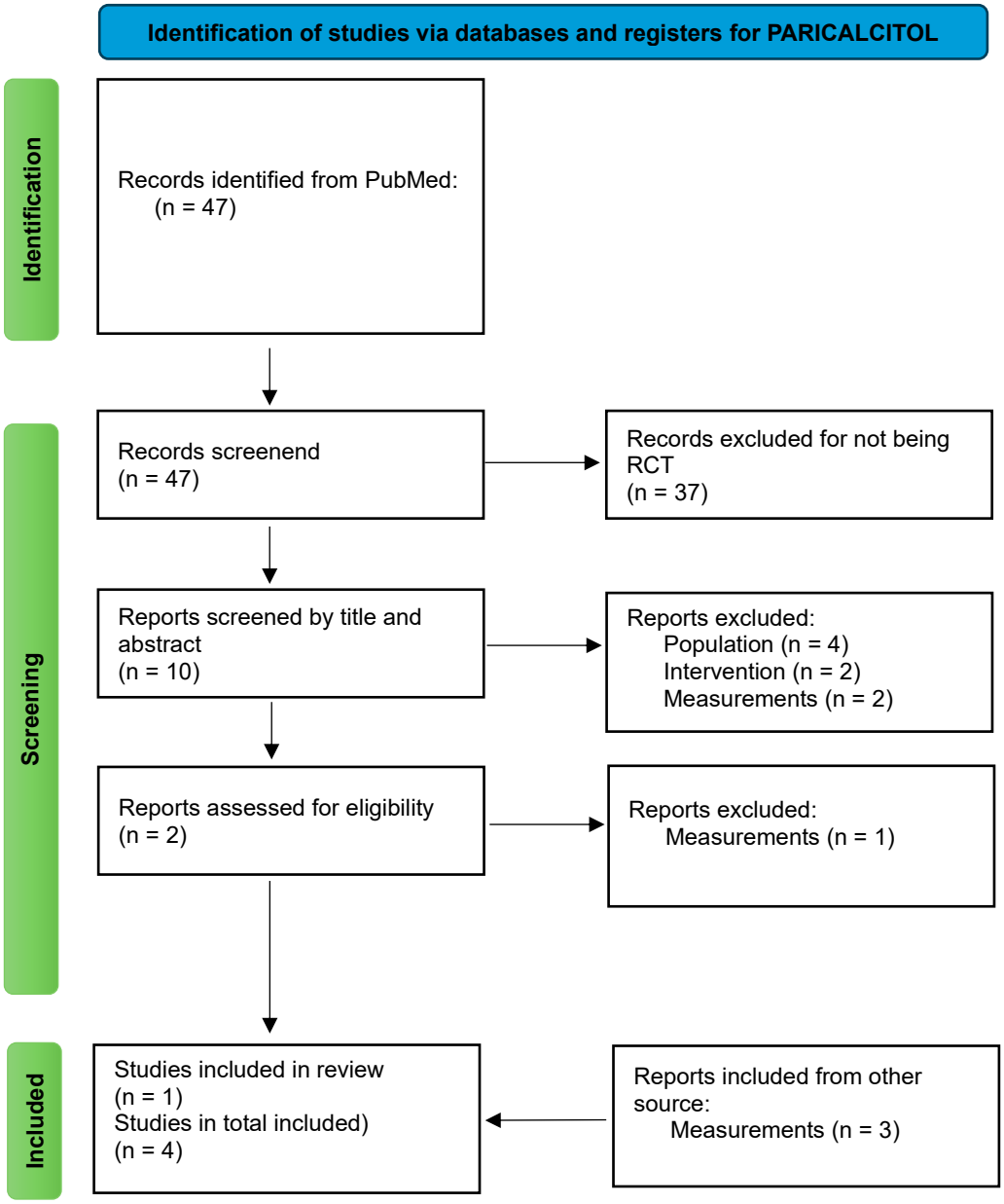


Figure 12. Prisma flowchart for paricalcitol

4.2 SUMMARY OF THE INCLUDED STUDIES

Finerenone

Bakris *et al.*, 2023 – FIDELIO (52)

The Fidelio study was a double-blinded, placebo-controlled, multicenter RCT with 5734 patients investigating 20 mg finerenone once daily versus placebo for 44 to 48 months. Participating patients had an average age of 65.6 years, and 70.2% were male. Eligibility criteria were UACR >30-<300 mg/g with eGFR >25-<60 ml/min/1.73m² or UACR >300-<5000 mg/g with eGFR >25-<75 ml/min/1.73m² and DMT2, the duration of which was on average 16.6 years, and pretreatment with ACEi or ARBs.

The final measurements included a decrease in UACR of -29.3% from baseline of 798.79 mg/g in the intervention group in comparison to an increase of +4.1% from baseline UACR of 814.73 mg/g in the placebo group. The eGFR in the intervention group decreased from baseline until month 4 of treatment by -3.18 ml/min/1.73m² from initially 44.4 ml/min/1.73m² (CI 95% -3,44 to -2,91) as compared to a decrease in the control group with -0.73 ml/min/1.73m² from initially 44.3 ml/min/1.73m² (CI 95% -1,03 to -0,44). The eGFR slope decreased after 4 months until the end of study by -2.66 ml/min/1.73m² (CI 95% -2.96 to -2.36) significantly less than in the placebo group with -3.97 ml/min/1.73m² (CI 95% -4.27 to 3.66).

The main renal composite outcomes were a decrease of eGFR >57% in 5.9% in the intervention group versus 11.5% in the placebo group (HR 0.76, CI 95% 0.65-0.90) and kidney failure in 7.3 % versus 8.3% (HR 0.87, CI 95% 0.72-1.05). Kidney failure was defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per 1.73 m2 for a period of at least 4 weeks. The total cardiovascular composite outcomes occurred in 9.2% of the intervention group and in 11.8% of the control group (HR 0.78, CI 95% 0.66-0.92 with non-fatal myocardial infarctions 2.5% in the intervention group and 3.1% in the placebo group (HR 0.80, CI 95% 0.58-1.09), non-fatal stroke similarly 3.2% versus 3.1% (HR 1.03, CI 95% 0.76-1.38) and death due to cardiovascular cause 4.5% versus 5.0% (HR 0.86, CI 95% 0.68-1.08). Overall mortality was 7.7% in the intervention group versus 8.6% in the placebo group (HR 0.90, CI 95% 0.75-1.07).

Pitt *et al.*, 2021 – FIGARO (53)

The Figaro study was a double-blinded, placebo-controlled, multicenter RCT with 7352 patients investigating 20 mg finerenone once daily versus placebo for 44 to 48 months. Participating patients had an average age of 64.1 years and 69.4% were male. Eligibility criteria were UACR >30-<300 mg/g with eGFR >25-<90 ml/min/1.73m² or UACR >3000-<5000 mg/g

and eGFR >60 ml/min/1.73m² and DMT2, on average 14.5 years duration, and pretreatment with ACEi or ARBs.

The main renal composite outcomes were a decrease in eGFR >57% of 2.9% in the intervention group versus 3.8% in the placebo group (HR 0.77, CI 95% 0.6-0.99), kidney failure in 1.2% versus 1.7% (HR 0.72, CI 95% 0.49-1.05) and hyperkalemia in 10.8% versus 5.3% in placebo. Kidney failure again was defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per 1.73 m2 for a period of at least 4 weeks. The total cardiovascular composite outcomes occurred in 12.4% of the intervention group and in 14.2% of the control group (*P*= 0.030; HR 0.87, CI 95% 0.76-0.98), non-fatal myocardial infarctions equally 2.8% in both trial groups (HR 0.99, CI 95% 0.76-1.31), non-fatal stroke similarly 2.9% versus 3.0% (HR 0.97, CI 95% 0.76-1.26) and death due to cardiovascular cause 5.8% versus 9.0% (HR 0.9, CI 95% 0.76-1.09). Overall mortality was 9.0% in the intervention group versus 10.1% in the placebo group (HR 0.89, CI 95% 0.77-1.04).

Agarwal *et al.*, 2021 – FIDELITY (54)

The Fidelity study was a combined analysis of the Fidelio and Figaro patients emphasizing overall renal and cardiovascular outcomes. The Fidelity study was basically a double-blinded, placebo-controlled, multicenter RCT comprising 13026 patients investigating 20 mg finerenone once daily versus placebo for 44 to 48 months. Participating patients were on average 64.8 years of age and 69.8% were male. Eligibility criteria were UACR >30-<5000 mg/g with eGFR >30->90 ml/min/1.73m² and DMT2 on average 15.4 years duration, and pretreatment with ACEi or ARBs.

The final measurements showed a decrease of -27.0% from baseline UACR of 445.4 mg/g in the intervention group in comparison to an increase of +2.0% from baseline UACR of 454.3 mg/g in the placebo group. Serum potassium increased slightly more by +0.13 mEq/L from initially 4.35 mEq/L in the intervention group than in the control group with an increase of +0.03 mEq/L from initially 4.35 mEq/L at baseline.

The main renal composite outcomes were a decrease of eGFR >57% in 5.5% in the intervention group versus 7.1% in the placebo group (*P*= 0.0002, HR 0.77, CI 95% 0.67-0.88) and kidney failure in 3.9 % versus 4.6% (*P*= 0.039, HR 0.84, CI 95% 0.71-0.99). Kidney failure was again defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per 1.73 m2 for a period of at least 4 weeks. Total cardiovascular composite outcomes occurred in 12.7% of the intervention group and in 14.4% of the control group (*P*= 0.0018, HR 0.86, CI 95% 0.78-0.95), non-fatal myocardial infarctions 2.7% in the intervention group and

2.9% in the placebo group (*P*= 0.360, HR 0.91, CI 95% 0.74-1.12), non-fatal stroke equally 3.0% in both groups (*P*= 0.950, HR 0.99, CI 95% 0.82-1.21) and death due to cardiovascular cause 4.9% versus 5.6% (*P*= 0.092, HR 0.88, CI 95% 0.76-1.02). Overall mortality was 8.5% in the intervention group versus 9.4% in the placebo group (*P*= 0.051, HR 0.89, CI 95% 0.79->1.0).

Paricalcitol

De Zeeuw *et al.*, 2010 – VITAL (55)

The Vital study was a double-blinded, placebo-controlled, multicenter RCT with 281 patients investigating 1 µg and 2 µg paricalcitol capsules once daily versus placebo for 24 weeks. Participating patients had an average age of 64.0 years and 69.6% were male. Eligibility criteria were UACR 11–339 mg/mmol with eGFR 15–90 mL/min per 1·73 m² and DMT2, on average duration of 17.0 years, and pretreatment with ACEi or ARBs.

Measurements for UACR were provided in mg/mmol and were converted to mg/g by multiplying by factor 8.84 (56) using online MediCalc (57). The initial average baseline UACR in the 1 µg daily paricalcitol group decreased by -14.0% (CI 95% -24% to -1%) from 63 mg/mmol (557.52 mg/g) to 54 mg/mmol (477.88 mg/g) after 24 weeks. Initial measurement baseline UACR in the 2 µg daily paricalcitol group decreased by -20.0% (CI 95% -30% to -8%) from 61 mg/mmol (539.82 mg/g) to 49 mg/mmol (433.63 mg/g). UACR in the combined intervention groups decreased by -16% (CI 95% -24% to -9%) from 62 mg/mmol (548.67 mg/g) to 51 mg/mmol (451.33 mg/g). The initial measurement of baseline UACR for the placebo group decreased by -3.0% (CI 95% -16% to +13%) from 61 mg/mmol (539.82 mg/g) to 60 mg/mmol (530.97 mg/g). The eGFR in the 1 µg paricalcitol group decreased from 41.0 ml/min/1.73m² to 39.0 ml/min/1.73m², while eGFR in the 2 µg paricalcitol group decreased from 42 ml/min/1.73m² to 37.0 ml/min/1.73m². The placebo control group did not experience any change of eGFR of 39 ml/min/1.73m².

The main renal composite outcomes were acute kidney failure in 2.0% in the 2 µg and 1.0% in the µg group versus 0.0% in the placebo group, while chronic kidney failure occurred in 1.0% of the 2 µg group, 0.0% in the 1 µ group and 1.0% in the placebo group. A definition of acute or chronic kidney failure was not given. Congestive cardiac failure occurred in 1.0% only in the 2 µg intervention group. Non-fatal myocardial infarctions and non-fatal stroke were not reported. Death was reported only in 1% of the 2 µg group due to cardiac arrest.

Wang *et al.*, 2013 – OPERA (58)

The Opera study was a double-blinded, placebo-controlled, single-center RCT with 60 patients investigating 1 µg oral paricalcitol once daily versus placebo for 52 weeks. Participating patients were on average 61.5 years of age and 52.2% were male. Eligibility criteria were CKD stages 3-5 and left ventricular hypertrophy. 34.85% of the patients had DMT2, more specifically 27.7% in the intervention group and 43.0% in the control group. 81.7% of patients were treated with ACEi or ARBs.

Baseline and final UACR measurements were not initially provided but were possible to estimate from 24-hour urine analysis. The Table 3 of Visram *et al.* was used to calculate linear graphs between adjacent values using the formula y = m*x+b, with m = (y2-y1)/(x2-x1))*x and b = (m*x1)-y1. y is the 24-hour urine and x is UACR (Table 4).

Table 3. Relationship of 24-hour urine and UACR, source: (59)

24-hour urine (mg) prediction	**Discriminant UACR (mg/g)**	**Area under the curve**	**Sensitivity (%)**	**Specificity (%)**
<200	131	0.938	95	82
>500	283	0.989	94	97
>1000	707	0.988	93	96
>5000	3580	0.976	94	94

Table 4. Calculation of 24-h urine to UACR from the Opera study

Group	**24-hour urine protein in g/d**	**Formula**	**Estimated UACR in mg/g**
Intervention baseline	0.59 (SD 0.50-1.20)	y=0.848x−141	359.32
Intervention final measurement	0.41 (SD 0.23-1.05)	y=0.5067x+29.66	237,41
Placebo baseline	1.06 (SD 0.24-1.95)	y=0.71825x−11.25	750.10
Placebo final measurement	0.49 (SD 0.21-1.50)	y=0.5067x+29.66	277,94

The final measurements included a decrease of -30.51% from baseline 24-h urine albumin of 0.59 g/d (estimated UACR baseline value 359.32 mg/g) to 0.41 g/d (estimated UACR final value 237.41 mg/g) in the intervention group in comparison to a decrease of -53.77% from 24-h urine albumin of 1.06 g/d (estimated UACR baseline value) to 0.49 g/d (estimated UACR final value 277,94 mg/g) in the placebo group. So surprisingly the 24-h urine had only a decrease of -0.05 g/d (SD -0.34 g/d to +0.10 g/d) in the intervention group compared to -0.14 g/d (SD -0.83 g/d to + 0.02 g/d) in the placebo group (*P*= 0.400). Baseline measurement of eGFR was 19.7 ml/min/1.73m² for the intervention group 23.9 ml/min/1.73m² in the control group. In the study, a significant decline in eGFR in the paricalcitol group is mentioned (*P*= 0.002); however, no explanation was given.

The main renal composite outcomes were kidney failure without further definition with identical 6.67 % in both groups and hyperkalemia with 0.0% in the intervention group and 6.67% in the placebo group. Total cardiovascular composite outcomes occurred in 0.0% of the intervention group and in 16.67% of the control group (*P*= 0.700 / HR 0.88, CI 95% 0.47 to 1.63;), non-fatal myocardial infarctions 0.0% in the intervention group and 3.33% in the placebo group and finally non-fatal stroke also 0.0% versus 6.67%.

Mendes *et al.*, 2019 (60)

The observational study included 42 patients with intention to treat without a control group investigating 1 µg paricalcitol once daily for 3 months. Participating patients had an average age of 70.07 years and 65.0 % were male. Eligibility criteria were UACR <1000 mg/g with eGFR >15-<90 ml/min/1.73m² and DMT2, on average 17.92 years duration, 92.9% were pretreated with ACEi or ARBs.

The initial measurement of baseline UACR of 503.07 mg/g decrease to 381.40 mg/g (*P*= 0.001 / CI 95% 51.2-692.15) after 12 weeks. The baseline eGFR of 43.07 ml/min/1.73m² increased to 44.77 ml/min/1.73m² (*P*= 0.359 / CI 95% (-5.39) – (+2.00)) after 12 weeks.

Manson *et al.*, 2020 (61)

The second Vital study was a double-blinded, placebo-controlled, US-nationwide RCT with 25871 patients investigating 2000 IU once daily versus placebo vitamin D_3 over a period of 5.3 years. The aim of the study was to observe cardiovascular outcomes and incidents of invasive cancer when supplementing vitamin D prophylactically. Participants were a diverse cohort of patients with an average age of 67.1 years and 49.4% were male. 13.7% of the patients

were diagnosed with DMT2. Exclusion criteria were a history of cancer, myocardial infarction, stroke, transient ischemic attack or coronary artery revascularization.

Total cardiovascular composite outcomes occurred in 3.06% of the intervention group and in 3.16% of the control group (HR 0.97, CI 95% 0.85-1.12), non-fatal myocardial infarctions 1.31% in the intervention group and similarly 1.36% in the placebo group (HR 0.96, CI 95% 0.78-1.19), non-fatal stroke similarly 1.09% in the intervention group and 1.15% in the control group (HR 0.95, CI 95% 0.76-1.20) and death due to cardiovascular cause 1.18% versus 1.07% (HR 1.11, CI 95% 0.88-1.4). Overall mortality was 3.75% in the intervention group versus 3.81% in the placebo group (HR 0.99, CI 95% 0.87-1.12).

The following Table 5 provides an overview of the KDIGO classification and in which category the patients of each study belong to, to take this into consideration when evaluating the results.

Table 5. Comparison of the severity of albuminuria and eGFR between included studies

eGFR in ml/min/1.73m²	**Albuminuria cathegories Albumin:Creatinine ratio spot urine**		
	A1 (<29 mg/g)	**A2 (30-299 mg/g)**	**A3 (>300 mg/g)**
G1 (eGFR >90)			Figaro
G2 (60-89)	Mendes	Figaro, Fidelity // Vital, Mendes	Figaro, Fidelio, Fidelity // Vital, Mendes
G3a (45-59)	Opera, Mendes	Figaro, Fidelio, Fidelity // Vital, Opera, Mendes	Fidelio, Fidelity // Vital, Opera, Mendes
G3b (30-44)	Opera, Mendes	Figaro, Fidelio, Fidelity // Vital, Opera, Mendes	Fidelio, Fidelity // Vital, Opera, Mendes
G4 (15-29)	Opera, Mendes	Vital, Opera, Mendes	Vital, Opera, Mendes
G5 (<15)	Opera	Opera	Opera

Table 6 provides an overview of the comparison of populations in between included studies.

Table 6. Comparison of populations between included studies

Study	**Bakris *et al.*, 2023**	**Pitt *et al.*, 2021**	**Agarwal *et al.*, 2021**	**De Zeeuw *et al.*, 2010**	**Wang *et al.*, 2013**	**Manson *et al.*, 2020**	**Mendes *et al.*, 2019**
Patients number	5734	7352	13026	281	60	25871	42
Average age	65.6 y	64.1 y	64.8 y	64.0 y	61.5 y	67.1 y	71.1 y
Male in %	70.2 %	69.4 %	69.8%	69.6 %	52,2%	49.4 %	65.0 %
CKD risk group (mostly)	Very high risk	High risk	High and very high risk	Very high risk	Very high risk	No eligibility criteria	All risk groups
UACR mg/g	> 30 - < 5000	> 30 - < 5000	> 30 - < 5000	97 - 3000	N/A	N/A	<1000
eGFR ml/min/1.73m²	> 25 - < 90	> 30 - < 90	> 25 - < 90	15 - 90	< 59	N/A	N/A
DMT2 in %	100 %	100 %	100 %	100 %	34,9%	13.7 %	100 %
DMT2 in years	16.6 y	14.5 y	15.4 y	17.0 y	N/A	N/A	17.9 y
HbA1c in %	7.7 %	7.7 %	7.7 %	7.5 %	N/A	N/A	7.8 %
Initial blood pressure in mmHg	138/76	Systolic 135.8	Systolic 136.7	142/73	133/75	N/A	137/75
History of hypertension in %	97 %	95.8 %	N/A	99.0 %	100%	49.8 %	92.9 %
Treatment with ACEi/ ARBs in %	99.9 %	99.9 %	99.8 %	99.3 %	81,65%	N/A	92.9 %
BMI in kg/m²	31.1	31.4	N/A	32.0	26.4	28.1	N/A
Current smokers in %	14.2 %	N/A	N/A	10.6 %	10.0%	7.2 %	N/A

4.3 METHODOLOGICAL QUALITY ASSESSMENT

Table 2 shows the detailed assessment of quality by the two independent investigators. 23.5 to 27 was the average rating of a maximum of 27, excluding the RCT by Mendes *et al*., which was by definition only able to score a maximum of 21. All studies showed a low risk of bias. The lowest scoring study was an RCT by Manson *et al*., whereas score 27 was reached by Bakris *et al*. The inter-investigator agreement was assessed and expressed by Cohens kappa and was found to be nearly excellent, as kappa scored above 0.81.

4.4 OUTCOME ANALYSIS

The UACR decreased after 44-48 months of treatment in finerenone groups by -29.3% (52) and -27% (54) and increased slightly in the placebo group by +4.1% (52) and +2% (54). In the Vital study on paricalcitol for 24 weeks, the UACR decreased in the intervention group by -14.0% (1 µg daily) and -20.0% (2 µg) daily and in the control group by -3.0% (55). In the Opera study on paricalcitol for 52 weeks, 24-hour urine protein decreased by -30.51% in the intervention group and -53.77% in the placebo group (58), while UACR decreased in the observational study on paricalcitol by Mendes *et al.* by -24.19%. Figure 13 shows the comparison of baseline and final UACR changes between intervention and control group and between studies providing data. Figure 14 shows the increase or decrease of UACR from baseline to end of study in percent. This shows that there is a reliable positive influence on UACR on finerenone treatment compared to placebo. For paricalcitol, all studies show a decrease of UACR, however, not only in the intervention but also in the placebo group, which suggests that there was an additional UACR influencing factor in these studies. The largest decrease in the control group was in the Opera study, which should be interpreted cautiously due to the restricted nature of estimated UACR based on numbers for 24 hour albuminuria.

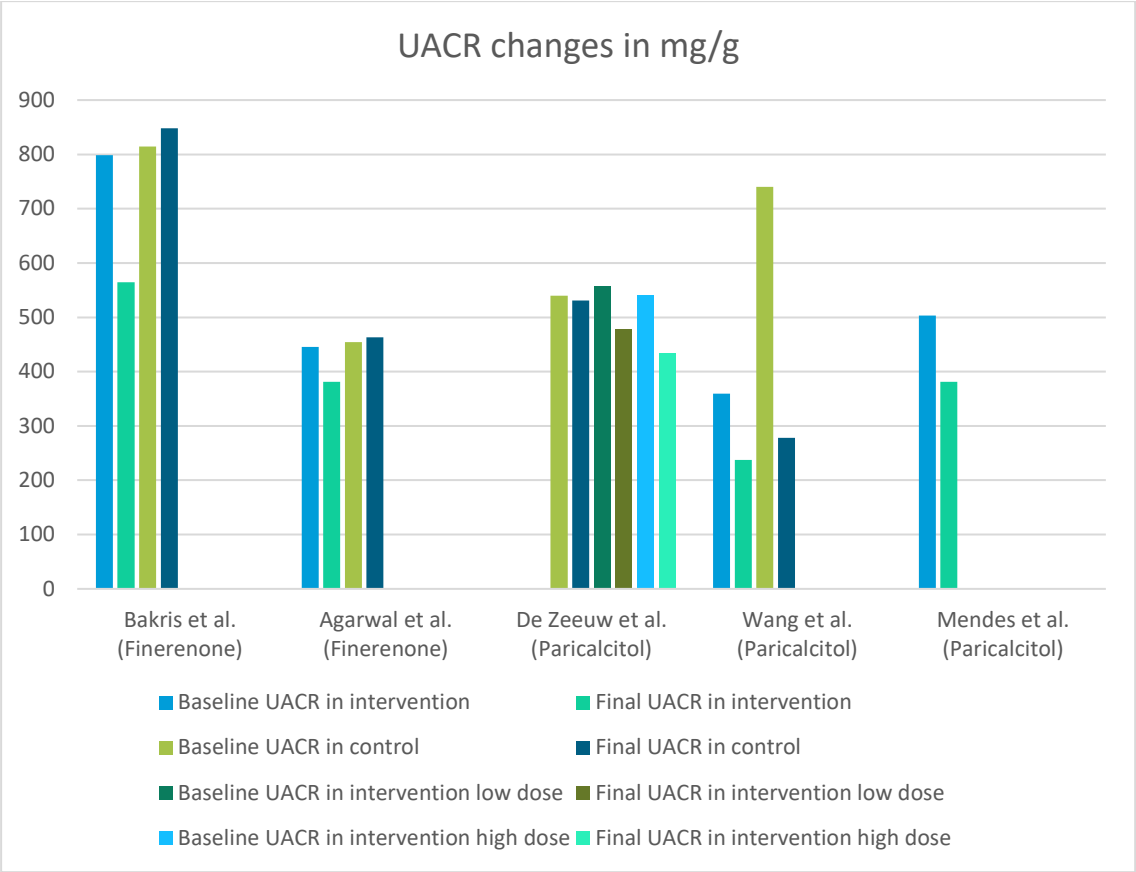


Figure 13. Comparison of baseline and final UACR changes between intervention and control

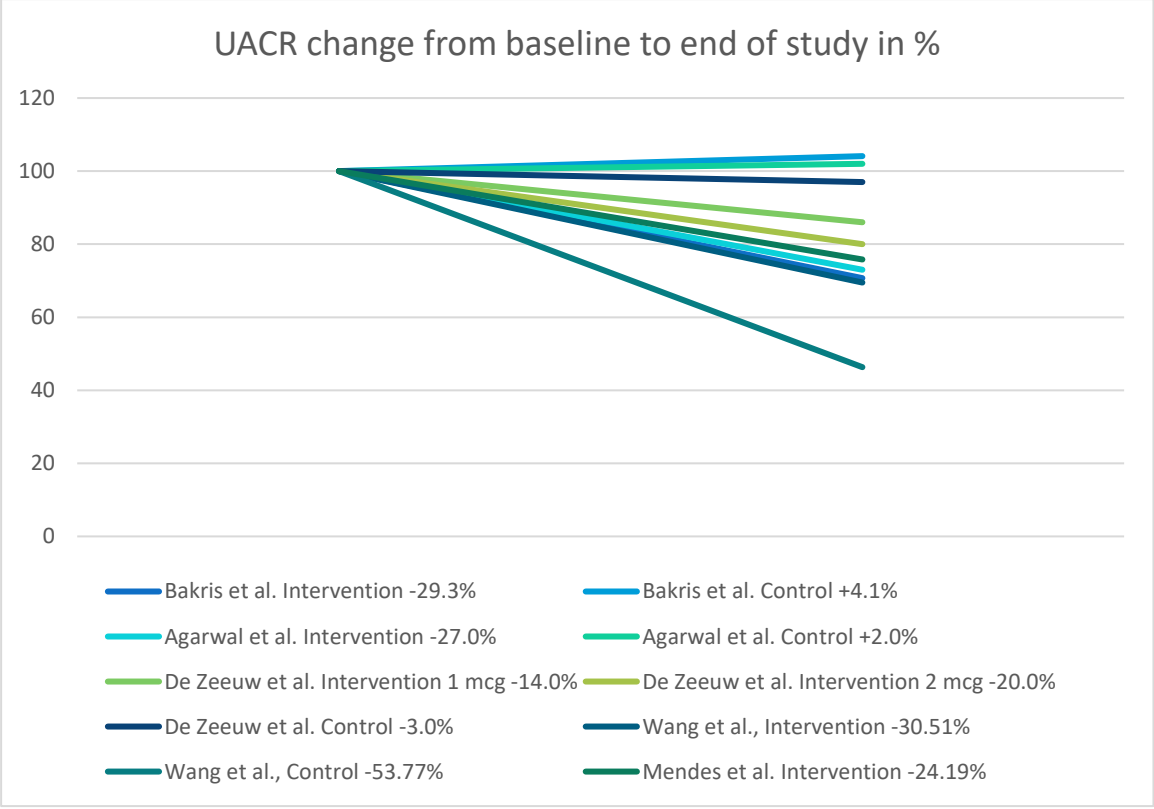


Figure 14. Comparison of change of baseline to final UACR changes

The eGFR in the Fidelio study with finerenone decreased from baseline until four months of treatment more in the intervention group by -3.18 ml/min/1.73m² than in the control group by -0.73 ml/min/1.73m² (52), which was the data inserted into Figures 15 and 16. From month 4 until the end of study the decrease of eGFR slows down significantly compared to the placebo, where eGFR declines by -2.66 ml/min/1.73m² on finerenone, whereas the decrease was -3.97 ml/min/1.72m², which was provided in the Fidelio appendix (52) and can be seen in Figure 17. After about 24 months of treatment a cross over of finerenone and placebo can be observed, when the eGFR is better in the intervention group, showing a significant difference between groups after 40 months of treatment and an increasing difference to month 44. The Figaro and Fidelity study did not provide any final measurements for eGFR.

Regarding paricalcitol, the results differed as visible in Figures 15 and 16, while the eGFR decreased in the Vital study by -3.0 ml/min/1.73m² in the intervention group and did not change in the control group at the end of treatment after 24 weeks (55), the eGFR increased in the study by Mendes *et al.* slightly by +0.85 ml/min/1.73m² after 3 months of treatment (60). No final measurements for eGFR are provided in the Opera study, whereas they did mention a significant decline, keeping in mind, that they did have the patients with the overall lowest baseline eGFR compared to the other studies in this analysis.

Overall, the results for eGFR show a slower progression of the decrease of eGFR in finerenone over the course of several years. Results for paricalcitol are only available for one year or less in patients with CKD and did not show consistent positive changes for a slower progression of decrease of eGFR.

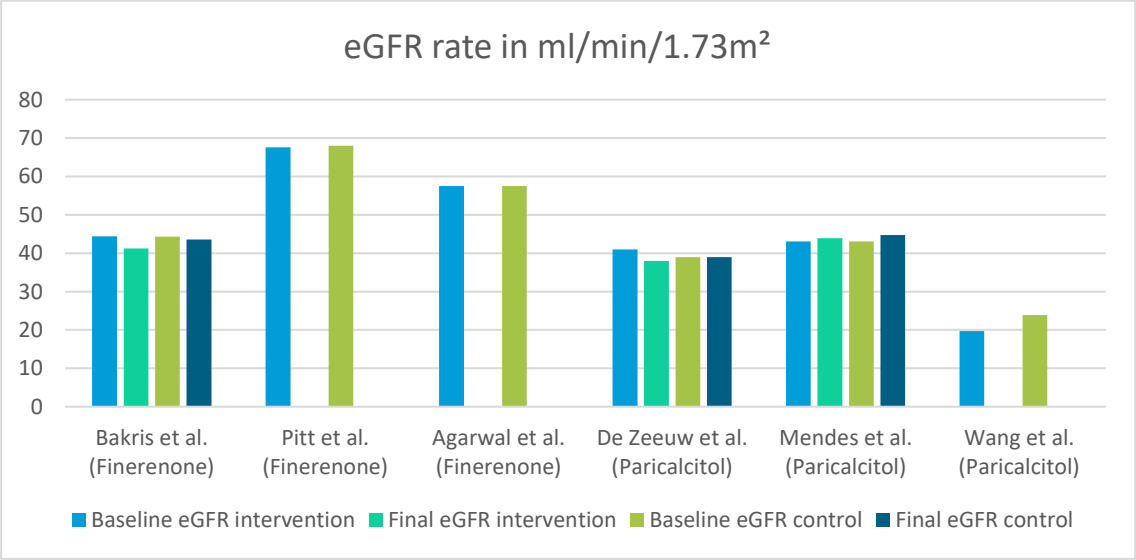


Figure 15. Comparison of baseline and final eGFR changes between intervention and control

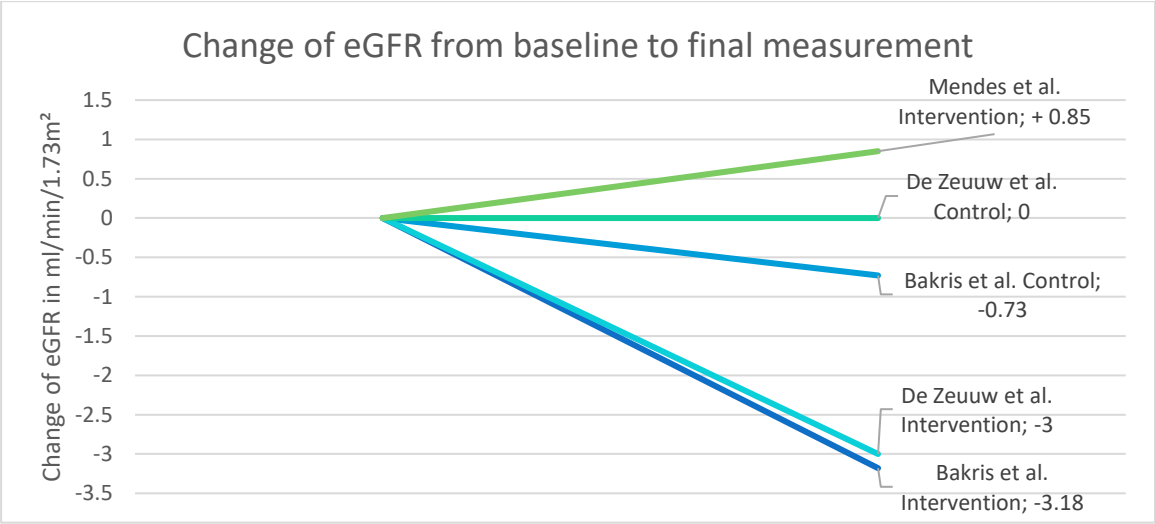


Figure 16. Comparison of change of baseline to final eGFR changes

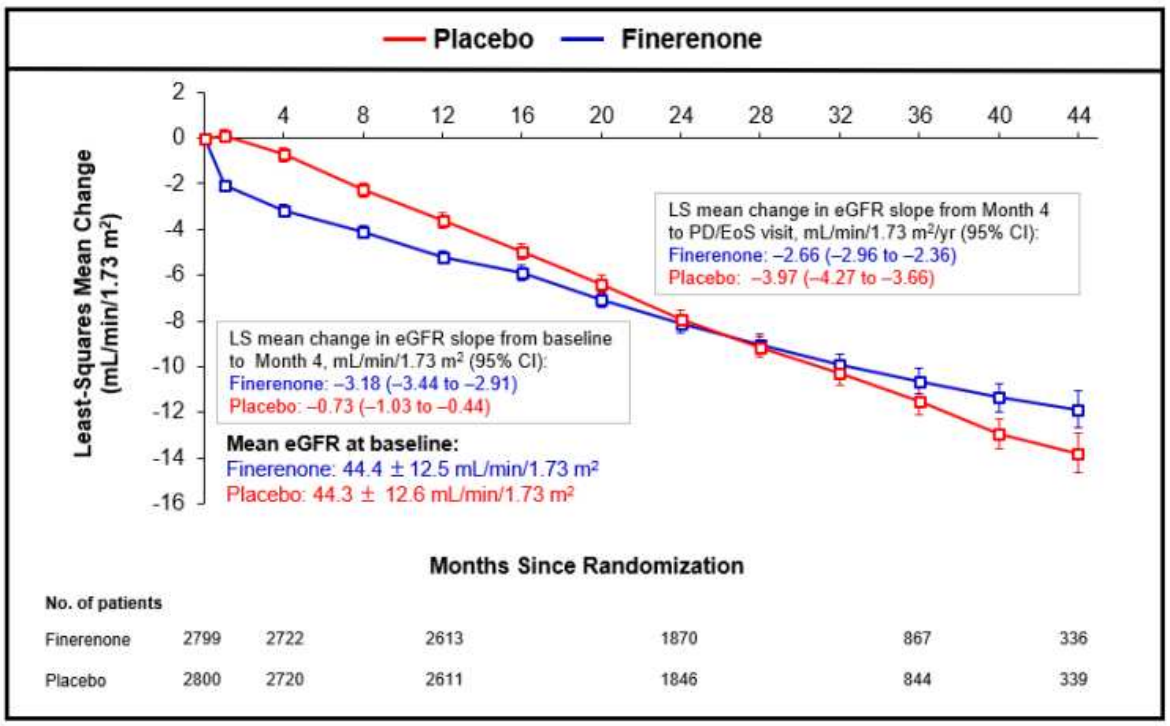


Figure 17. Effects of finerenone and placebo on eGFR in the Fidelio study (appendix) (52)

Shown are the change from the baseline level in eGFR in the full-analysis set. Data are least-square mean ± 95% CI

CI, confidence interval; Eos, end of study; LS, least-squares; PD, permanent discontinuation

Adverse renal outcomes on finerenone after 44-48 months of treatment were defined as a decrease of over 57% of eGFR, kidney failure and hyperkalemia (Figure 18). In the Fidelio study, only 5.9% of the treated patients experienced a >59% decrease in eGFR versus 11.5% in the control group (52). Kidney failure, defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per 1.73 m2 for a period of at least 4 weeks, occurred rarer in the intervention group with 7.3% versus 8.3% in the control group (52). Hyperkalemia was not described in Fidelio, but in Figaro and Fidelity. Figaro showed 2.9% of intervention group patients experiencing a decrease of >59% eGFR versus 3.8% in the control group (53). Kidney failure, as defined in Fidelio, occurred in 1.2% in the intervention group versus 1.7% on placebo (53). Hyperkalemia without further definition occurred more often in the intervention group with 10.8% versus 5.3% in the control group (53). Similar results can be observed in the Fidelity study, where 5.5% versus 7.1% experienced an eGFR decrease over 57% and kidney failure, defined as in Fidelio, in 3.9% versus 4.6% (54). Also, hyperkalemia occurred more often in the intervention group with 14.0% versus 6.9% (54).

Adverse renal outcomes are barely described in all paricalcitol studies, which lasted 24 and 52 weeks (Figure 18). The Vital study described numbers for acute kidney failure without further definition with 2.0% in the high dose and 1.0% in the low dose groups versus 0.0% in controls. Chronic kidney failure was noted in 1.0% in the high dose group, in 0.0% in low dose group and in 1.0% in placebo (55). A decrease in eGFR or hyperkalemia are not mentioned. The Opera study described kidney failure without definition in both the intervention and control group with 6,67% and hyperkalemia with 0.0% in the intervention group versus 6,67% in the control group (58). It should be noted that paricalcitol did have several incidents of hypercalcemia throughout the studies, being 1% in the 2µg paricalcitol group versus none in the other groups of the Vital study (55) and 43.3% in the intervention group versus 3.3% in the placebo group (P= <0.001) in the Opera study (58).

Overall, adverse renal outcomes of decreased eGFR and kidney failure occurred more often in the placebo group than on finerenone. Regarding paricalcitol, only adverse effects pertaining to kidney failure were documented, which seemed to be rare for both the intervention and control group. Hyperkalemia in finerenone was more problematic in the intervention group than in the control group. Paricalcitol does not tend to increase the risk for hyperkalemia, supported by the fact, that the search paricalcitol AND hyperkalemia in PubMed did not provide any results.

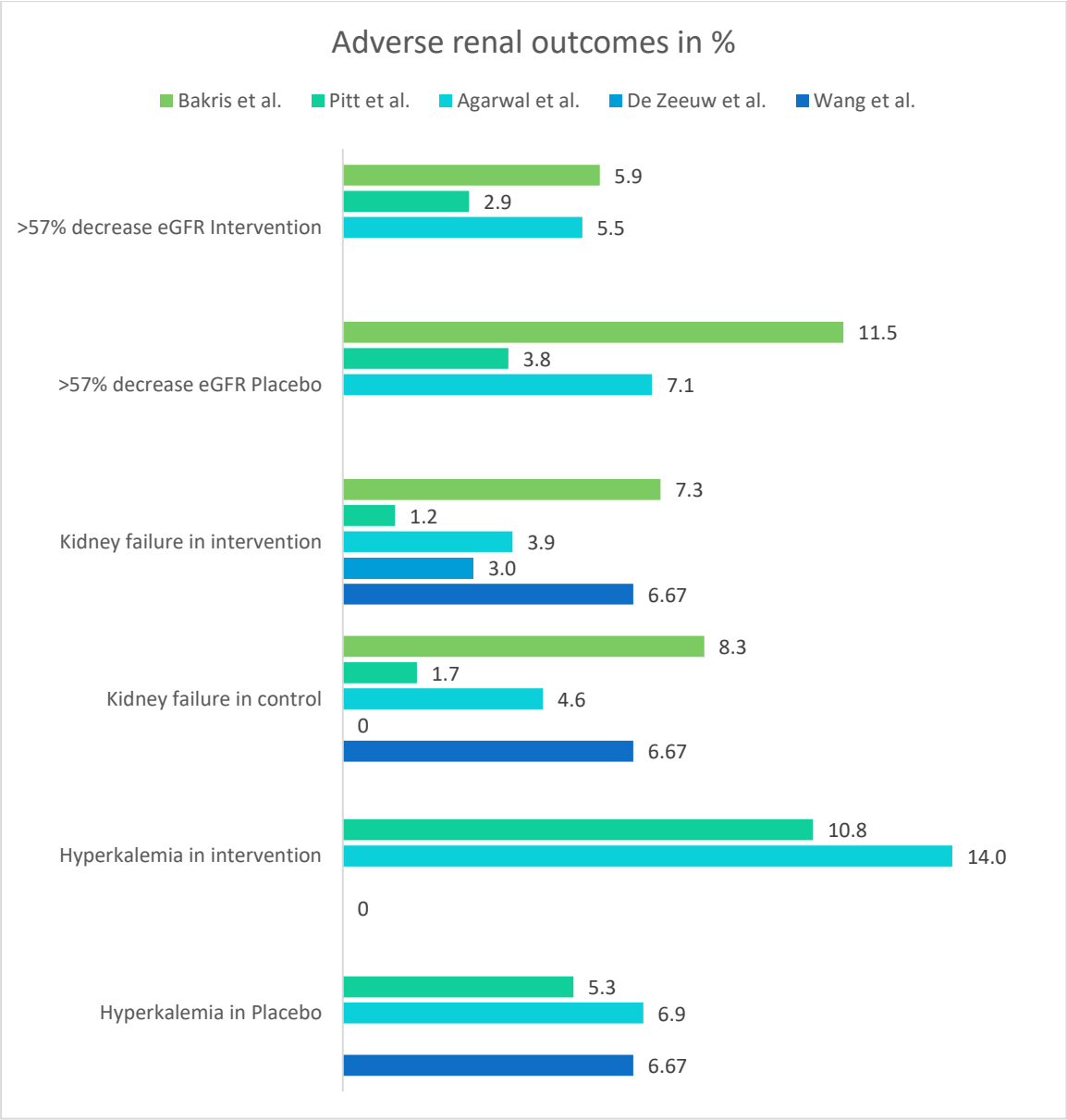


Figure 18. Comparison of adverse renal outcomes between included studies

Adverse cardiovascular outcomes documented were overall cardiovascular outcomes, heart failure, non-fatal myocardial infarction, non-fatal stroke and cardiovascular death (Figure 19). Three finerenone studies lasting 44-48 months provided data for adverse cardiovascular outcomes, i.e. Fidelio, Figaro and Fidelity. In the Fidelio study, overall cardiovascular composite outcomes occurred with 9.2% rarer in the intervention group than in the control group with 11.8% (52). Heart failure occurred in 4.9% versus 5.7%, non-fatal myocardial infarction in 2.5% versus 3.1%, non-fatal stroke in 3.2% versus 3.1% and cardiovascular death in 4.5% versus 5.0% (52). In the Figaro study, overall cardiovascular composite outcomes occurred with 12.4% rarer in the intervention group than in the control group with 14.2%. Heart failure occurred in 3.2% versus 4.4%, non-fatal myocardial infarction identically with 2.8%,

non-fatal stroke in 2.9% versus 3.0% and cardiovascular death in 5.3% versus 5.8% (53). In the combined Fidelity study, overall cardiovascular composite outcomes occurred with 12.7% rarer in the intervention group than in the control group with 14.4%. Heart failure occurred in 3.9% versus 5.0%, non-fatal myocardial infarction in 2.9% versus 3.0%, non-fatal stroke identically with 3.0% and cardiovascular death in 4.9% versus 5.6% (54).

Regarding paricalcitol, the Vital study lasting 24 weeks only provided data for adverse cardiovascular outcomes with 1.0% in the intervention group and 0.0% in the control group and for heart failure with 0.5% in the intervention group and 0.0% in the control group (55). The Opera study described adverse cardiovascular outcomes in 0.0% of the intervention group and 16.67% in the control group, non-fatal myocardial infarction in 0.0% versus 3.33% and non-fatal stroke in 0.0% and 6.67% respectively over a study duration of 52 weeks (58).

For additional insight, I included the study by Manson *et al.*, even though they conducted a cohort study with patients without a history of cancer, myocardial infarction, stroke, transient ischemic attack or coronary artery revascularization. The study lasted 5.3 years. Albeit comparability is not given totally, a slight indication is given, how study results with CKD and DMT2 could look like. Overall cardiovascular composite outcomes occurred with 3.06% rarer in the intervention group than in the control group with 3.16%. Heart failure data were not provided. Non-fatal myocardial infarction occurred in 1.31% versus 1.36%, non-fatal stroke in 1.09% versus 1.15% and cardiovascular death in 1.18% versus 1.07% (61).

Regarding overall cardiovascular composite outcomes for finerenone, the ARR between intervention and placebo was 2-3% in Fidelio, Figaro and Fidelity. In the Fidelio study, there was the largest RRR of 22,03% (52), underlining the advantage of finerenone. All other comparisons of intervention and placebo within each study in each category diverged by less than 1% and were comparable to each other study also within a 1% margin of difference. The largest difference of 1,2% was noted in the Figaro study between finerenone and placebo for heart failure (53), making a RRR of 27.27% between groups. For the Vital and Opera paricalcitol studies, only little information regarding cardiovascular composite outcomes was available and was overall low in comparison to all finerenone studies. As expected, cardiovascular composite outcomes were much rarer within the vitamin D_3 cohort study of individuals without CKD, but overall, there were less incidents of composite cardiovascular outcomes in paricalcitol versus placebo considering a very large number of 25871 patients over a long duration.

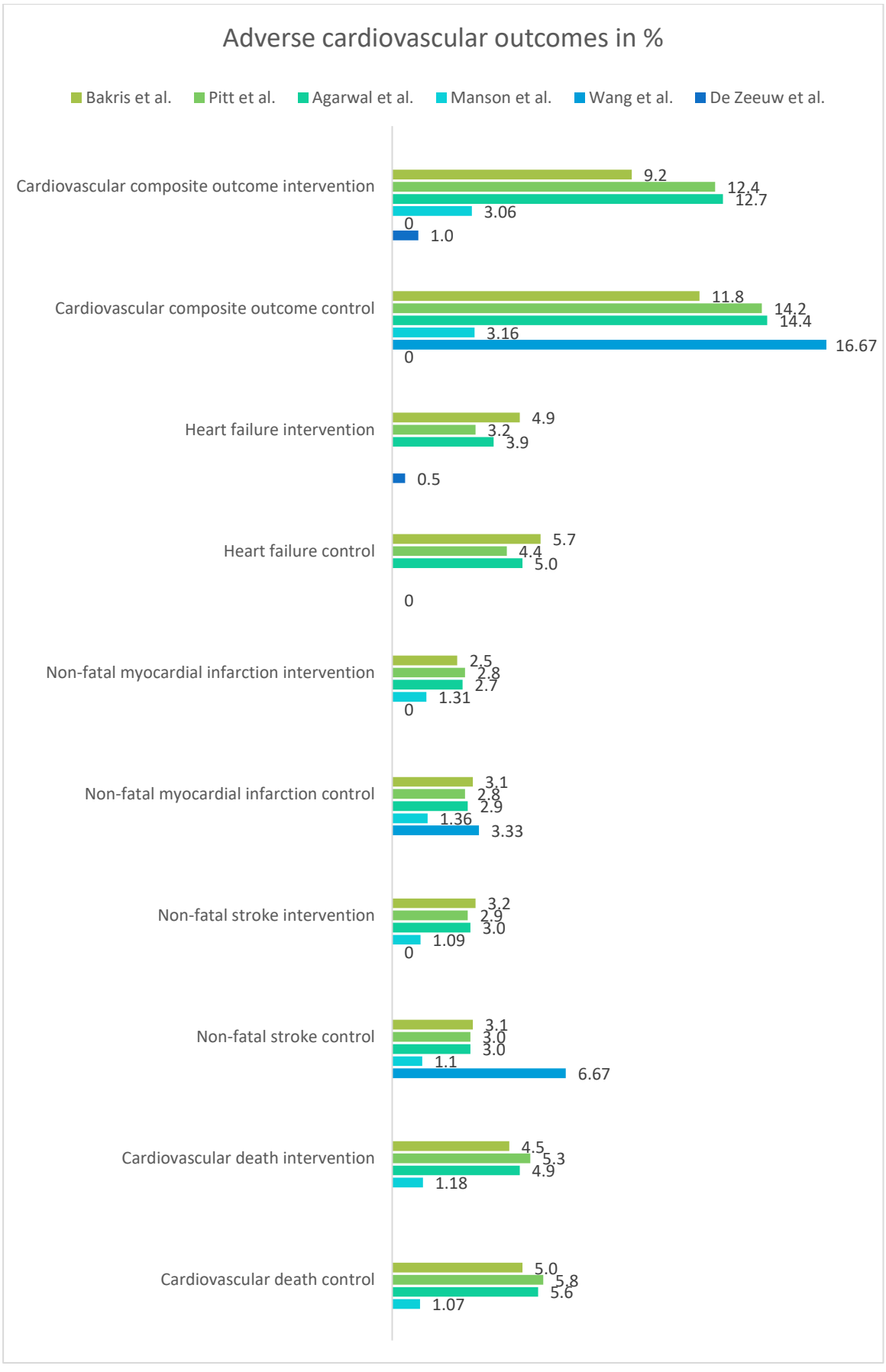


Figure 19. Comparison of adverse cardiovascular outcomes between included studies

The difference in overall mortality (Figure 20) between the finerenone studies all lasting 44-48 months showed an ARR within 2%. In the Fidelio study, overall mortality in the intervention group was 7.7% and in the control group 8.6% (52). In the Figaro study, it was 9.0% versus 10.1% (53), which was the largest RRR of 10.89%. In the Fidelity study, it was 8.5% versus 9.4% (54). In the Vital study only 1% of overall mortality was reported in the intervention group due to one patient dying of cardiac arrest (55). In the study of Manson *et al.* 485 cases (3.75%) and 493 cases (3.81%) of death due to any cause, including cardiovascular and cancerous death, were reported (61). No data were provided by Wang *et al.* and Mendes *et al.*, possibly due to the shorter time of study duration.

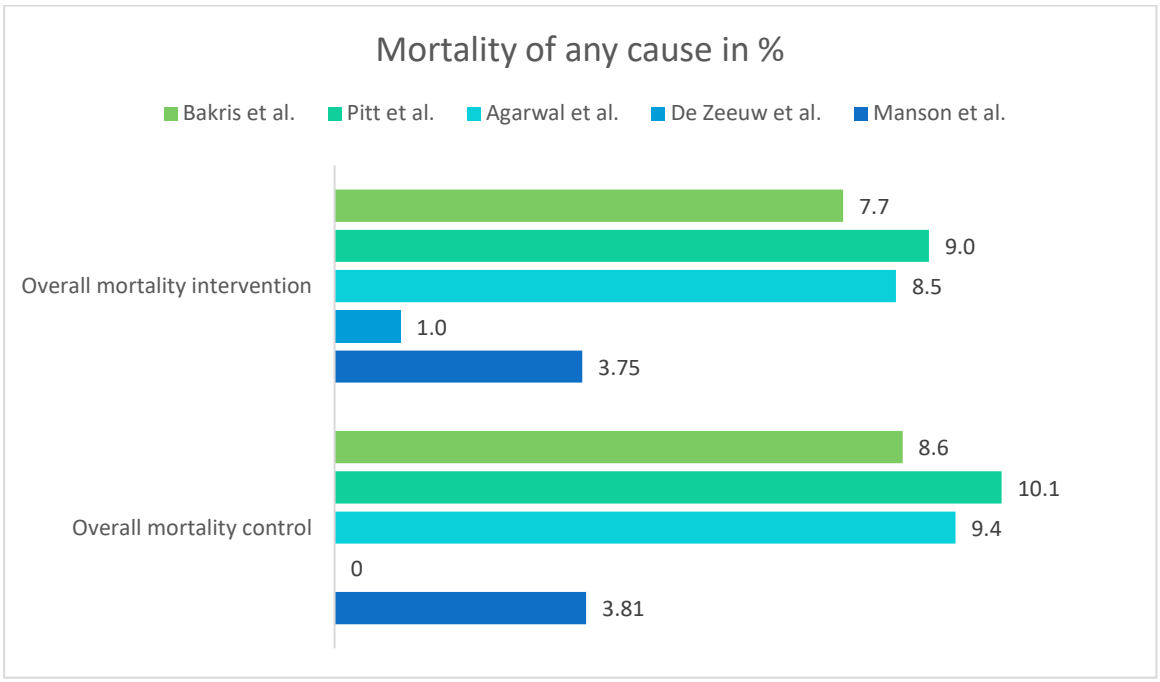


Figure 20. Comparison of mortality between included studies

5. DISCUSSION

The results of this meta-analysis suggest that there is no overall superiority of paricalcitol over finerenone in the progression of CKD as measured by albuminuria and eGFR. An association between renal protection and a decrease of adverse cardiovascular events has been proven for finerenone and would appear possible also for paricalcitol.

This meta-analysis includes seven studies of which three studies investigated finerenone and four studies investigated paricalcitol. Six studies were prospective, double-blind, placebo-controlled RCTs and one study was an observational study without placebo-control. The three finerenone studies included 5734, 7352 and 13026 patients, the four paricalcitol studies included 281, 60, 42 and 25871 patients. Overall, the studies had comparable populations of patients with ages varying from 61.5 to 71.1 years and a male population from 49.4% to 70.2%. Except for the study by Manson *et al.*, which investigated a population without a history of cancer, myocardial infarction, stroke, transient ischemic attack or coronary artery revascularisation, all patients had CKD in various stages and DMT2 for 14.5 to 17.9 years with HbA1c of 7.5% to 7.8%. If available, average systolic blood pressure varied between 135 mmHg and 142 mmHg. Hypertension was consistent in 92.9% to 100.0% of the populations and between 81.65% to 99.9% of patients were treated with ACEi or ARBs, wheeas the study of Manson *et al.* was an exception with only 49.8% of patients with hypertension. Overall, the patients were obese with a BMI of 26.4 to 32.0 kg/m². Available data documented, that 7.2% to 14.2% were current smokers.

The UACR decreased in all measured finerenone groups by -27% (54) to -29.3% (52) contrasting with an UACR increase by +2.0% (54) to +4.1% (52) in the control groups. Regarding paricalcitol, results showed a decrease of UACR of -24.19% (60) to -30.51% (58) in the intervention groups, but also a decrease of UACR of -20.0% (55) to -53.77% (58) in the control group. Thus, although a reduction in albuminuria has been documented in several studies regarding paricalcitol, this effect appears inconsistent. The primary reductions in UACR are similar on finerenone and paricalcitol. However, it is striking, that in the paricalcitol studies there was an equal or even more pronounced decrease in the control groups, whereas UACR increased overall in the control groups of the finerenone studies. This suggests, that there could have been an additional cause of UACR decrease in the paricalcitol studies.

Estimated GFR decreased within the first four months of treatment in the intervention and in the control group on finerenone by respectively -3.18 ml/min/1.73m² and -0.73 ml/min/1.73m² (52). However, the eGFR slope decreased after 4 months until the end of study

by only -2.66 ml/min/1.73m², which was significantly less than in the placebo group with -3.97 ml/min/1.73m². A cross over of the decrease of eGFR in intervention versus placebo can be observed after 24 months of treatment with a significant superiority of finerenone compared to placebo after 40 months, which further increases in measurements at month 44. Mixed results were presented in the paricalcitol trials, where the Vital study showed a decrease of eGFR by -3.0 ml/min/1.73m² and a stable eGFR in the control (55), while in the study by Mendes *et al.* eGFR increased slightly by +0.85 ml/min/1.73m² (60). Unfortunately, regarding eGFR, long-term paricalcitol versus placebo data are not available, as paricalcitol and other active vitamin D substances were primarily developed and introduced to ameliorate secondary hyperparathyroidism (39). It is a possibility that paricalcitol could have a similar slope in eGFR as in finerenone with an overall advantage of paricalcitol versus placebo after a longer duration of treatment.

Adverse renal effects were mainly reported for finerenone, where events were consistently higher in the control group. A decrease of eGFR >59% varied from 2.9% (53) to 5.9% (52) in the intervention group and from 3.8% (53) to 11.5% (52) in the control group. Since the Fidelio study included more severe cases of CKD, this might be considered as the more powerful result, showing an ARR of incidents of 5.6% or a RRR of 48.7% between intervention and control group for eGFR >59% decrease. Renal failure, defined as end-stage kidney disease or an eGFR of less than 15 ml per minute per 1.73 m², and end-stage kidney disease, which was defined as the initiation of long-term dialysis (for ≥90 days) or kidney transplantation, occurred more often in the Fidelio study with 7.3% in the intervention group and 8.3% in the control group (52), which is a lowering of the relative risk of 12,05%. Renal failure varied in the other studies from 1.2% (53) to 3.9% (54) in the intervention group and from 1.7% (53) to 3.9% (54) in the control group. Overall, the paricalcitol studies showed only rare occasions of renal failure in 3.0% (55) to 6.67% (58) in the intervention group and 0.0% (55) to 6.67% (58) in the control group, leading to the conclusion of no risk reduction. Due to limitation of information, a safe statement pertaining to the superiority for adverse renal events of one drug cannot be given. For hyperkalemia, the cases on finerenone were nearly double the amount in the intervention group with 10.8% (53) and 14.0% (54) versus only 5.3% (53) and 6.9% (54) in the control. The only study documenting hyperkalemia on paricalcitol was the Opera study, which had no cases in the intervention group and 6.67% in the control group (58). No cases were reported in other paricalcitol studies, even though they mentioned vaguely other electrolyte derailments. This could lead to the conclusion, that paricalcitol is safer regarding hyperkalemia. On the other hand, there were several reports of hypercalcemia in the paricalcitol

groups with a significant increase in absolute risk by 40.0% and a relative increase in risk of 92.38% in the intervention group (58).

Overall, cardiovascular adverse events did occur more often in the finerenone than in the paricalcitol trials. The Opera study provided little insight into cardiovascular outcomes, but unfortunately, no data were provided by de Zeeuw *et al*. and Mendes *et al*. The study by Manson *et al.* reported on 3.06% of cardiovascular events in the intervention group versus 3.16% in the controls, however, the study investigated individuals without CKD, rendering the potentially true superiority of paricalcitol unclear. Generally, adverse cardiovascular events occurred 9.2% (52) to 12.7% (54) in the finerenone intervention group, while in the intervention group 11.8% (52) to 14.4% (54) were affected, leading to the conclusion, that the benefits of finerenone correlated positively with the progression of CKD by a maximal ARR of 2,6% and a RRR of 22,03% in the Fidelio study (52). In contrast to this, the overall cases of cardiovascular events were low in available paricalcitol studies ranging from 0.0% (58) to 3.06% (61) in the intervention group versus 0.0% (55) to 16.67% (58) in the control group. Other adverse effects including heart failure, non-fatal myocardial infarction and non-fatal stroke for finerenone varied from 2.5% (52) to 4.9% (52) in the intervention group versus 2.8% (53) to 5.7% (52) in the control group. For paricalcitol, incidents were 0.5% (55) to 1.31% (61) in intervention groups versus 0.0% (55) to 1.36% (61) in the control group. This leads to the conclusion, that paricalcitol patients were less affected by cardiovascular events, keeping in mind, that the main results originated from studies with less diseased individuals. Cardiovascular death was more common in the finerenone group with about 4.5% (52) to 5.3% (53) in the intervention group and 5.0% (52) to 5.8% (53) in control versus only 1.18% (60) on paricalcitol and 1.07% (60) in the control group, again keeping in mind, that these were cohort patients without consistent CKD.

Overall mortality was higher in the control group with 8.6% (52) to 10.1% (53) versus 7.7% (52) to 9.0% (53) in the intervention group on finerenone. The most significant results were from Figaro study with an ARR of 1.1% between intervention and control, which is a RRR of 10.89%. Mortality was lower with 1.0% (55) to 3.75% (61) in the intervention group on paricalcitol versus 0.0% (55) to 3.81% (61) in the control group, which equates to a RRR of 1.57% in the study by Manson *et al.* This leads to the conclusion of better survival for all finerenone groups compared to their control groups, even though the incidence of death was rarer in all paricalcitol groups. This could be caused by the shorter duration and follow up of patients, but pertaining specifically to Manson *et al.*, his positive results could be due to the difference of the health status of the patients at the beginning of the study.

As this was literature research, few limitations of this meta-analysis should be named. The studies for paricalcitol were from the years 2010 until 2020, whereas finerenone studies took place from 2021 until 2023. More recent studies show much larger patient populations than the older studies, giving more precise insight, especially about the number of adverse effects. Furthermore, the patient population do differ in the mostly in the study by Manson *et al*., but also in the Opera study. Still these studies were included due to valuable information about adverse effects. Also, some studies were included, even though they did not provide all data for all hypotheses in this analysis, but rather each answered few questions. The aim was to provide a fuller picture of the advantages and disadvantages of each drug in several categories. The largest limitation of this meta-analysis is the difference between study durations. As finerenone shows, there was a significant difference between intervention and placebo group for eGFR diverging after 40 months of treatment. Studies of paricalcitol ended latest after 12 months, which leaves room for investigation, if the treatment with paricalcitol is more beneficial after a longer treatment such as finerenone. It would be also very interesting to evaluate inflammatory parameters, such as Dickkopf 3, for both drugs. Studies about paricalcitol in correlation to inflammation have taken place before, but the options of biomarkers have been increasing during the last years, leaving room for improvement. Finerenone has not been tested on its anti-inflammatory properties in connection to renoprotection.

6. CONCLUSIONS

Overall, general superiority of one drug over another can not be entirely proven, suggesting more investigations. At present, finerenone is more beneficial for CKD diseased patients by improving albuminuria and overall survival, additionally stabilizing eGFR in the long-term. Finerenone carries a risk of hyperkalemia. Finerenone could positively influence cardiovascular outcomes through renoprotection, as the mediation analysis of Agarwal suggests (8).

Paricalcitol can be carefully suggested to individuals with high risk for hyperkalemia and adverse cardiovascular events to improve overall survival and decrease their UACR with the intention of stabilizing eGFR in the long-term. However, paricalcitol can induce hypercalcemia, and thus, regular laboratory follow-up is required. Present data suggest leaning more towards 1 µg of paricalcitol daily than 2 µg, since an overall increase of adverse effects was observed with the higher dosage. Paricalcitol could also be useful in CKD patients with DMT2 for renoprotection, if they are resistant to RAAS (55). However, more investigation of these drugs is warranted, especially considering the duration of treatment.

Both drugs apparently have anti-inflammatory properties. Possible measurements for investigation could be the new biomarker DKK3 (Dickkopf 3), which is an indicator for the progression on CKD, more specifically tubulointerstitial fibrosis. This is a more accurate biomarker than albuminuria and eGFR. Few studies have been performed to investigate the progression of CKD with DKK3, but, so far, none of these have investigated finerenone and paricalcitol. This offers a breakthrough for future studies.

7. REFERENCES

1. Endspurt Vorklinik, Anatomie 2. 3rd ed. Stuttgart, Germany: Georg Thieme Verlag, 2015. 48-51 p.
2. Endspurt Vorklinik, Histologie. Stuttgart, Germany: Georg Thieme Verlag, 2015. 62-65 p.
3. Endspurt Vorklinik, Physiologie 2. 3rd ed. Stuttgart, Germany: Georg Thieme Verlag, 2015. 32-36 p.
4. Endspurt Klinik, Innere und Chirurgie 4. Stuttgart, Germany: Georg Thieme Verlag, 2013. 86-101 p.
5. Hilton R. Defining acute renal failure. CMAJ. 2011;183:1167-9.
6. Vaidya SR, Aeddula NR. Chronic kidney disease [Internet]. StatPearls: StatPearls Publishing; 2022 [Updated 2022 Oct 24; cited 2024 Feb 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535404/
7. Wilson S, Mone P, Jankauskas SS, Gambardella J, Santulli G. Chronic kidney disease: Definition, updated epidemiology, staging, and mechanisms of increased cardiovascular risk. J Clin Hypertens (Greenwich). 2021;23:831-34.
8. Agarwal R, Tu W, Farjat AE, Farag YMK, Toto R, Kaul S et al. Impact of finerenone-induced albuminuria reduction on chronic kidney disease outcomes in type 2 diabetes: A mediation analysis. Ann Intern Med. 2023;176:1606-16.
9. Fey H. Effekte von Paricalcitol auf Inflammation und Kalzifikationsregulation bei Hämodialysepatienten. Würzburg, Germany: Universität Würzburg; 2013.
10. Di Cesare M, Bixby H, Gaziano T, Hadeed L, Kabudula C, McGhie D et al. World heart report 2023, confronting the worlds number one killer [Internet]. Geneva, Switzerland: World Heart Federation; 2023 [cited 2024 Feb 12] Available from: https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf
11. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389:1238-52.
12. Textor SC. Ischemic nephropathy: where are we now? J Am Soc Nephrol. 2004;15:1974-82
13. Kitamoto Y, Tomita M, Akamine M, Inoue T, Itoh J, Takamori H et al. Differentiation of hematuria using a uniquely shaped red cell. Nephron. 1993;64:32-6.
14. Anderson S, Rennke HG, Brenner BM. Antihypertensive therapy must control glomerular hypertension to limit glomerular injury. J Hypertens Suppl. 1986;4:S242-4.

15. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20:2075-84.
16. Flannery O´Leary M. Hematocrit [Internet]. New York, USA: Medscape; 2022 [cited 2024 Feb 12]. Available from: https://emedicine.medscape.com/article/2054320-overview?form=fpf
17. Sachdeva B, Zulfiqar H, Aeddula NR. Peritoneal Dialysis [Internet]. Treasure Island, USA:Pubmed; 2023 [Updated 2024 Jan; cited 2024 Feb 12]. Available from: brihttps://pubmed.ncbi.nlm.nih.gov/30422574/
18. Kara Rogers. Britannica [Internet]. Chicargo, USA; 2024 [Updated 2024 Aug 15; cited 2024 Aug 18]. Available from: https://www.britannica.com/science/inflammation#ref214901.
19. Ciaccia L. Fundamentals of inflammation. Yale J Biol Med. 2011;84:64–5.
20. Farris AB, Colvin RB. Renal interstitial fibrosis: mechanisms and evaluation. Curr Opin Nephrol Hypertens. 2012;21:289-300.
21. Porrini E, Ruggenenti P, Mogensen CE, Barlovic DP, Praga M, Cruzado JM et al. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2015;3:382-91.
22. Sciascia S, Barinotti A, Radin M, Cecchi I, Menegatti E, Terzolo E et al. Dickkopf Homolog 3 (DKK3) as a prognostic marker in lupus nephritis: A prospective monocentric experience. J Clin Med. 2022;11:2977.
23. Karwowski W, Naumnik B, Szczepański M, Myśliwiec M. The mechanism of vascular calcification - a systematic review. Med Sci Monit. 2012;18:RA1-11.
24. Budoff MJ, Yu D, Nasir K, Mehrotra R, Chen L, Takasu J et al. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J. 2005;149:695-700.
25. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005;111:1313-20.
26. Pohle K, Mäffert R, Ropers D, Moshage W, Stilianakis N, Daniel WG et al. Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. Circulation. 2001;104:1927-32.
27. Schurgin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. Diabetes Care. 2001;24:335-8.

28. Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. JAMA. 2000;283:2810-5.
29. Reaven PD, Sacks J; Investigators for the VADT. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. Diabetologia. 2005;48:379-85.
30. Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y et al. Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2007;49:417-25.
31. Nelson RG, Gohdes DM, Everhart JE, Hartner JA, Zwemer FL, Pettitt DJ et al. Lower-extremity amputations in NIDDM. 12-yr follow-up study in Pima Indians. Diabetes Care. 1988;11:8-16.
32. Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. Arterioscler Thromb Vasc Biol. 1998;18:1400-7.
33. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Böhm R et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet. 2003;361:827-33.
34. Coen G, Pierantozzi A, Spizzichino D, Sardella D, Mantella D, Manni M et al. Risk factors of one year increment of coronary calcifications and survival in hemodialysis patients. BMC Nephrol. 2010;11:10.
35. Wu-Wong JR, Nakane M, Ma J, Ruan X, Kroeger PE. Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. Atherosclerosis. 2006;186:20-8.
36. Aihara K, Azuma H, Akaike M, Ikeda Y, Yamashita M, Sudo T et al. Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem. 2004;279:35798-802.
37. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM. 2002;95:787-96.

38. Neves KR, Graciolli FG, dos Reis LM, Graciolli RG, Neves CL, Magalhães AO, Custódio MR et al. Vascular calcification: contribution of parathyroid hormone in renal failure. Kidney Int. 2007;71:1262-70.
39. Drugs.com. Paricalcitol Injection Prescribing Information [Internet]. Ewing, USA: eHealthcare Solutions, Inc.; 2024 [Updated 2024 Aug 14; cited 2024 Aug 17]. Available from: https://www.drugs.com/pro/paricalcitol-injection.html.
40. AbbVie Deutschland. Zemplar® 1/-2 Mikrogramm Weichkapsel [Internet]. Frankfurt, Germany; Rote Liste; 2024 [Updated 2024 Aug 1; cited 2024 Aug 17]. Available from: https://www.rote-liste.de/suche/praep/21392-0/Zemplar%C2%AE%201%2F-2%20Mikrogramm%20Weichkapsel
41. Ratiopharm. Paricalcitol-ratiopharm Weichkapseln [Internet]. Ulm, Germany; Ratiopharm; 2022 [Update 2022 Oct; cited 2024 Aug 17]. Available from: https://www.fachinfo.de/fi/pdf/020627.
42. Tan X, Wen X, Liu Y. Paricalcitol inhibits renal inflammation by promoting vitamin D receptor-mediated sequestration of NF-kappaB signaling. J Am Soc Nephrol. 2008;19:1741-52.
43. Gerisch M, Heinig R, Engelen A, Lang D, Kolkhof P, Radtke M et al. Biotransformation of finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist, in dogs, Rats, and humans, in vivo and in vitro. Drug Metab Dispos. 2018;46:1546-55.
44. Epstein M. Aldosterone and Mineralocorticoid Receptor Signaling as Determinants of Cardiovascular and Renal Injury: From Hans Selye to the Present. Am J Nephrol. 2021;52:209-16.
45. Bayer. Kerendia, full prescribing information [Internet]. Wippany, USA; FDA;2021 [cited 2024 Aug 17]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215341s000lbl.pdf
46. Bayer. Kerendia® 10 mg/-20 mg Filmtabletten [Internet]. Frankfurt, Germany; Rote Liste; 2022 [Update 2023 Feb; cited 2024 Aug 17]. Available from: https://www.fachinfo.de/fi/detail/023695/kerendia-r-10-mg-20-mg-filmtabletten
47. Marcath LA. Finerenone. Clin Diabetes. 2021;39:331-2.
48. Palanisamy S, Funes Hernandez M, Chang TI, Mahaffey KW. Cardiovascular and Renal Outcomes with Finerenone, a Selective Mineralocorticoid Receptor Antagonist. Cardiol Ther. 2022;11:337-54.

49. Moher D, Liberati A, Tetzlaff J, Altman DG et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
50. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377-84.
51. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-74.
52. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020;383:2219-29.
53. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021;385:2252-63.
54. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 ;43:474-84.
55. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet. 2010;376:1543-51.
56. Hatlen G, Romundstad S, Hallan SI. The accuracy of predicting cardiovascular death based on one compared to several albuminuria values. Kidney Int. 2014;85:1421-8.
57. MediCalc. Albumin:Creatinine Ratio (Unit Conversion) [Internet]. Houston, USA: MedML; 2021 [Cited 2024 Aug 3].. Available from: https://www.scymed.com/en/smnxps/psdjb222_c.htm.
58. Wang AY, Fang F, Chan J, Wen YY, Qing S, Chan IH et al. Effect of paricalcitol on left ventricular mass and function in CKD - the OPERA trial. J Am Soc Nephrol. 2014;25:175-86.
59. Visram A, Al Saleh AS, Parmar H, McDonald JS, Lieske JC, Vaxman I et al. Correlation between urine ACR and 24-h proteinuria in a real-world cohort of systemic AL amyloidosis patients. Blood Cancer J. 2020;10:124.

60. Mendes F, Carias E, Silva A, Neves P. The Role of Paricalcitol In Urinary Albumin-To-Creatinine Ratio in Patients with Type 2 Diabetes and Chronic Kidney Disease. Diabetes Complications. 2019;3:1-7.
61. Manson JE, Bassuk SS, Buring JE; VITAL Research Group. Principal results of the VITamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. J Steroid Biochem Mol Biol. 2020;198:105522.

8. SUMMARY

Objective: The aim of the study was to investigate and evaluate the available data regarding the progression of CKD and extent of proteinuria in view of the association between CKD and cardiovascular outcomes and, furthermore, between the extent of proteinuria and its association with progression of CKD.

Material and Methods: PubMed was searched using the search key words (finerenone) or (paricalcitol) AND (albuminuria). All patients with CKD, DMT2 and treatment with ACEi or ARBs were eligible. The paricalcitol study by Manson *et al.* was included for the comparison of cardiovascular outcomes, even though investigating a cohort without a history of cancer and major cardiovascular events without a focus on CKD, attempting to demonstrate a prophylactic effect. For methodological quality assessment, Downs and Black scale was utilized.

Results: A total of seven studies, three finerenone and four paricalcitol, were included in this meta-analysis. Six of these studies were prospective, double-blind, placebo-controlled and randomized, while Mendes *et al.* was an observational study. Six studies included patients with CKD, DMT2 (mean duration > 14.5 years) and at least 81.65% were pretreated with ACEi or ARBs, while Manson *et al.* observed a cohort without CKD as mentioned above. The duration was 44-48 months for finerenone and 3-12 months for paricalcitol. UACR decreased in all finerenone and paricalcitol studies. The eGFR showed an initial decrease on finerenone over four weeks but proceeded more mildly than in the control group, while the data for paricalcitol were overall insufficient for evaluation of eGFR. The ARR on finerenone for a decrease of eGFR >57% was 5.6% and 48.7% in RRR. Very few cases were reported for paricalcitol. Hyperkalemia occurred more often on finerenone, whereas hypercalcemia occurred more often on paricalcitol. Cardiovascular adverse events occurred more often on finerenone, possibly influenced by the comparison with an inhomogeneous cohort with and without CKD. For cardiovascular events, a maximal ARR of 2.6% and a RRR of 22.03% was proven in the Fidelio study, compared to inhomogeneous reductions in paricalcitol. Overall mortality was lower in all intervention groups of both drugs compared to the control group, reducing the relative risk by maximal 10.89% (53) in finerenone and by 1.57% in paricalcitol (61).

Conclusion: Both drugs positively influence the UACR and albuminuria, thus, potentially slowing down the progression of CKD. Cardiovascular morbidity and mortality are more reduced on finerenone. Estimated GFR on finerenone stabilizes after an initial dip to a slower progression. This was insufficiently investigated in paricalcitol, which leaves room for further investigation. Overall adverse effects did occur rarest in the 1 µg paricalcitol group.

9. CROATIAN SUMMARY

Naslov: Usporedba kliničkih parametara parikalcitola i finerenona u usporavanju progresije kronične bubrežne bolesti

Cilj: Cilj studije bio je istražiti i procijeniti dostupne podatke o progresiji KBB-a te opseg proteinurije s obzirom na povezanost između KBB-a i kardiovaskularnih ishoda te, nadalje, između opsega proteinurije i njezine povezanosti s progresijom KBB-a.

Materijal i metode: PubMed je pretražen pomoću ključnih riječi za pretraživanje (finerenone) ili (parikalcitol) I (albuminurija). Svi bolesnici s kroničnom bubrežnom bolesti, DMT2 i liječenjem ACEi ili ARB-ima bili su podobni. Studija parikalcitola Mansona et al. uključena je za usporedbu kardiovaskularnih ishoda, iako je istraživala kohortu bez povijesti raka i velikih kardiovaskularnih događaja bez fokusa na KBB, pokušavajući pokazati profilaktički učinak. Za metodološku procjenu kvalitete korištena je Downova i Black skala.

Rezultati: Ukupno sedam studija, tri finerenonom i četiri parikalcitolem, uključeno je u ovu meta-analizu. Šest od ovih studija bile su prospektivne, dvostruko slijepe, placebo kontrolirane i randomizirane, dok su Mendes et al. bile opservacijske studije. Šest studija uključilo je bolesnike s kroničnom bubrežnom bolesti, DMT2 (prosječno trajanje > 14.5 godina) i najmanje 81.65% njih je bilo prethodno liječeno ACEi ili ARB-ima, dok su Manson et al. promatrali kohortu bez KBB-a kao što je gore spomenuto. Trajanje je bilo 44-48 mjeseci za finerenon i 3-12 mjeseci za parikalcitol. UACR se smanjio u svim studijama finerenona i parikalcitola. eGFR je pokazao inicijalno smanjenje na finerenonu tijekom četiri tjedna, ali je nastavio blaže nego u kontrolnoj skupini, dok su podaci za parikalcitol ukupno bili nedostatni za procjenu eGFR. ARR na finerenonu za smanjenje eGFR >57% bio je 5.6% i 48.7% u RRR-u. Za parikalcitol je zabilježeno vrlo malo slučajeva. Hiperkalijemija se češće javljala na finerenonu, dok se hiperkalcemija češće javljala na parikalcitolu. Kardiovaskularni štetni događaji javljali su se češće na finerenonu, na što je vjerojatno utjecala usporedba s nehomogenom kohortom sa i bez KBB. Za kardiovaskularne događaje, maksimalni ARR od 2.6% i RRR od 22.03% dokazan je u studiji Fidelio, u usporedbi s nehomogenim smanjenjem parikalcitola. Ukupna smrtnost bila je niža u svim intervencijskim skupinama oba lijeka u usporedbi s kontrolnom skupinom, smanjujući relativni rizik za najviše 10.89% [57] u finerenonu i za 1.57% u parikalcitolu [65].

Zaključak: Oba lijeka pozitivno utječu na UACR i albuminuriju, čime potencijalno usporavaju progresiju KBB-a. Kardiovaskularni morbiditet i mortalitet više su smanjeni na finerenonu. Procijenjena GFR na finerenonu stabilizira se nakon početnog pada do sporije progresije. To nije dovoljno istraženo u parikalcitolu, što ostavlja prostora za daljnja istraživanja. Sveukupni štetni učinci javljali su se najrjeđe u skupini koja je primala 1 µg parikalcitola