Novel drugs and intervention strategies for the treatment of chronic kidney disease

Hiddo Jan Lambers Heerspink & Dick de Zeeuw

Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Correspondence

Dr Hiddo Lambers Heerspink PharmD,
Department of Clinical Pharmacology,
University Medical Center Groningen,
University of Groningen, Ant. Deusinglaan
1, 9713 AV Groningen, the Netherlands.
Tel.: +31 50 363 2810
Fax: +31 50 363 2812
E-mail: h.j.lambers.heerspink@umcg.nl

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Chronic kidney disease (CKD) is a worldwide health problem. The disease is most often progressive of nature with a high impact on patients and society. It is increasingly recognized that CKD can be detected in the early stages and should be managed as early as possible. Treatment of the cause, but in particular control of the main risk markers, such as high blood pressure, glucose and albuminuria, has been instrumental in delaying the progression to end-stage renal disease (ESRD). However, despite the state of the art therapy, the absolute risk of renal and cardiovascular morbidity and mortality in CKD patients remains devastatingly high. Novel drugs are therefore highly desirable to halt effectively the progressive renal (and cardiovascular) function loss. Recently, several novel strategies have been tested targeting traditional risk factors such as blood pressure (combination therapy of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) and novel mineralocorticoid receptor antagonists) as well as dyslipidaemia (statins) with surprising results. In addition, drug targets specifically related to the kidney, such as vitamin D, uric acid, erythropoietin and phosphate, have been the subject of clinical trials, in some instances with unexpected results. Finally, novel targets including endothelin receptors and inflammatory pathways are increasingly explored as potential avenues to improve renal and cardiovascular protection, albeit that the drugs tested have not been unequivocally successful. In this article we review novel drugs or intervention strategies for the management of CKD, we try to provide explanations for the failure of some promising drugs and hypothesize on the potential success of new strategies.

Introduction

Epidemiology

People with impaired kidney function face a high risk of progressive renal function loss. This often leads to complete loss of kidney function, so called end-stage renal disease (ESRD) for which people require ongoing dialysis or renal transplantation. In addition to the high incidence of ESRD, there is an even higher risk in these chronic kidney disease (CKD) patients for cardiovascular complications or premature mortality even before they start dialysis. The provision of dialysis places a high burden on individual patients as well as on national health care budgets and society. For example, in Europe, average health care expenditure for a patient with ESRD is around 40.000 euros per year [1].

Many studies over the last decades in various populations have shown that low estimated glomerular filtration rate (eGFR) or proteinuria are associated with renal disease

progression. In a recent meta-analysis involving more than 1 million individuals it was shown that the risk gradient for ESRD according to eGFR is flat at eGFR above approximately $70 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ and linearly increases below this level [2]. On the other hand, however, the risk association between albuminuria and ESRD is linear across the full albuminuria range without evidence of a threshold [2]. The lack of a threshold indicates that small increases in albuminuria, even within the normal range, (i.e. $<30 \text{ mg albumin g}^{-1} \text{ creatinine}$) confers clinical risk and necessitates clinical attention.

CKD is nowadays defined by a reduced glomerular filtration rate (GFR) and/or increased albuminuria [3]. Life expectancy substantially reduces when proteinuria levels increase or GFR levels decline. A study from Canada showed that patients aged 30 years with eGFR 30–44 and $15\text{--}29 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ had a reduction in life expectancy of approximately 17 and 25 years, respectively, compared with those with normal kidney function (eGFR >

60 ml min⁻¹ 1.73 m⁻²) [4]. A reduction in life expectancy was also observed for patients with increasing levels of proteinuria. Subjects with mild or heavy proteinuria had a life expectancy that is reduced by approximately 10 and 18 years compared with subjects without proteinuria. These figures indicate that people with CKD require appropriate monitoring and proper therapy.

Significant progress has been made in the treatment of CKD in the past decades. Early detection of high risk patients in combination with increased secondary prevention efforts aimed at blood pressure, glycaemic and lipid control have improved the outlook of patients with CKD.

Pharmacological intervention

State of the art treatment

Current treatment of CKD is focused on optimizing renal and cardiovascular risk factors. The current treatment algorithm for CKD patients is based on the knowledge and experience of treating cardiovascular risk in general. Thus, it includes, next to lifestyle changes (dietary measures, stop smoking, exercise):

- 1 Control of high blood pressure
- 2 Control of albuminuria
- 3 Control of blood glucose
- 4 Control of blood lipids

However, the evidence for these therapies or strategies is not necessarily clear:

Treatment of high blood pressure is of paramount importance for preventing and delaying the progression of CKD. Blood pressure lowering therapy is vital during any stage of CKD and is the mainstay of renal (and cardiovascular) protective therapy. Agents that block the renin-angiotensin-aldosterone-system (RAAS) are the first choice agents. The renoprotective effects of ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) are demonstrated in various studies in patients with different aetiologies of renal disease including diabetic nephropathy, hypertensive nephrosclerosis and various non-diabetic nephropathies [5–7]. A common finding in these studies is that the benefits of RAAS inhibiting drugs go beyond that expected from blood pressure lowering alone and are, to a large extent, explained by their anti-albuminuric effects [8–12].

Albuminuria lowering slows the progressive rate of renal function loss in patients with CKD and should therefore be considered a separate target for renoprotective therapy. The presence of albuminuria is not only a sign of renal impairment but it can also cause renal damage itself. Recent studies have shown that increased urinary albumin leakage stimulates inflammatory (e.g. monocyte chemotactic agent-1, RANTES) [13, 14], vasoactive (e.g. endothelin) and fibrotic (TGF- β , collagens) processes [15],

causing interstitial damage ultimately leading to irreversible renal impairment. It is well known that RAAS blockade decreases albuminuria. As mentioned above, the benefits of RAAS blockade go beyond blood pressure lowering alone. In fact, studies in diabetic and non-diabetic patients with CKD have shown that the reduction in albuminuria during the first months of therapy is one of the strongest determinant of long term renoprotection [11, 16]. RAAS blockade is not the only drug class that decreases albuminuria and affords renoprotection. Other interventions, such as a low protein diet [17], non-steroidal anti-inflammatory drugs [18] and corticosteroids [19], also decrease albuminuria and slow progression to ESRD.

Glucose lowering has been shown to prevent the development and progression of abnormal levels of albuminuria in people with diabetes. The Diabetes Control and Complication Trial (DCCT) showed that in 1441 patients with type 1 diabetes with no or mild retinopathy intensive glucose control with insulin injections reduced the risk of development of macroalbuminuria by 54% after a mean follow-up of 6.5 years [20]. At the end of the DCCT trial 1375 of these patients transitioned into the observational Epidemiology of Diabetes Interventions and Complications (EPIC) study. After 22 year follow-up of the combined DCCT/EPIC cohort eight patients in the intensive therapy group and 16 patients in the conventional therapy group developed ESRD (relative risk reduction 50%) illustrating the benefit of early intensive glucose control in type 1 diabetes [21]. In patients with type 2 diabetes, a recent *post hoc* analysis from the ADVANCE trial determined whether intensive glucose lowering prevented or slowed the progression to ESRD. In the ADVANCE trial 11140 patients with type 2 diabetes with at least one risk factor for vascular disease were randomly allocated to a gliclazide based intensive glucose lowering therapy (aiming for a HbA1c target of 6.5% or less) vs. conventional glucose lowering therapy (HbA1c target defined by local guidelines). The study showed that intensive glucose lowering therapy protects against the development of ESRD, albeit that only 27 ESRD events were recorded during the trial [22]. Studies that are properly powered to assess the benefits of glycaemic control on hard renal outcomes are required to substantiate these findings.

Lipid lowering therapies have undoubtedly contributed to improved cardiovascular morbidity rates in the last decades. The cardiovascular benefits of lipid lowering are also observed in subjects with CKD. The SHARP trial demonstrated that the combination of simvastatin and ezetimibe conferred a 17% cardiovascular risk reduction in CKD [23]. The relative low reduction (compared with the cardiovascular protective effect of statin therapy in non-CKD patients) may be due to the fact that other factors than LDL-cholesterol contribute to cardiovascular risk in the CKD patient [24]. Further research is required to identify the causes of cardiovascular risk in these CKD patients

and importantly to identify specific drug targets for further reduction of the high cardiovascular risk.

The renal protective effects of lipid lowering are not (yet?) definitively proven. Most lipid trials have involved subjects at cardiovascular risk and the number of ESRD events recorded in these trials is low. In SHARP a non-significant reduction of 7% ($P = 0.09$) was observed in the incidence of doubling of serum creatinine or ESRD in subjects allocated to simvastatin/ezetimibe [23]. Whether the lack of renal benefits in SHARP specifically relates to the drug combinations used or whether it can be extrapolated to each lipid lowering agent is unknown. Based on the PLANET trials one could argue that different statins exert different renoprotective effects. The PLANET trial compared head-to-head atorvastatin 80 mg day⁻¹ and rosuvastatin 10 mg day⁻¹ and 40 mg day⁻¹ in subjects with diabetic and non-diabetic CKD. Atorvastatin decreased proteinuria and did not appreciably change eGFR over time, while both doses of rosuvastatin did not decrease proteinuria and 40 mg day⁻¹ rosuvastatin was associated with a significant fall in eGFR despite a similar (or even better) degree of cholesterol lowering [25]. Unfortunately, the PLANET trial did not include a placebo arm and thus a placebo-controlled comparison could not be made. Another randomized controlled trial assessed the anti-proteinuric effect of fluvastatin in patients with chronic kidney disease who had proteinuria more than 0.5 g day⁻¹ despite receiving a combination of an ACEi and ARB. In that trial fluvastatin did not reduce proteinuria but further reduced serum lipids [26]. These findings illustrate that different statins may have different effects on proteinuria and eGFR and suggest that the SHARP results may not be directly extrapolated to each statin. Results of other trials also point to a potential renoprotective effect of atorvastatin. In the ASCOT trial in 10 305 subjects with hypertension and at least three cardiovascular risk factors, atorvastatin significantly improved eGFR over time compared with placebo treatment [27]. In addition, a recent meta-analysis involving more than 120 000 patients showed that lipid lowering therapies attenuate the rate of progressive renal function loss over time from 0.87 to 0.67 ml min⁻¹ 1.73 m⁻² year⁻¹ [28]. Taken together, it seems that in general lipid lowering produces a modest decline in the rate of renal function loss but it may well be true that the degree of renoprotection depends on the off-target effect of the specific lipid lowering agent rather than being the result of the effect of cholesterol lowering *per sé*.

The above treatments by themselves or in combination have led to a considerable reduction in renal and cardiovascular risk in the CKD patient. However, despite the increased awareness of CKD and advances in the prevention of renal complications, there remains an enormous unmet need. This may be explained by the fact that the CKD patient runs an extremely high absolute risk for ESRD as well as cardiovascular morbidity and mortality, and the relatively small absolute risk reductions of proven

therapies. Novel therapies to mitigate renal complications are therefore highly desirable. Table 1 provides an overview of novel intervention strategies for the prevention and treatment of CKD.

Novel treatments and ongoing trials

Targeting traditional risk factors

Novel RAAS blockade strategies RAAS plays an important role in progressive organ function loss in CKD patients as highlighted by the results of several randomized controlled trials and meta-analyses demonstrating that inhibition of the RAAS with either ACEi or ARB affords renal and cardiovascular protection [5, 7, 29, 30]. However, during single RAAS inhibition therapies (either ACEi or ARB) circulating RAAS remains fairly active. This has led to an expectation that enhancing RAAS blockade may provide greater protection against major adverse renal and cardiovascular outcomes. In analogy to effective diuretic treatments in which one combines blockade of systems at different crucial levels, the combination of ACEi and ARB was started, as well as recently ACEi or ARB with a direct renin inhibition (DRI). Indeed, dual therapy with both an ACEi and an ARB, or in combination with DRIs, has been shown to be more effective in reducing urinary albumin excretion and blood pressure than single agent therapy [31]. However, large scale randomized controlled trials have reported contradictory results. In the ONTARGET trial, in patients with established cardiovascular disease rather than kidney disease, dual blockade with the ACEi ramipril (10 mg day⁻¹) and ARB (telmisartan 40 mg day⁻¹) did not enhance cardiovascular protection [32]. In addition, dual blockade increased the risk for adverse renal outcomes compared with either monotherapy, in spite of better reduction of blood pressure and albuminuria [33]. It should be noted that most patients in the ONTARGET trial had urinary albumin concentrations in the normal range (i.e. had low renal risk) rendering the impact of dual blockade on renal end-points uncertain. The cardiovascular and renal protective effect of the combination of ACEi or ARB with a DRI (aliskiren) was tested in the ALTITUDE trial in diabetic patients who were selected for their high renal and cardiovascular risk profile. The safety monitoring board of the ALTITUDE trial recommended early trial termination, based on an interim analysis showing more cases of worsening of renal function, hyperkalaemia and increased risk of stroke. The final efficacy results confirmed the excess rate of adverse effects and provided definitive evidence of a lack of cardio-renal protection with aliskiren added to single RAAS blockade in patients with type 2 diabetes [34]. It has been suggested that dual agent RAAS blockade might be salutary in people with high albuminuria or low renal function. The Nephron-VA-D trial tested the combination of ACEi and ARB therapy on hard renal end-points in patients with type 2 diabetes, macroalbuminuria and moderate to severe renal impairment (eGFR 30 to

Table 1

Novel intervention strategies for the treatment of CKD

	Population	Study treatment	Primary end point	Results
Hard end point trials with combinations of RAAS inhibitors				
ALTITUDE (n = 8592) [34]	Type 2 diabetes at high renal-cardiovascular risk	Aliskiren vs. placebo on top of ACEi or ARB	Composite renal or cardiovascular end point	Prematurely terminated. No renal/cardiovascular protection
VA-Nephron-D (n = 1850) [35]	Type 2 diabetes and nephropathy (eGFR 30 to 90 ml min ⁻¹ 1.73 m ⁻²)	Lisinopril plus losartan vs. lisinopril	Composite renal end point	Prematurely terminated. No renal/cardiovascular protection
HALT-PKD (n = 1018) [105]	Autosomal Dominant Polycystic Kidney disease	Telmisartan vs. placebo on top of lisinopril	Composite renal end point	Trial is ongoing; estimated completion date 2013
Hard end point trials with other interventions on top of RAAS blockade				
Lipids				
SHARP (n = 9270) [23]	Diabetic and non-diabetic chronic kidney disease	Simvastatin plus ezetimibe vs. placebo	Major vascular event (MI, stroke, cardiac death, arterial revascularization)	17% reductions in major atherosclerotic events; non-significant 9% renal risk reduction
PLANET I and II [25]	Type 1 / type 2 diabetes (PLANET I) or non-diabetes (PLANET II) and proteinuria > 500 mg g ⁻¹	Atorvastatin vs. rosuvastatin	Rate of eGFR decline	Greater reduction in proteinuria and less eGFR decline with atorvastatin compared with rosuvastatin
Erythropoietin stimulating agent				
TREAT (n = 4038) [54]	Type 2 diabetes and anaemia	Darbepoietin-alpha vs. placebo	Composite renal or cardiovascular end point	No renal or cardiovascular protection; Darbepoietin increased stroke risk
CHOIR (n = 1432) [55]	Chronic kidney disease (eGFR 15 to 50 ml min ⁻¹ 1.73 m ⁻²) and anaemia	Epoietin-alpha randomized to haemoglobin target 13.5 or 11.3 mg l ⁻¹	MI, CHF, stroke, death	No cardiovascular benefit of targeting higher haemoglobin levels
Endothelin antagonist				
ASCEND (n = 1300) [77]	Type 2 diabetes and nephropathy (serum creatinine 1.3 to 3.0 mg dl ⁻¹)	Avosentan vs. placebo	DSCR, ESRD or death	Prematurely terminated due to increase in CHF events
Glycosaminoglycans				
SUN-Macro (n = 1176) [106]	Type 2 diabetes and nephropathy (serum creatinine 1.3 to 3.0 mg dl ⁻¹)	Sulodexide vs. placebo	DSCR, ESRD	Prematurely terminated due to futility
Anti-inflammatory agents				
BEACON (n = 2200) [86]	Type 2 diabetes and nephropathy (eGFR 15 to 30 ml min ⁻¹ 1.73 m ⁻²)	Bardoxolone-methyl vs. placebo	Dialysis / cardiovascular death	Prematurely terminated due to increased mortality
PREDIAN (n = 169) [88]	Type 2 diabetes and nephropathy	Pentoxifylline vs. placebo	Rate of eGFR decline	Results expected in 2013
Pyridorin CSG study (n = 317) [95]	Type 2 diabetes and nephropathy (serum creatinine 1.3–3.5 mg dl ⁻¹ and protein : creatinine > 1200 mg g ⁻¹)	Pyridorin vs. placebo	Rate of eGFR decline	No renal protection
Uraemic toxin absorbent				
AST-120 (n = 2035) [94]	Chronic kidney disease	Kremezin vs. placebo	DSCR or ESRD	No renal protection
Surrogate end point trials with other interventions on top of RAAS blockade				
VITAL (n = 281) [62]	Type 2 diabetes and nephropathy and albuminuria 300–3500 mg g ⁻¹	Paricalcitol vs. placebo	Albuminuria reduction	Paricalcitol 2 µg day ⁻¹ decreased albuminuria over time
RADAR (n = 153)	Type 2 diabetes and nephropathy and 300–3500 mg g ⁻¹	Atrasentan vs. placebo	Albuminuria reduction	Results expected 2013
Bindarit study (n = 73) [91]	Type 2 diabetes with micro- or macroalbuminuria	Bindarit vs. placebo	Albuminuria reduction	Bindarit decreased albuminuria in subjects with macroalbuminuria but not in those with microalbuminuria
CCXB-140	Type 2 diabetes and macroalbuminuria	CCXB-140 vs. placebo	Albuminuria reduction	Results expected 2013

CHF, congestive heart failure; DSCR, doubling of serum creatinine; ESRD, end-stage renal disease; MI, myocardial infarction.

90 ml min⁻¹ 1.73 m⁻²) [35]. However, again the trial was prematurely discontinued because of severe hyperkalaemia and acute renal function loss in people allocated to dual agent RAAS blockade. Hence, in people with high albuminuria and renal impairment, dual RAAS blockade failed to afford renoprotection which casts major doubt on the efficacy and safety of dual RAAS blockade. All together, the lack of cardio-renal protection and excess rate of adverse events in three independent large clinical trials indicate that in general there is no place for dual RAAS blockade in the prevention and treatment of CKD. However, the response to RAAS blockade varies considerably among individuals and some patients show a marked reduction in blood pressure and albuminuria without developing hyperkalaemia or acute renal impairment. In such patients, dual RAAS blockade could be considered.

The mechanisms underlying the adverse outcomes of dual RAAS blockade are not fully established. Pharmacological effects are important to consider. The focus of RAAS blockade therapy is to improve blood pressure and albuminuria control, as it did in all of the above hard outcome trials. This view may thus be too narrow. RAAS blockade exerts a broad range of additional effects, i.e. on renal filtration pressure [36], potassium status [37], haemoglobin [38], uric acid [39] and inflammatory factors [40], all with prognostic impact. Since each of these parameters determines renal or cardiovascular risk, drug induced changes in these parameters will influence the ultimate renal or cardiovascular outcome, either favourably or harmful. It might be useful, therefore, to interpret drug effects on hard outcomes in terms of composite effects, rather than effects on blood pressure or albuminuria alone. For dual RAAS blockade, theoretically, the balance may tilt to harm (for instance by inducing hyperkalaemia or inducing hypotension) in patients in whom effects on blood pressure or albuminuria are relatively trivial. Further studies on the response profiles for multiple parameters in individual patients are necessary to clarify to what extent such mechanisms are indeed at play.

A lot of attention has been paid to mineralocorticoid receptor antagonists (MRAs) since the publication of the first study demonstrating that the MRA spironolactone decreases proteinuria in CKD subjects [41]. Numerous experimental and clinical studies followed and confirmed the profound anti-albuminuric effects of MRAs [42–44]. These beneficial effects render MRAs promising drugs for the prevention of ESRD and cardiovascular morbidity and mortality in patients with nephropathy. However, in particular in the population with CKD, the use of MRAs is limited by the risk of development of life-threatening hyperkalaemia, which is the consequence of the potassium-sparing properties of these agents in low filtration conditions. The risk of hyperkalaemia clearly restricts the widespread application of MRA therapy among CKD patients. Nevertheless several possibilities exist to prevent or control hyperkalaemia as recently reviewed by Roscioni

[45]. These measures include limiting potassium rich food consumption, discontinuation of drugs that impair potassium excretion (e.g. non-steroidal anti-inflammatory drugs) or prescribing potassium binders. With respect to the latter, a new non-absorbable polymer (RLY5016) designed to bind potassium in the gastro-intestinal tract was recently tested in patients with heart failure receiving spironolactone treatment. The results indicated that this polymer caused significant reductions in serum potassium, prevented hyperkalaemia, and was well tolerated [46]. Long term studies are needed to assess the long term safety of this therapy. In addition, novel MRAs are currently in development with high affinity and selectivity for the MR receptor, such as BR4628 and SM368229 [47, 48]. Pre-clinical studies have shown that these drugs exert powerful anti-albuminuric effects but have limited effect on plasma potassium concentrations. Clinical studies are ongoing to characterize the dissociation between the anti-albuminuric effects and potassium-sparing effects of these agents in humans.

Glycaemic control Dipeptidylpeptidase inhibitors are a new class of hypoglycaemic drugs. DPP-IV inhibitors inhibit the degradation of glucagon-like peptide -1 (GLP-1). By inhibiting the degradation of GLP-1 these agents enhance insulin secretion in the pancreas and reduces glucagon release, resulting in a reduction in fasting plasma glucose and HbA1c. Various DPP-IV inhibitors are available for clinical use such as sitagliptin, saxagliptin and linagliptin. The HbA1c lowering effects of the various DPP-IV inhibitors seem to be comparable. However, the pharmacokinetic properties vary among the different agents which could render a specific agent particularly useful for a certain sub-population. For example, linagliptin is mainly metabolized and eliminated by the liver. No dose adjustments are required for patients with impaired kidney function which makes linagliptin particularly attractive for the patient with diabetes and nephropathy. Whether DPP-IV inhibitors delay the progression towards ESRD is unknown but some studies support a potential renoprotective effect. Sitagliptin has been shown to decrease albuminuria by 20% in a prospective observational study [49]. More recently, a meta-analysis of 13 randomized controlled trials involving nearly 5500 individuals demonstrated that linagliptin causes a 16% (95% CI 3, 28%, $P < 0.05$) reduction in a composite renal end point consisting of micro- or macro-albuminuria, loss of eGFR >50% from baseline, acute renal failure or death [50]. Future long term controlled trials are warranted to confirm these findings.

Sodium-glucose transport inhibition is another new target to achieve glycaemic control. SGLT2 inhibitors reversely inhibit the SGLT-2 transporter which is located in the proximal tubule. The SGLT-2 transporter is responsible for the nearly complete reabsorption of glucose in order to maintain appropriate glucose concentrations (under

normal physiologic circumstances). Treatment with SGLT-2 inhibitors increases urinary glucose excretion and decreases fasting plasma glucose and HbA1c [51]. Apart from their effect on metabolic parameters, SGLT-2 inhibitors also decrease blood pressure, body weight and albuminuria [51]. Large clinical outcome trials with the SGLT-2 inhibitors dapagliflozin, (NCT01730534) canagliflozin, (NCT01032629) and empagliflozin (NCT01131676) are ongoing to characterize the long term renal and cardiovascular protective efficacy and safety of this new drug class.

Targeting kidney related risk factors

Erythropoietin stimulating agents Observational studies have suggested that anaemia is another risk marker of renal and cardiovascular disease next to and independent of blood pressure, hyperglycaemia and hypercholesterolaemia. Earlier studies with erythropoietin stimulating agents have shown that in patients with severe anaemia, increasing haemoglobin markedly increased quality of life and reduced requirements of blood transfusions [52, 53]. These convincing results led to the general belief that increasing haemoglobin levels would decrease the risk of renal and cardiovascular disease and resulted in the widespread use of these agents. However, recent randomized clinical trials documented that treating low haemoglobin levels to targets above 13.0 g dl^{-1} in diabetic or 13.5 g dl^{-1} in non-diabetic CKD did not decrease the incidence of renal or cardiovascular events [54, 55]. These results tempered the promise that early correction of anaemia delays renal disease progression. Again, this may not be due to the fact that correction of anaemia would not result in renal and/or cardiovascular protection, but the drugs and or the dose of the drugs used to correct anaemia, may induce other (negative) effects that offset a potential renal cardiovascular protection. Indeed, it was shown in TREAT study that the harmful effects were particularly observed in the group of patients who needed high darbepoietin- α , the so-called non-responders [56]. The results of the TREAT and CHOIR trials are now translated in treatment guidelines which recommend not to intentionally target haemoglobin to levels above 115 g l^{-1} (11.5 g dl^{-1}) [57].

Vitamin D Emerging data suggest that vitamin D plays a vital role in renal and cardiovascular health. People with CKD have lower vitamin D concentrations than healthy individuals and observational studies have demonstrated that CKD patients treated with vitamin D receptor activators have a survival benefit compared with untreated patients [58]. Several studies have reported that vitamin D receptor activators decrease albuminuria in both diabetic and non-diabetic nephropathy [59–61]. The largest study in this respect was the VITAL study. The results showed that paricalcitol in addition to ACEi or ARB therapy appears to reduce albuminuria in a dose-dependent fashion and was

well tolerated [62]. Whether vitamin D activators delay the progression to ESRD is not investigated and needs to be proven. A large clinical trial in 20 000 people with evidence of heart disease is currently ongoing investigating whether vitamin D supplementation (cholecalciferol) or omega-3 fatty acids reduces the risk of developing cancer, heart disease and stroke (NCT 01169259). The effects of vitamin D or fish oil on kidney disease progression will be assessed as well (<http://www.vitalstudy.org>).

Phosphate Control of serum phosphate by restricting dietary phosphate or phosphate binders has been a mainstay in the treatment of CKD to manage bone disease for many years. However, recent observational studies link high serum phosphate to accelerated progressive renal function loss and cardiovascular disease [63]. In addition, emerging data demonstrate that fibroblast growth factor-23, a phosphaturic hormone, is elevated in early CKD and linked with renal and cardiovascular outcomes, suggesting a pathophysiological role of impaired phosphate control in the onset and progression of CKD. Intervention trials to test the efficacy of phosphate-lowering strategies on hard renal or cardiovascular end points are lacking but are clearly warranted.

Uric acid A number of studies have shown that uric acid predicts the progression of renal function loss in diabetic and non-diabetic CKD [64, 65]. Uric acid is generated during the metabolism of nucleotides and represents the end product of purine metabolism. Uric acid appears to have a broad range of adverse effects including activation of pro-inflammatory pathways resulting in increased synthesis of chemokines and inflammatory markers [66], decreasing the bioavailability of nitric oxide leading to endothelial dysfunction [67] and activation of systematic and intra-renal RAAS [68]. These pathogenic effects of uric acid in combination with the independent association between uric acid and renal and cardiovascular outcome raise the possibility that interventions that reduce uric acid may afford renal (and cardiovascular) protection. A small prospective intervention study involving 113 subjects with CKD of mixed aetiology reported that allopurinol caused a mean increase in eGFR of $1.3 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ whereas in the placebo group eGFR fell by $3.3 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ over the 24 months follow-up period [69]. Febuxostat is a non-purine selective xanthine oxidase inhibitor and is approved for use in patients with hyperuricaemia and gout. An analysis of a 5 year open label trial in 116 patients treated with febuxostat demonstrated an inverse correlation between serum uric acid reduction and rate of eGFR decline so that individuals with the greatest reduction in serum uric acid following febuxostat treatment experienced the slowest rate renal function decline [70]. Finally, a meta-analysis, involving 11 clinical trials and 753 participants, found that urate lowering therapy decreased serum creatinine and increased eGFR suggesting that urate

lowering therapy may have beneficial effects on delaying the progression of renal disease [71]. These small scale studies and the meta-analysis support the conduct of a large confirmatory trial specifically designed to determine the renoprotective effects of urate lowering therapies.

Targeting novel risk factors

Endothelin antagonists The endothelin system is chronically activated in patients with nephropathy. Binding of endothelin to the endothelin type A receptor (ET_A receptor) elicits pronounced vasoconstriction, sodium retention, and promotes podocyte dysfunction leading to glomerular damage, proteinuria and renal function loss [72, 73]. In contrast, endothelin type B receptor activation causes vasodilatation and sodium excretion. Specific blockade of the ET_A receptor, may thus be a promising target to ameliorate renal complications. Intriguingly, endothelin seems to interact with tubular proteins thereby promoting renal fibrosis. It has been shown that exposure of tubular cells to increasing amounts of albumin causes a dose-dependent increase in the generation of endothelin-1 [74]. Endothelin-1 mediates secretion of pro-inflammatory cytokines and growth factors, such as TGF- β , which contribute to interstitial remodelling and scarring [75, 76].

Avosentan, an endothelin receptor blocker, significantly reduced proteinuria in patients with type 2 diabetes and nephropathy. However, a large phase 3 trial, testing the effect of avosentan on hard renal outcomes (ASCEND), was terminated prematurely because of an excess of congestive heart failure (CHF) and mortality in the avosentan treatment arm [77]. The excess number of CHF events observed in the ASCEND trial may be due to the high-doses of avosentan and the lack of specific investigator guidelines to prevent or treat sodium and fluid retention. A recent *post hoc* analysis of the ASCEND trial showed that the rise in body weight during avosentan therapy serves as an early risk marker for the development of CHF events [78]. Thus, another hard outcome trial was prematurely terminated. In this case the drug had again the expected effect on the surrogate marker (proteinuria) but had simultaneously detrimental effects (in this case tubular sodium handling) which led to an excess of CHF events.

Recently, more specific ET_A receptor antagonists than avosentan, such as sitaxsentan and atrasentan, became available for clinical research. The higher selectivity of these agents for the ET_A receptor could theoretically mean that adverse events related to fluid overload and oedema are less likely to happen. A recent study with sitaxsentan in patients with CKD showed that sitaxsentan decreased blood pressure and proteinuria and had favourable effects on various other renal and cardiovascular biomarkers including pulse wave velocity, uric acid and asymmetric dimethylarginine (ADMA) [79]. The proteinuria lowering in this study was modest (25% reduction) as compared with the effects of atrasentan in patients with diabetic

nephropathy. In a randomized controlled double-blind trial in 89 subjects who were on stable doses of ACEi or ARB treatment with atrasentan for 8 weeks resulted in significant reductions in albuminuria from baseline for subjects receiving 0.75 mg day⁻¹ atrasentan (42% reduction, $P = 0.023$) and 1.75 mg day⁻¹ (36% reduction, $P = 0.073$) compared with placebo (11% reduction) [80]. The larger RADAR trial, which is currently ongoing (NCT01356849), will further characterize the efficacy and safety of atrasentan in patients with diabetes and nephropathy.

Anti-inflammatory agents The risk factors that cause cardiovascular and renal morbidity and mortality such as high blood pressure and albuminuria involve a pathophysiological mechanism of which low grade inflammation makes up an important part. Indeed mounting evidence supports a key role of inflammation in the progression of CKD. In recent years many novel inflammatory markers have been identified. The discovery of these inflammatory molecules may provide novel insight into therapeutic targets for pharmacological intervention. Various randomized controlled trials have been conducted or are ongoing targeting inflammatory pathways. The majority of these trials focus on diabetic nephropathy most likely because inflammatory molecules are typically elevated in patients with diabetes and inflammation and subsequent extracellular matrix expansion is a common pathway of renal damage in diabetes.

Bardoxolone Bardoxolone-methyl is an anti-oxidative and anti-inflammatory drug which activates the nuclear factor-erythroid-2-related factor (Nrf2)-Keap1 pathway. Nrf2 regulates the induction of multiple antioxidant genes. As such, it exerts anti-oxidative and anti-inflammatory effects and thus serves as a defense factor against kidney injury [81–83]. In a previous non-randomized 8 week trial, treatment with bardoxolone-methyl resulted in a significant increase in eGFR in patients with type 2 diabetes and CKD stage 3 or 4 [84]. A subsequent 52 week follow-up study showed that the early bardoxolone-methyl-induced rise in eGFR was sustained throughout the 52 week follow-up period [85]. These promising results led to the initiation of the BEACON trial which was designed to assess whether bardoxolone-methyl decreases the incidence of dialysis and can be safely used in patients with type 2 diabetes and nephropathy [86]. The Data Safety Monitoring Board recommended however early trial termination due to excess mortality in the bardoxolone-methyl treatment arm (<http://www.reatapharma.com>). Analyses are ongoing to elucidate these unexpected results.

Pentoxifylline Pentoxifylline is a methyl xanthine derivative that acts *in vivo* as a phosphodiesterase inhibitor. A number of clinical studies have shown the anti-albuminuric properties of pentoxifylline and a combined meta-analysis of these trials documented that oral

pentoxifylline reduced albuminuria by nearly 300 mg day⁻¹ vs. control therapy [87]. The effect of pentoxifylline on the progression of renal function decline is not (yet) established but currently under investigation in the ongoing Pentoxifylline for Renoprotection in Diabetic Nephropathy (PREDIAN) trial [88]. The results of this trial are expected in 2013.

CTP-499 CTP-499 is an active metabolite of pentoxifylline. CTP-499 is under development based on previous studies showing anti-albuminuric effects of pentoxifylline. CTP-499 is thought to have an improved metabolic profile. Specifically, a pre-clinical study has shown that CTP-499 possesses anti-inflammatory, anti-fibrotic and anti-oxidant properties [89]. A 24 week phase 2 randomized placebo controlled trial is currently ongoing to assess whether CTP-499 exerts anti-albuminuric effects in 170 patients with type 2 diabetes and nephropathy (NCT01487109).

Monocyte chemoattractant protein-1 inhibition Monocyte chemoattractant protein-1 (MCP-1), a potent cytokine, plays a key role in initiating and sustaining chronic inflammation in renal tissues. MCP-1 is secreted in response to high glucose concentrations. MCP-1 promotes monocytes and macrophage activation and activates other pro-inflammatory cytokines. Urinary MCP-1 concentrations correlate with the degree of albuminuria in patients with diabetes and interestingly the reduction of albuminuria induced by ACEi correlates with the degree of urinary MCP-1 reduction [90]. These findings support the idea that inhibition of MCP-1 reduces albuminuria and improves long term renal function. A prospective randomized controlled study showed that pharmacological inhibition of MCP-1 synthesis reduced albuminuria on top of ACEi or ARB therapy relative to placebo in subjects with type 2 diabetes and macroalbuminuria but it did not change albuminuria in subjects with microalbuminuria [91]. To our knowledge no hard renal outcome trials are ongoing.

MCP-1 is a ligand for the C-C chemokine receptor 2 (CCR2). CCR2 is found on monocytes and macrophages and involved in initiating and sustaining inflammation. Blockade of the CCR2-receptor is another strategy to inhibit the detrimental effects of MCP-1. Pre-clinical studies have shown that the CCR2 antagonist CCX140 reduces albuminuria in a mouse model of diabetic nephropathy [92]. A phase 2 clinical study is currently ongoing to evaluate the anti-albuminuric effects of CCX140 in patients with type 2 diabetes and macroalbuminuria (NCT01440257). Results of this study are expected in 2013.

Uraemic toxin absorbants Kremezin (AST-120) is a charcoal agent that absorbs uraemic toxins, such as indoxyl sulphate and methylguanidine, in the gastro-intestinal tract. In addition, AST-120 inhibited TGF- β in animal

models of diabetic nephropathy [93]. AST-120 has been mainly studied in Asian countries and small clinical studies have suggested that AST-120 retards renal disease progression. Kremezin was approved in Japan in 1991 for prolonging the time to dialysis and improving uraemic symptoms. Two randomized placebo controlled trials (EPPIC1/EPPIC2) were recently completed involving in total 2035 subjects with CKD from Europe or the United States. The combined analysis showed that kremezin did not afford renal protection and 35% and 36% of subjects in the kremezin and placebo arms, respectively, reached the primary end point of ESRD or doubling of serum creatinine [94].

Vitamin B therapy Pyridoxamine is a metabolic derivative of vitamin B₆ and inhibits the formation of advanced glycation end products (AGE). AGEs are formed in hyperglycaemic milieu through a chemical reaction of a glucose molecule with a NH₂ end product of a protein which in turn becomes glycosylated. AGE formation has a direct pathological effect in the kidney resulting in thickening glomerular basement membrane through expansion of the extracellular matrix. A recent clinical trial was designed to test the hypothesis whether pyridoxamine delayed the progressive renal function loss in patients with type 2 diabetes, nephropathy and marked proteinuria. The results showed no difference in the rate of renal function decline between pyridoxamine and placebo treated patients, although a *post hoc* analysis suggested that pyridoxamine may delay the loss of renal function in subjects with the lowest serum creatinine concentrations at baseline [95]. Other B vitamins have also not been successful in halting the progression of renal disease or reducing urinary albumin excretion rates [96]. In fact, a multicentre clinical trial of high dose vitamin B therapy (vitamin B₆, B₁₂ and folic acid) showed a three-fold increase in the rate of renal function loss and a two-fold increase in the risk of cardiovascular disease [97].

It is important to note that most of the trials conducted so far with anti-inflammatory agents (with the exception of the BEACON and EPPIC trials) involved less than 300 patients and have only evaluated the effects on surrogate end points of renal disease progression. Although the results of some of these trials look promising they have to be confirmed in large hard outcome trials.

Innovative treatment strategies

Multiple risk marker targeting

The vast majority of intervention trials target a single risk factor (e.g. blood pressure or HbA_{1c}). A multi-factorial approach simultaneously targeting the various pathways involved in the pathogenesis of CKD may lead to more salutary long term outcomes. A formal multifactorial intervention trial aimed at behavioural modifications, (smoking

Table 2

On-target and off-target effects of various drugs used in the management of CKD

Drug class	On-target parameter	Off-target parameters
Antihypertensive drugs		
RAAS intervention	Blood pressure ↓	Albuminuria ↓; K ⁺ ↑; Hb ↑; Uric acid ↓ (losartan)
Diuretics	Blood pressure ↓	K ⁺ ↓; Uric acid ↑
Antihyperglycaemic drugs		
Metformin	Glucose ↓	VCAM ↓; ICAM ↓
DPP-IV inhibitors	Glucose ↓	Blood pressure ↓; Albuminuria ↓
SGLT-2 inhibitors	Glucose ↓	Blood pressure ↓; Body weight ↓; Uric acid ↓; albuminuria ↓
Lipid lowering drugs		
Statins	LDL-cholesterol ↓	C-reactive protein ↓; albuminuria ↓
Bone metabolism		
Vitamin D receptor activators	PTH ↓	Albuminuria ↓; Blood pressure ↓
Haematopoiesis		
Erythropoietin stimulating agents	Hb ↑	Blood pressure ↑

Hb, haemoglobin; HDL, high-density lipoprotein; ICAM, intercellular cell adhesion molecule; K⁺, potassium; LDL, low-density lipoprotein; VCAM, vascular cell adhesion molecule.

cessation and diet changes) and intensive blood pressure, lipids, glucose and body weight control vs. conventional therapy has been conducted in patients with diabetes. The results demonstrate that an intensive multi-factorial treatment approach causes a nearly 50% relative renal and cardiovascular risk reduction [98]. A similar multifactorial treatment programme consisting of lifestyle modification and optimal risk factor control has been implemented in proteinuric CKD patients. Interestingly, patients who participated in that multifactorial treatment programme had a nearly four-fold reduction in eGFR decline compared with matched controls who received ACEi therapy titrated to optimal blood pressure control [99]. These results undoubtedly support the implementation of integrated multifactorial treatment approaches aimed at improving lifestyle behaviour and optimal risk factor control.

Optimizing personalized therapy

In spite of the proven efficacy of renoprotective interventions, mainly single RAAS blockade and glycaemic control in diabetes, at a group level the long term protective effects of these interventions show a marked heterogeneity between individual patients. For example, the renoprotective effects of ACEi or ARB have been convincingly shown in large randomized controlled trials. Yet, at the individual level, the effects of these agents range from a complete arrest of renal function loss to no beneficial effects or even harm in some patients. Insight into the marked inter-individual heterogeneity in treatment response may provide clues to optimize the treatment for the individual. With respect to ACEi and ARB, it has been shown that genetic factors [100], dietary factors [101], obesity [102] and the type and severity of renal disease [103] modulate the efficacy of these agents.

The marked heterogeneity between individuals in long term drug effects may also be explained by the variability

in drug response in multiple parameters within an individual (so called intra-individual variability). It is known that single drugs affect multiple parameters next to the parameter the drug is developed and targeted to. Many of these so-called off-target parameters also beneficially or adversely affect long term renal outcome. Examples of on-target and off-target parameters of drugs used in the management of CKD patients are shown in Table 2. These on-target and off-target responses in multiple parameters to a single drug differ per individual. This constitutes so called discordance in response. For example, ARB may lower blood pressure, lower albuminuria and/or increase serum potassium. The response in these parameters is discordant within individual patients [104]. This suggests that the composite effect of a drug on multiple parameters (blood pressure, albuminuria, serum potassium etc) in individual patients should be determined and be optimized to improve the ultimate effect on clinical outcomes. Prospective trials are needed to validate this concept.

Summary and future perspectives

Given the large number of drugs that failed to afford reno-(cardiac-) protection in the last 5 years it seems impossible to develop new drugs for the management of CKD. One could conclude that it would be better to stop investing money and effort into developing new treatments for CKD. Before drawing such conclusions we believe that we should first identify the underlying reasons why so many drugs failed in the late stage of drug development.

From Table 1 it becomes clear that many trials failed due to severe adverse side effects. The severity and frequency of these adverse effects and their impact on the main study outcome were unexpected, in particular because the drugs under development had shown

favourable effects on renal and cardiovascular risk factors, such as blood pressure, cholesterol or proteinuria, so-called on-target risk markers. Thus, the drugs did not deliver what could be anticipated based on their beneficial effects on the renal and cardiovascular risk markers. As highlighted throughout this review, the explanation for the failure of many drugs appears to be that the drugs exerted effects on multiple other risk markers, so called off-target effects. Many of these drug effects on off-target risk markers have beneficial or adverse effects on the long term renal or cardiovascular outcome. In the case of adverse effects, they offset the beneficial on-target risk marker effect. Hence, to estimate drug effects based on changes in renal or cardiovascular risk markers one should not only focus on the on-target risk marker but integrate all drug induced risk marker changes. Such an approach of drug efficacy (and safety) estimation based on multiple risk markers has at least two implications. First, drug effects on all potential renal or cardiovascular risk markers should be carefully examined already in early clinical drug development. This means rigorous measurement and monitoring of all drug effects, not only the on-target drug effect. Second, if off-target effects exist that could blunt the protective treatment effect, management protocols should be developed and applied to prevent or minimize off-target effects in vulnerable patients. For example, an endothelin antagonist may increase fluid retention in some patients. Changes in body weight should be closely monitored to identify individuals who may experience fluid retention. Subsequently, in patients with body weight increases, treatment with diuretics should be started to reverse the fluid retaining effects, or patients should discontinue the drug. The same could be imagined when applying drugs or drug combinations that induce a rise in serum potassium. This should lead to measures to control serum potassium and if not successful withdrawal of therapy. In doing so, the harmful off-target effects are minimized and the overall drug effect is maximized.

Conclusion

Despite the successful use of lifestyle changes, metabolic control and blood pressure control including ACEi and ARB therapy, the residual renal and cardiovascular risk in patients with CKD remains very high, leaving them with a clear unmet need. Novel treatment strategies are imperative to improve the prognosis of these patients. As outlined in this review, various drugs are in the pipeline that may offer additional renoprotection and have the potential to reduce the high morbidity and mortality. However, we have to be vigilant for off-target effects that may counteract the beneficial promising effects of these novel drugs. Confirmatory hard outcome trials should therefore be designed in such a way that all off-target effects are closely

monitored and managed in order to avoid more drug failures in the future.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare HJLH and DdZ had no support for the submitted work. HJLH has financial relationships (consultancy agreements) with any of the following organizations that might have an interest in the submitted work in the previous 3 years: Abbvie, Astellas, Johnson & Johnson, Reata Pharmaceuticals and Vitae. All honoraria are paid to his institution. DdZ has consultancy agreements with the following companies: Abbvie, Astellas, Bristol-Meyers Squibb, Hemocue, Johnson & Johnson, Merck Sharpe & Dohme, Novartis, Reata Pharmaceuticals and Vitae. All honoraria are paid to his institution. HJLH and DdZ are employed by University of Groningen, University Medical Center of Groningen and have no other relationships or activities that could appear to have influenced the submitted work.

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