Niereninsuffizienz und ACE-Hemmer: ist mehr immer besser?


**Schlüsselwörter** ACE-Hemmer – Angiotensin-Rezeptorblocker – glomeruläre Filtratraten – Nierenversagen – Überblick

**Summary** The dose-response relationship between pharmacological blockade of the renin-angiotensin system (RAS) and angiotensin II concentration in the circulation, on the one hand, and decrease of blood pressure, on the other hand, has been well established. In contrast it is currently unclear which dose of ACE inhibitors and/or angiotensin receptor blockers is optimal for nephroprotection. Clinical studies are rendered quite complex by an early decrease of glomerular filtration after RAS blockade and by side effects at higher doses such as renal sodium loss, hyperkalemia, anemia, etc. Animal experiments and recent clinical studies suggest that the doses of ACE inhibitors or angiotensin receptor blockers required for maximal reduction of proteinuria (as a surrogate marker) and for optimal nephroprotection (retardation of the loss of glomerular filtration) exceed those required for maximal lowering of blood pressure. Ongoing studies try to define the relative merits of high dose monotherapy (ACE inhibitors or angiotensin receptor blockers) versus a combination therapy of the two.

**Key words** ACE inhibitors – angiotensin receptor blockers – glomerular filtration rate – renal failure – review
When captopril was introduced for the treatment of patients with renal disease, it was noted that high doses of the drug caused a number of side effects [1], both immunologically mediated and non-immunologically mediated [2, 3], including an unwanted increase in serum creatinine concentration [4]. While the immune-mediated changes are currently thought to be the result of the presence of a highly reactive SH group in captopril, a number of further side effects can be predicted, based on the physiological action of angiotensin II including increased renal sodium loss, hyperkalemia, anemia and particularly decreased glomerular filtration rate (GFR) as a result of lowered glomerular pressure. The latter is explained by the fact that in the damaged kidney the resistance of the efferent arteriole is increased by angiotensin II [4]. This mechanism is also marshalled when renal perfusion and glomerular filtration are threatened distal to a stenosed renal artery or during hypotension, thus explaining renal failure in patients with renal artery stenosis of a single kidney, with bilateral renal artery stenosis [5, 6] or with “pseudostenosis”, i.e., widespread stenosing intrarenal vascular lesions [7]. The constriction of the efferent arteriole is also relieved by ACE inhibitors in patients with parenchymatous renal disease, causing a decrease in glomerular capillary pressure and as a result of this a decrease in the GFR.

The rise in the serum creatinine concentration (and the complementary decrease in GFR) have been a matter of widespread concern. The question arises whether these changes in renal function limit the acceptable dose of ACE inhibitors or whether on the contrary the dose of ACE inhibitors should even be increased as postulated recently by many investigators in this field [8–10]. The following analysis tries to give a fair evaluation of the pros and cons of high dose ACE inhibitor treatment in patients with renal disease.

**Critical debate**

- **Contra: High dose ACE inhibitors may aggravate renal dysfunction**

  In patients with renal disease, ACE inhibitors frequently cause an abrupt increase in serum creatinine [11]. The decrease in GFR is the consequence of the therapeutically desired decrease of the glomerular capillary pressure, relieving glomerular hypertension. As one down-side, however, when ACE inhibitor treatment is started in patients with advanced renal failure, but not yet dialysis dependent, they may experience a further increase in serum creatinine and become acutely dialysis dependent. Indeed, we had observed a series of patients whom we could take off dialysis when ACE inhibitors were stopped [12] – but without exception dialysis independence was only temporary, obviously because the underlying renal disease progressed further. It is therefore wise to refrain from administering ACE inhibitors or angiotensin receptor blockers if the serum creatinine concentration is approximately 6 mg/dl or the estimated GFR <20 ml/min. In our outpatient clinic we had documented that even in the absence of the above specified etiologies, such as renal artery stenosis, serum creatinine may rise by up to 50% when patients with renal failure are started on ACE inhibitors.

  In this context, another question is also often raised: whether in advanced renal failure one should stop ACE inhibitors in the hope of thus achieving a decrease in S-creatinine. In our experience this is never seen when there has been a history of a continuous monotonous increase of S-creatinine; this lucky outcome is observed only when patients had recently experienced an acute increase in S-creatinine in response to the administration of ACE inhibitors.

  Thus, in conclusion, it is certainly not wise to start ACE inhibitor treatment when patients are already in preterminal renal failure.

- **Pro: Administration of ACE inhibitors is renoprotective despite an acute decrease in GFR**

  Is the acute decrease of GFR after administration of ACE inhibitors a matter of legitimate concern? Apart from the above specified etiologies in patients with renal disease, an increase in serum creatinine (reflecting a decrease in glomerular filtration) is not necessarily an unwanted side effect. It may actually even be beneficial in the long run. Both in diabetic [13] and non-diabetic [14] patients with renal disease, a correlation was found between the initial decrease in glomerular filtration rate and the long-term reduction of the loss of GFR. This can be explained by the fact that in a damaged kidney with a reduced number of nephrons, the glomerular filtration pressure is higher (single nephron hyperfiltration). In the long run such elevated pressure is injurious and contributes to glomerular scarring. Predictably reduction of such elevated glomerular filtration pressures will acutely reduce GFR and thus increase the serum creatinine concentration, but will in the