

# Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with chronic kidney disease

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## ABSTRACT

Since about three decades, inhibitors of the renin-angiotensin system have been available in clinical practice. Although angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) were primarily aimed at treatment of hypertension and heart failure, more of their positive effects were discovered later on. Patients with chronic kidney disease were recognised to profit the most from treatment with these agents; however some blind spots are still present. Patients with advanced renal failure are almost always excluded from the trials; patients with end-stage renal disease form the least studied population of all and outcomes of treatment with ACEi/ARB are still uncertain in these cohorts. The aim of this review is to summarise and update the evidence about effects of AII inhibitors in patients with chronic kidney disease with the specific emphasis on patients treated with dialysis. Lately a novel indication for ACEi/ARB administration, especially for peritoneal dialysis patients, has been proposed. It is based on the capacity of these drugs to inhibit the local tissue renin-angiotensin system, which results in less development of peritoneal fibrosis and a longer life for the peritoneal membrane. The most recent available data are presented in this review.

## KEYWORDS

ACE inhibitors, angiotensin II receptor blockers, chronic kidney disease, dialysis

## CONTROLLING HYPERTENSION

Hypertension is the major risk factor in developing and progression of nondiabetic and diabetic chronic kidney

disease (CKD). Currently the prevalence of hypertension in the general population is about 1 billion people worldwide and a further rise is predicted for the near future.<sup>1</sup> Development of hypertension is highly associated with older age (over 60 years), non-Hispanic black race and body mass index  $\geq 30$ .<sup>2</sup> In order to prevent end-organ damage and development of major cardiovascular events, blood pressure (BP) should be well-controlled. However the current situation is far from optimal worldwide, especially in CKD patients.<sup>2,3</sup> In patients with existing nephropathy, the goal of hypertension management involves not only cardiovascular protection by lowering BP to the appropriate level, but also slowing the progression of kidney disease. The latter often includes management of proteinuria, which is itself associated with both the risk of cardiovascular disease and progression to end-stage renal disease.<sup>4</sup> Therefore, it is of great importance to choose an appropriate antihypertensive agent for patients with CKD.

An increase in the renin-angiotensin-aldosterone activity is one of the major factors involved in the hypertension seen in patients with CKD. Angiotensin II (AII) is known to mediate systemic haemodynamic changes as well as changes in intrarenal circulations.<sup>5</sup> Moreover, this hormone has been recognised to play a key role in sustaining proteinuria and progression of kidney disease.<sup>5,6</sup> Therefore, inhibiting effects of AII and lowering blood pressure with drugs that block the renin-angiotensin system (RAS) is a major component of CKD treatment.<sup>7</sup> Can ACEi and ARB achieve the optimal blood pressure target? This usually depends on how aggressive BP management should be. According to the different guidelines, the majority of CKD patients would benefit from a BP level lower than 130/80 mmHg. However, one should be aware about serious side effects of aggressively lowering BP in patients with

advanced kidney disease and end-organ damage. Besides, there is currently no evidence whether diabetic patients and patients with nondiabetic nephropathy with proteinuria >1 g/d would definitely benefit from the low BP target.<sup>8</sup> In patients without diabetes and a level of proteinuria between 0.3 and 1g/dl strong consideration is given to achieving a BP level lower than 130/80 mm/Hg, unless a specific trial were to show otherwise.<sup>8</sup> However, as stated above, one should be aware of the difficulty to reach such a BP target, especially in diabetic patients. In four randomised controlled trials (RCTs) in diabetic nephropathy, the usual number of antihypertensive drugs needed to achieve a diastolic BP of <85 mmHg was three, which indicates that such a task requires multiple drug therapy.<sup>9-11</sup> However, in patients with CKD, AII inhibitors should be considered a first-line therapy because of their effects beyond BP control alone and additional benefit for high-risk patients.

## AII INHIBITORS AND CARDIOVASCULAR PROTECTION

Primary ACEi were aimed to treat hypertension and management of heart failure. Knowing AII to be involved in vasoconstriction, hypertrophy of cardiovascular cells as well as in the fibrotic process in the heart and vessels, cardiovascular protection can be expected from ACEi/ARB treatment.<sup>12,13</sup> The classical SAVE and SOLVD trials showed a significantly lower mortality risk in patients with heart failure receiving the ACEi captopril and enalapril.<sup>14,15</sup> Later the HOPE study confirmed these findings by showing a reduction in the risk of myocardial infarction, stroke and risk of death due to a CV event by 20 to 30% in patients with or without heart failure treated with ramipril.<sup>16</sup> Afterwards two trials with contradicting results were published: one showed that perindopril reduced CV mortality, nonfatal MI and cardiac arrest in patients with stable angina pectoris,<sup>17</sup> the other could not confirm such results by using trandolapril.<sup>18</sup>

Cardiovascular disease (CVD) is a leading cause of death among CKD patients.<sup>19</sup> Retrospective analyses of the SAVE and HOPE trials came to the conclusion that treatment with ACEi was associated with an equal or even a greater risk reduction of all-cause mortality in the group of patients with renal insufficiency compared with the ones with a normal glomerular filtration rate (GFR).<sup>20,21</sup> A substudy of HOPE showed that adding ramipril to the antihypertensive regimen in patients at high risk of cardiovascular events decreased cardiovascular events by 25%.<sup>22</sup> Medications that inhibit the RAS are known to reduce CVD complications in patients with diabetic nephropathy.<sup>9,11,23</sup> In diabetic nephropathy two studies reported CVD outcome as a secondary endpoint. One showed that congestive heart failure was less frequent in

the losartan-treated group compared with placebo or the group treated with amlodipine.<sup>11</sup> However, in this trial no difference was shown with regard to CV morbidity, such as the occurrence of MI, stroke, or unstable angina. Another trial also reported less admissions for heart failure and a trend towards less nonfatal MI for patients receiving losartan.<sup>9</sup> However, neither of these trials were aimed to study cardiovascular morbidity and mortality in the first place.<sup>24</sup> Recently, new data have become available: results of a big multinational RCT in which primary outcomes were cardiovascular events in high-risk individuals with various vascular disease, treated either with ARB alone or in combination with ACEi.<sup>25</sup> In the ONTARGET trial both ramipril and telmisartan appeared to be equally effective to prevent a major cardiovascular event in a wide range of high-risk patients, including ones with CKD.

Overall there is not enough evidence on effects of ACEi/ARB treatment of patients with CKD and CVD to reduce cardiovascular complications. Patients with advanced kidney disease are very often excluded from the big RCTs and therefore a clinical trial powered specifically for such outcomes in high-risk CKD patients is required.

## EFFECTS ON PROTEINURIA AND PROGRESSION OF KIDNEY DISEASE

Proteinuria is very often present in CKD and its magnitude directly influences the rate of renal function deterioration.<sup>26</sup> For more than a decade ACEi/ARB are known to have pronounced antiproteinuric and renoprotective properties, independently from their primary antihypertensive effect. This was first shown in patients with type 1 diabetic nephropathy in a CAPTOPRIL trial in 1993.<sup>23</sup> The study showed that compared with placebo, in patients receiving captopril there was a 30% reduction in proteinuria, 43% reduction in the risk of doubling of serum creatinine and a 50% reduction in the combined endpoint of death, need for dialysis or transplantation. These changes were observed independently of the BP levels.

In the last ten years a number of studies have been performed investigating the ability of ACEi/ARB to decrease the rate of progression of proteinuria and diabetic nephropathy.<sup>27-29</sup> The main findings of the biggest trials performed with AII inhibitors in patients with CKD I-IV were primary focused on renal outcomes and are summarised in *table 1*.

In patients with nondiabetic kidney disease several large studies confirmed the pronounced antiproteinuric and renoprotective effects of ACEi: ramipril was associated with a major reduction of proteinuria, slower GFR decline and risk of doubling serum creatinine or progression to end-stage renal disease (ESRD).<sup>30,31</sup> Two studies comparing benazepril with placebo on top of other antihypertensive

**Table 1.** Randomised controlled trials on effects of ACEi/ARB with primary renal endpoints in patients with diabetic nephropathy, mild to moderate renal insufficiency and proteinuria

Study	Number of patients	Regimen compared	Mean follow-up	Effect on reduction of proteinuria	Effect on renal function preservation	Other effects
CAPTOPRIL, 1993	409	Captopril vs placebo	3 years	+		Reduction in combined endpoint of death and need for dialysis
RENAAL, 2001	1513	Losartan vs placebo	3.4 years	+	+	Reduction in combined endpoint of death, progression to ESRD
IDTN, 2001	1715	Irbesartan vs amlodipine vs placebo	2.6 years	+	+	Reduction in combined endpoint of death, progression to ESRD
BENEDICT, 2004	1200	Trandolapril vs verapamil vs both vs placebo	48 months	+	+	ACEi slowed progression to microalbuminuria
REIN-2, 2005	338	Ramipril vs ramipril +felodipine; normal vs low BP target	19 months	-	-	No differences in renal outcomes

BP = blood pressure; ESRD = end-stage renal disease; ACEi = angiotensin-converting enzyme inhibitors.

regimens confirmed the above effects of ACEi.<sup>32,33</sup> It is worth mentioning that one of them, an AIPRI study, was focused on renoprotective properties of benazepril in patients with CKD of various aetiologies, but patients with glomerular disease were found to have the greatest profit from such treatment compared with the ones with polycystic kidney disease, nephrosclerosis or interstitial nephritis.<sup>33</sup> The data on major trials in patients with nondiabetic CKD are given in *table 2*.

The classic CAPTOPRIL study provided evidence that the stage of CKD and the amount of proteinuria are the main factors that determine the benefit from the use of an AII inhibitor. Patients with serum creatinine of >180 mmol/l had the greatest effect from using ACEi when compared with those with minor renal insufficiency (<90 mmol/l).

A couple of other studies together with a meta-analysis showed ACEi/ARB to have their best renoprotective effect in patients with the largest amounts of proteinuria<sup>31,33</sup> and an estimated GFR of <60ml/min.<sup>34</sup> Therefore, ACEi/ARB have renoprotective qualities, which are the most pronounced in patients with proteinuria and advanced kidney disease.

#### ACEi 'vs' or 'and' ARB?

Generalising all the information available today, it appears that both ACEi and ARB can provide sufficient renal and cardiovascular protection.<sup>8,24</sup> However, more evidence is needed to prove these medications to be equivalent in patients with similar clinical conditions. A few trials already contributed to this. One compared telmisartan

**Table 2.** Randomised controlled trials on the effects of ACEi/ARB on primary renal endpoints in patients with nondiabetic nephropathy, moderate renal insufficiency and proteinuria

Study	Number of patients	Regimen compared	Mean follow-up	Effect on reduction of proteinuria	Effect on renal function preservation
AIPRI, 1996	583	Benazepril vs placebo	3 years	+	Reduction of risk of doubling of serum creatinine or progress to ESRD
REIN, 1997	166	Ramipril vs placebo	16 months	+	Lower risk of GFR decrease, doubling of serum creatinine or progression to ESRD
AASK, 2001	1094	Ramipril vs metoprolol vs amlodipine; normal vs low BP goal	3-4 years		Lower risk of combined end-point of death, 50% decrease of GFR or reaching ESRD
Hou <i>et al.</i> , 2006	224	Benazepril vs placebo	3-4 years	+	Decreased risk of doubling of serum creatinine, ESRD or death

BP = blood pressure; ESRD = end-stage renal disease; GFR = glomerular filtration rate.

and enalapril with regard to their effects on the change of GFR, proteinuria, serum creatinine, BP level, rates of ESRD and cardiovascular events and all-cause mortality in patients with type 2 diabetes.<sup>35</sup> The study's conclusion was that these two agents are similar in providing long-term cardioprotection and renoprotection. One of the main objectives of the recent ONTARGET trial was to compare long-term cardiovascular effects of telmisartan and ramipril in high-risk patients with different vascular illnesses. The investigators found ACEi and ARB to be equal from that prospective. With regard to renal outcomes, although this was not the primary aim of the study, it appeared that telmisartan's effects on major renal outcomes were similar to ramipril in patients with a high vascular risk.<sup>36</sup> However the same trial confirmed the earlier observation, that ARB in general are better tolerated than ACEi which have a higher incidence of hyperkalaemia, cough and may induce angioedema.<sup>37</sup> On the other hand more evidence is available for the effectiveness of ACEi in clinical practice. Together with the higher cost of ARB this may influence the clinician's choice. With regard to the combination of ACEi and ARB there is a still ongoing discussion. In theory such a combination could provide better blockade of the RAS and therefore be more effective in reaching the goal to protect renal function. However, the up-to-date findings are controversial. On one hand such a combination was shown to be effective in terms of treatment of proteinuria regardless of BP changes.<sup>8,38,39</sup> On the other hand, the recent ONTARGET trial did not show any advantage over monotherapy with regard to the decline of GFR and the need for chronic dialysis,<sup>4,36</sup> as well as the rate of cardiovascular events. Additionally, monotherapy has been proven to be well tolerated while combination therapy showed a higher risk for developing hypotension and hyperkalaemia.

To summarise all of the above, it should be noted that for patients with chronic kidney disease both ACEi and ARB can provide appropriate control of blood pressure and proteinuria as well as similar renal and cardiovascular protection. Today there is still more evidence for efficacy of ACEi, but already many good-quality studies have shown ARB to be equivalent. Regarding the combined use of these two RAS blocking agents, more evidence is needed to answer specific questions for the treatment of patients with different types and severity of CKD.

#### **Use of ACEi/ARB in patients treated with dialysis**

After reaching the end stage of chronic kidney disease, the majority of patients will start renal replacement therapy with one of the two types of dialysis. It has been stated that in dialysis patients the risk of cardiovascular mortality is 10 to 20-fold higher than in age- and sex-matched general population without kidney damage.<sup>40</sup> Hypertension is one of the most important risk factors of cardiovascular

complications in patients treated with dialysis.<sup>41</sup> About 80% of patients requiring dialysis treatment are hypertensive.<sup>42</sup> Controlling hypertension in patients with ESRD is a well-recognised problem which often requires administration of multiple medications. Antihypertensive agents of different groups are applicable for blood pressure control; however there is a lack of evidence about their efficacy and about BP targets for patients on dialysis. A couple of recent systematic reviews and meta-analyses collected evidence from randomised trials and concluded that hypertension should be treated in patients on dialysis; however, no superiority of any antihypertensive medications was proven.<sup>43,44</sup>

Although  $\beta$ -blockers, calcium-channel blockers and AII inhibitors have been shown to be suitable for BP control in patients on dialysis,<sup>44,45</sup> the last mentioned may provide an additional benefit in this high-risk patient population. Activation of the RAS is recognised to be essential for hypertension and the increased risk of cardiovascular events in dialysis patients. It has been shown that in such patients a chronic overactivity of RAS is often present, together with increased activity of plasma renin.<sup>46</sup> These factors together with expansion of the extracellular volume and interdialytic weight gain create a vicious circle in which management of hypertension in haemodialysis (HD) patients remains difficult. However, there is enough evidence to state that HD patients, especially those with increased plasma renin activity (PRA), would benefit from adding drugs that inhibit AII into their antihypertensive regimen. A number of studies have been done, which showed significantly reduced mortality risk for ESRD patients with cardiovascular disease treated with ACEi.<sup>47,48</sup> Two studies showed a survival benefit for HD patients receiving ACEi;<sup>49,50</sup> however, data suggest that only 30 to 50% patients on dialysis are prescribed these medications.<sup>45,46,51-53</sup>

Apart of their direct effect on BP, ACEi/ARB have also shown the ability to reduce an increased sympathetic nerve discharge in patients with chronic kidney disease and high renin levels.<sup>54</sup> Patients on HD often have overactivity of the sympathetic nervous system, which is another reason for the development of hypertension.<sup>55</sup> Such symptoms as xerostomia and thirst were found to be highly associated with higher interdialytic weight gain and chronic fluid overload.<sup>56</sup> The latter direct impact on hypertension in HD patients and makes it more treatment resistant. AII has also been claimed to be a dipsogenic agent and couple of studies have shown previously that ACEi could reduce thirst in patients undergoing HD.<sup>57-59</sup> In the first double-blind, placebo-controlled trial with a crossover design in 25 HD patients, the use of enalapril was associated with a reduction in thirst, oral fluid intake and, consequently, in weight gain between dialysis sessions.<sup>58</sup> However, the other studies could not confirm such an effect of ACEi and ARB.<sup>60,61</sup> One recent study investigated the antidipsogenic

effect of dual blockade of RAS with ACEi and ARB, and also failed to confirm the hypothesis.<sup>62</sup> The possible explanations for such discrepancy could be the small size of the referenced studies (usually less than 30 patients), as well as differences in the studied population; however antidipsogenic properties of AII inhibitors need more investigation.

#### *ACEi/ARB use in patients on peritoneal dialysis*

Until recently AII inhibitors were generally used in patients undergoing peritoneal dialysis (PD) because of their effects on the cardiovascular system. In the last ten years, a number of studies have been done to investigate the ability of these medications to suppress local RAS and attenuate peritoneal fibrosis development, and therefore to prolong the 'effective life' of the peritoneal membrane. Experimental and clinical studies which were focused on specific effects of AII inhibitors in long-term peritoneal dialysis patients are presented in the last part of this review.

#### *AII inhibitors as antifibrotic agents*

PD has a survival advantage over haemodialysis in the first couple of years of renal replacement therapy (RRT).<sup>63</sup> However, after long-term PD (>2 years) the technique and patient survival deteriorates.<sup>63-65</sup> This could partially be explained by loss of the residual renal function (RRF) and changes in the peritoneal membrane.<sup>66</sup> During long-term treatment with peritoneal dialysis the peritoneal membrane is affected by solutions with high concentrations of glucose and glucose degradation products (GDPs).<sup>67</sup> Besides, uraemic toxins as well as inflammatory cytokines induced by acute and chronic inflammation may also contribute to the damaging process.<sup>66</sup> Morphological changes in the peritoneal membrane associated with long-term peritoneal dialysis treatment include interstitial fibrosis, loss of the mesothelial cell layer, neoangiogenesis and vasculopathy.<sup>66,68,69</sup> These are associated with the main functional disturbances – high solute transport and ultrafiltration failure – which lead to inadequate PD treatment.<sup>70,71</sup> The changes in the peritoneal membrane are mediated by several growth factors. The most relevant ones are vascular endothelial growth factor (VEGF)<sup>72-75</sup> and transforming growth factor  $\beta_1$  (TGF- $\beta_1$ ).<sup>76-79</sup> The latter appears to be related to the AII, which is produced by the local RAS, and is present in human peritoneal mesothelial cells (HPMC).<sup>80</sup> Locally produced AII regulates cell growth and synthesis of extracellular matrix and therefore has all the properties of a growth factor.<sup>81,82</sup> In HPMC, AII acts as a profibrotic agent, inducing production of a fibronectin and glucose-induced TGF- $\beta_1$ .<sup>80,83</sup> It has been shown that their expression can be significantly reduced by the ACEi and ARB.<sup>80,84</sup> Production of VEGF, the growth factor essential for the development of ultrafiltration

failure, was also shown to be attenuated by ACEi/ARB in a recent *in vitro* study.<sup>85</sup>

#### Animal studies

A number of studies have been done in experimental animal models, which confirmed the findings of the above cell culture studies. The use of ACEi enalapril and lisinopril in rats showed decreased fibrosis and angiogenesis.<sup>86-88</sup> Also lisinopril and valsartan (an ARB) have been found to reduce levels of TGF- $\beta_1$  and VEGF in rats' PD effluent.<sup>89</sup> The ARBs irbesartan and olmesartan were also shown to protect against peritoneal fibrosis caused by bacterial peritonitis and PD fluid with an acidic pH.<sup>90,91</sup> ACE inhibition was also beneficial in a murine model of chlorhexidine/ethanol induced encapsulating peritoneal sclerosis (EPS); in this model oral administration of quinapril for up to 56 days markedly reduced peritoneal thickening.<sup>92</sup>

#### Studies in humans

Relatively little is known about specific effects of ACEi/ARB in PD patients. The most relevant of these include their impact on peritoneal membrane function, residual renal function, PD technique and patient survival.

#### Effects on peritoneal transport

Studies focused on effects of these medications on peritoneal membrane transport can be divided into short- and long-term. In the first short-term study a decrease in peritoneal protein loss was observed in 12 continuous ambulatory peritoneal dialysis (CAPD) patients treated with the ACEi captopril.<sup>93</sup> After a few years the same group found a similar effect for the ARB, irbesartan.<sup>94</sup> In contrast, the study by Favazza *et al.* comparing effects of clonidine, enalapril and nifedipine, showed higher peritoneal clearances of creatinine and  $\beta_2$ -microglobulin with enalapril.<sup>95</sup> Other authors were not able to show any effect of enalapril or losartan on peritoneal transport in CAPD patients in short term.<sup>96,97</sup> Given the discrepancy of these results, more studies are needed to provide clarity. Knowing that long-term peritoneal membrane changes do not occur before two to three years on PD, studies with sufficiently long follow-up could give an answer whether the long-term use of AII inhibitors can influence peritoneal transport. A first single-centre study focused on effects of ACEi/ARB on peritoneal membrane transport in long-term PD patients was performed by our group.<sup>98</sup> Our major finding was a different time course of small solute transport during the first three to four years of PD treatment. Patients treated with ACEi/ARB showed a slight decrease in the mass transfer area coefficient (MTAC) of creatinine and urea. This was different from the controls in which an increase in time of treatment was found. It suggested inhibition of peritoneal angiogenesis which

is in agreement with results from experimental studies. In another study we were able to confirm the above results on 217 incident CAPD patients participating in the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD) treated with PD for at least two years.<sup>52</sup> Once again, patients treated with ACEi/ARB showed a slight decrease of their 24-hour dialysate/plasma-creatinine ratio during the follow-up while an increase was observed in controls.

#### Effects on PD technique and patient survival

Given all of the above findings, it was also hypothesised that membranoprotective properties of ACEi/ARB could positively influence the technique survival of PD. Our study showed a tendency for patients treated with ACEi/ARB for at least 75% of their time on PD to have a better technique survival although such an assumption could not be statistically confirmed.<sup>52</sup> A possible explanation for this could be the fact that in the NECOSAD database only a very small number of patients are documented as being switched to HD due to problems with peritoneal transport, and therefore the real magnitude is hard to detect.<sup>65</sup>

With regard to survival of PD patients, the effects of ACEi/ARB were found to be controversial. Recently, Fang *et al* showed a significantly lower mortality risk in those receiving ACEi/ARB *vs* untreated patients.<sup>51</sup> Use of these medications was associated with reduced all-cause mortality. Factors, associated with mortality were age, low serum albumin and congestive heart failure. In contrast, a study done by our group did not find a survival benefit with regard to ACEi/ARB treatment.<sup>52</sup> A possible explanation for the discrepancy of these results is the difference between the studied cohorts. Besides, in observational studies it is hard to prove a link between treatment and outcome as confounding by indication can never be avoided.<sup>99</sup>

#### Effects on residual renal function

A number of clinical trials provided evidence for a survival benefit for PD patients with preserved residual renal function (RRF).<sup>100-103</sup> This can be explained by the fact that, unlike dialysis, native kidneys not only remove small solutes, but also protein-bound substances by active secretion in the proximal tubules. Better preserved RRF is also associated with less comorbidity,<sup>103-105</sup> better fluid and nutritional status.<sup>106,107</sup> Although there is plenty of evidence for the renoprotective effects of AII inhibitors in patients with chronic kidney disease stage I-IV,<sup>9,11,108</sup> the presence of such effect in PD patients is a subject of controversy. A large observational study in more than 1000 PD patients showed that development of anuria was delayed in those receiving ACE inhibitors.<sup>53</sup> However, these results were not confirmed by a smaller single-centre study.<sup>109</sup> Two

RCTs also suggested renoprotective properties of ACEi/ARB in PD: they both showed a different time course of residual glomerular filtration rate (rGFR) as well as a longer duration of anuria development for treated *vs* untreated patients.<sup>110,111</sup> However, the findings of these two RCTs are somewhat contradictory: one showed a temporary decrease of rGFR after the start of treatment with lisinopril, while the other reported a major increase after starting losartan.

The difference in the RCTs could be partially explained by confounding by indication, also known as selection by prognosis. The distinct difference between RCTs and observational studies, such as cohort studies, is that an RCT can provide evidence for a causal relationship because it has the potential to avoid confounding by indication.<sup>99,112</sup> The patients most often prescribed ACEi/ARB use these drugs because of hypertension, heart failure and diabetes mellitus. However, these conditions themselves are associated with a more rapid decline in residual renal function.<sup>53,113</sup>

#### **Use of ACEi/ARB in patients after kidney transplantation**

After receiving a kidney transplant CKD patients form another special cohort in which possible effects of other immunosuppressive medications have been barely studied. Not much evidence exists with regard to a potential positive influence of ACEi/ARB on cardioprotection, patient and graft survival. Available data from observational and randomised controlled trials provide rather controversial results. The most recent observational studies reported better outcomes in patients treated with ACEi/ARB compared with untreated patients, which included improved patient and graft survival.<sup>114-116</sup> On the other hand, recently published systematic review and meta-analysis of randomised controlled trials on the use of antihypertensives in kidney transplant recipients concluded that the use of ACEi/ARB led to clinically important reductions in GFR, and therefore may have detrimental effects on clinical outcomes.<sup>117</sup> However, it should be mentioned that such a conclusion was made on the basis of a few studies with a rather small patient cohort, which did not report highly relevant endpoints, such as graft loss, cardiovascular events and patient death. The controversy of existing results together with a general lack of evidence creates great diversity in ACEi/ARB use in kidney transplant recipients. This was confirmed by investigators of the ongoing Long-Term Deterioration of Kidney Allograft Function (DeKAF) study, who also showed that many patients taking these medications at the time of transplantation have them discontinued, due to a fear of suboptimal allograft function postoperatively, and possible contribution to significant anaemia after transplantation.<sup>118</sup>

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## CONCLUSION

Drugs that inhibit the RAS are proven to be effective in the treatment of hypertension and heart failure. In patients with chronic kidney disease these medications appeared to bring benefit beyond their direct effects on the cardiovascular system, resulting in preservation of renal and peritoneal function and improved patient survival. There is some evidence that patients with ESRD and after receiving kidney transplant may also profit from these main properties of ACEi/ARB, but more research is needed for clarity. It has been shown that ACEi/ARB are usually prescribed in less than a half of patients on dialysis, which means that these drugs are being underused. The novel effects of these drugs discovered makes the target population for their administration much wider, especially in patients on renal replacement therapy.

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