

Blockage of renin-angiotensin system in chronic kidney disease: where are we now?

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The number of patients having chronic kidney disease (CKD) is increasing worldwide

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urls></urls><language>eng</language></record></Cite></EndNote>[1]. In Taiwan, the
prevalence of CKD was 11.93% ADDIN EN.CITE ADDIN EN.CITE.DATA [2].
Patients with CKD have higher rates in cardiovascular and all-cause mortality than those
without CKD. The hypothesis of glomerular hyperfiltration ADDIN EN.CITE
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num><language>eng</language></record></Cite></EndNote>[3], which helped to
explain the progressive decline of renal function even after the disappearance of initial
insults, implied the possible therapeutic strategies, especially at the early stage of CKD.
However, there is still no target-specific therapy for CKD. The blockage of renin-
angiotensin system is the only and relatively specific renoprotective strategy.
Monotherapy of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin
receptors blockers (ARBs) have shown partial effect in reducing proteinuria and
decreasing the glomerular filtration rate (GFR) in proteinuric nephropathies. Lewis et al.
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urls></urls><language>eng</language></record></Cite></EndNote>[4] showed that treatment with captopril reduced 50% of risk for doubling serum creatinine independent of blood pressure lowering effect in patients of established diabetic nephropathy. Hou et al. ADDIN EN.CITE ADDIN EN.CITE.DATA [5] further showed that ACEI (benazepril) has renoprotective effect in patients of advanced renal failure without diabetes. ARB has similar renoprotection effect, too. In the trial of Irbesartan diabetic nephropathy trial (IDNT) ADDIN EN.CITE ADDIN EN.CITE.DATA [6] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) ADDIN EN.CITE ADDIN EN.CITE.DATA [7], both irbesartan and losartan were found to attenuate the risk for doubling serum creatinine. It is believed that ARBs are as effective as ACEIs in terms of the renal outcome of CKD. Since patients with CKD have high prevalence and mortality of cardiovascular diseases, we should also pay attention to the final conclusion about the issue of ARB-myocardial infarction paradox raised in 2004 ADDIN EN.CITE Verma2004 7 7</rec-number><foreign-

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[pii]10.1136/bmj.329.7477.1248</electronic-resource-
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meta-analysis did not show the adverse effect of ARBs on the mortality of myocardial infarction [9].

There are still debates on whether combination of ACEI and ARB can further improve renal outcomes in CKD patients. Some small and short-term studies revealed possible effect in halting the progression of CKD and reducing proteinuria but the results of long-term renal outcome are lacking in these studies [10, 11]. The renal outcomes of Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) examined the possible benefits of combination therapy and their long-term outcomes [12]. The result showed that when compared with monotherapy, the combination of telmisartan and ramipril increased adverse renal outcomes in patients with high risk of vascular events and diabetes despite of more pronounced decrease in proteinuria. Nevertheless, how well do these results generalize to patients with an eGFR less than 60 ml/min/1.73m² or significant proteinuria? These patients, however, made up only a very small portion of patients in the ONTARGET trial. In addition, the true renal endpoints (doubling of creatinine level and reaching end-stage renal diseases) accounted for only 2-2.5% of all patients. In fact, the ONTARGET trial is not really a renal trial, and studies assessing the effects of combination therapy on the progression of kidney disease in patients with CKD are lacking. Among the small subgroup of patients in the ONTARGET trial who had eGFR less than 60 ml/min/1.73m²,

combination therapy was not significantly worse. Thus, we should await the results of ongoing renal trials that examine the effects of combination therapy before concluding the role of combination therapy in treating CKD patients.

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