Renin-angiotensin blockade and kidney disease

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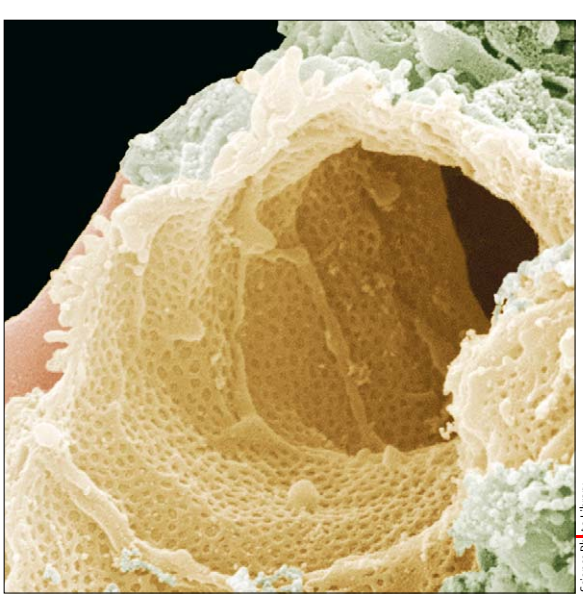
Blockade of the renin-angiotensin system is the main aim of therapy to slow progression of chronic kidney disease. Reduction of blood pressure with drugs that block the renin-angiotensin system (ie, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers) preserves kidney function better than other blood-pressure-lowering agents.[1] These observations are supported by more than a dozen trials in diabetic and non-diabetic nephropathy.[2,3] These trials, however, looked at progression of advanced nephropathy in patients with an estimated glomerular filtration rate of 60 mL/min or less, and all patients had high concentrations of urinary protein (ie, more than 300 mg per day). Although these trials support the hypothesis that blockade of the renin-angiotensin system slows progression of chronic kidney disease better than other antihypertensive drugs, whether these observations can be generalised to the entire range of the disease is still debatable.

A meta-analysis of 127 studies in patients who had varying concentrations of urinary protein and different stages of nephropathy evaluated whether blockade of the renin-angiotensin system slows progression of nephropathy across the spectrum of severity in chronic kidney disease.[4] Blockade of the renin-angiotensin system led to slow progression in people with advanced proteinuric nephropathy, but the effect was similar to that with conventional therapy in patients with normal or slightly raised urinary protein or an estimated glomerular filtration rate above 60 mL/min. Most studies in this meta-analysis, however, included renal outcomes as secondary endpoints and some did not include hard renal endpoints (ie, need for chronic dialysis or end-stage renal disease).

In today's *Lancet*, the ONTARGET investigators, in a randomised trial, evaluate progression of chronic kidney disease as a prespecified secondary outcome.[5] This trial does not answer the question about progression of chronic kidney disease in patients with advanced nephropathy, because few patients with advanced nephropathy were included. Moreover, the interpretation that the group receiving a combination regimen (ramipril and telmisartan) to block the renin-angiotensin system group had more renal events is troubling. Loss of estimated glomerular filtration rate in the combination group was 6 mL/min for 56 months, a decline of 1·29 mL min^{-1} $year^{-1}$ (the normal range[6,7] is between 0·6 and 1·1 mL min^{-1} $year^{-1}$). Thus, while slightly above the normal range, this would not be considered a major loss of kidney function. Only one other trial has assessed combination therapy to block the renin-angiotensin system in advanced proteinuric non-diabetic nephropathy. This trial, powered for renal outcomes as a primary endpoint, reported that the combination group had slower rates of decline in kidney function than did individual therapy—unfortunately, the results are widely viewed as being unreliable.[8]

The ONTARGET study does extend our knowledge about safety of blocking the renin-angiotensin system, either with single drugs alone or combinations, in a cohort with high cardiovascular risk in which about a third of patients were not hypertensive. ONTARGET was not powered to detect differences in renal outcomes, and although more than 6200 patients with stage III nephropathy or higher were evaluated for a composite renal endpoint, death was the main component of the composite endpoint that drove the analysis. Moreover, only 98 patients needed chronic dialysis, but how it was related to treatment versus concomitant medical conditions is unclear. The investigators make a point of noting that the secondary endpoint of dialysis and doubling of creatinine is statistically significant. Unfortunately, one needs to consider this significance in the context of a secondary analysis



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Scanning electron micrograph of kidney capillary

of a prespecified secondary endpoint. Additionally, this analysis counted total dialysis not just chronic dialysis, and thus is not reflective of how events are counted in trials that use primary nephropathy as an outcome.

In ONTARGET, combination therapy to block the renin-angiotensin system did not slow progression of chronic kidney disease compared with single-agent blockers, and was not associated with less use of chronic dialysis and lower rates of doubling of serum creatinine. The combination therapy was associated with decreased progression of developing macroalbuminuria compared with monotherapy, which is consistent with meta-analyses of smaller studies.[9] However, end-stage renal disease events were similar to those with monotherapy. Combination therapy was associated with an increased risk of acute dialysis, which was needed for hyperkalaemia only in two patients. Additionally, risk of hypotension was higher in the combination group, which might have contributed to the greater initial increases in serum creatinine.

These findings of ONTARGET support previous guidelines[2,10,11] that propose use of drugs to block the renin-angiotensin system as part of an antihypertensive regimen to lower blood pressure and urinary protein in chronic kidney disease. These data should not lead to guideline modifications. However, the admonishment against use of combination therapy to block the renin-angiotensin system in people at low risk of chronic kidney disease is clear. Combined with previous studies, ONTARGET supports the notion that use of single agents to block the renin-angiotensin system is well tolerated. It also confirms that angiotensin-receptor blockers have fewer side-effects than angiotensin-converting-enzyme inhibitors. One needs to interpret the ONTARGET findings in the context of the cohort studied and how renal endpoint data were collected. Data collection on kidney function was scant: specifically, urine albumin excretion was not assessed annually and the need for dialysis was established arbitrarily with no predetermined protocol and data assessed post hoc. A properly done prospective trial of patients with advanced proteinuric chronic kidney disease is still needed to answer definitively the question about the efficacy of combination therapy to block the renin-angiotensin system on progression of chronic kidney progression.

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Extracorporeal life-support in patients requiring CPR

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In today's *Lancet*, Yih-Sharng Chen and colleagues[1] show the possible benefits of extracorporeal life-support in adults receiving cardiopulmonary resuscitation (CPR) in hospital for more than 10 min for problems of cardiac origin. Irrespective of the advancements made in conventional CPR, median survivals to discharge after involvement of emergency medical services are only 6·4% for out-of-hospital cardiac arrest and 13·4–17·0% for in-hospital arrest.[2,3] The probable causes of high mortality in cardiac arrest are: a lack of return to spontaneous circulation; re-arrest after such a lack of return because of haemodynamic instability; and late death because of multiple organ dysfunction, including hypoxic brain injury due to ischaemic or reperfusion injury.