iv) The range and limitations of modern surgical techniques when seeking help for physical disabilities caused by this pernicious disease.

An attempt is made to suggest pathways for the provision of optimal care through a shared approach between the patient, primary care services, ancillary care and specialist rheumatology services, given the resource constraints everywhere. This is where we reach the realm of idealism wherein the best possible services are available for all and sundry. This is obviously not possible everywhere, even in the developed world, but the goals are certainly laudable and the paper does well to at least list the requirements until future medical advances make our jobs easier.

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Combination angiotensin-converting enzyme inhibitor and angiotensin receptor blockers: too much of a good thing?

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TITLE Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial

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SUMMARY

This study is the first to report renal outcomes in patients with cardiovascular disease but a low burden of advanced renal disease, using the angiotensin-converting enzyme inhibitor (ACEI) ramipril at 10 mg/day, the angiotensin receptor blocker (ARB) telmisartan at 80 mg/day, or both. More than 8,500 subjects were randomised to each therapeutic group and followed for a mean of 56 months. The primary outcome measures of the Global Endpoint Trial (ONTARGET) prospective randomised controlled study were death from cardiovascular disease, myocardial infarction, stroke or hospitalisation for heart failure. The analysis of the primary cardiac outcomes was published in a prior study,[1] which found that telmisartan was equivalent to ramipril, and the combination was associated with more adverse events.

The current study has focused on secondary analysis of a composite renal outcome of dialysis, doubling of serum creatinine or death in this cohort. Urine albumin-to-creatinine ratio and serum creatinine were measured before run-in and during follow-up. The glomerular filtration rate (eGFR) was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula. The baseline eGFR was 73.6 ml/min/1.73m^2, with a minority (1.02%) having an eGFR <30 ml/min/1.73m^2 and the majority (75.58%) having an eGFR >80.9 ml/min/1.73m^2. Microalbuminuria was present in 13.1% of participants and macroalbuminuria in 4.0%. The prevalence of chronic renal disease in this cohort was therefore not high.

The frequency of combined renal endpoints were similar in the ramipril (13.5%) compared with the telmisartan (13.4%) groups, but was significantly higher in the combination group (14.5%, p=0.037). The frequency of the secondary renal endpoint of doubling of serum creatinine alone was also significantly higher in the combination group (2.49%, p=0.038) compared with the ramipril (2.03%) and telmisartan (2.21%) groups. The need for acute dialysis, i.e. temporary need for dialysis <2 months, was also higher in the combination group (hazard ratio 2.19, 95% confidence interval 1.13–4.22 compared with ramipril alone) but did not differ between the ramipril and

telmisartan groups. There was no difference between groups in the need for chronic dialysis, i.e. no difference in end-stage renal disease.

Combination therapy tended to be most harmful in patients with low risk, i.e. no diabetes or hypertension. More patients in the combination group withdrew because of hypotension or renal abnormalities. Urine albumin excretion over two years increased in all groups, but significantly less in the combination or telmisartan groups compared with the ramipril group ($p < 0.001$ and $p = 0.0013$ respectively), and the risk of developing new onset proteinuria was significantly lower in the combination group compared with ramipril ($p = 0.003$), but did not differ between the ramipril and telmisartan groups. There was a trend towards improved outcome in the combination group in participants with overt diabetic nephropathy, but this did not reach statistical significance.

OPINION

Inhibitors of the renin angiotensin system have been shown to reduce cardiovascular morbidity as well as reduce proteinuria and progression of renal disease.[2] Their use is well founded in basic science, and plausibly addresses the pathophysiology of renal disease progression.[3] The reduction of proteinuria is a major therapeutic target in attempts to attenuate renal disease progression, and approaches to using inhibitors of the renin-angiotensin system have been based on the hypothesis that 'the more, the better'. It is well recognised that reduction in proteinuria is associated with slower renal disease progression in both diabetic and non-diabetic renal disease;[4–6] however, the benefits for patients with low-grade proteinuria are less clear. Several small studies have shown that the combination of ACEI and ARB reduces proteinuria more than either agent alone.[7] Clinical trials in nephrology have tended to rely on the surrogate endpoint of reduction in proteinuria as a marker of success, rather than hard endpoints such as the need for renal replacement therapy or death. It has thus far largely been presumed that reduction in proteinuria in all patients would inevitably translate into improved long-term outcomes, but long-term outcomes have not been rigorously studied.

The current study now suggests that the combination of ACEI and ARB in patients with low risk or prevalence of renal disease, in the presence of cardiovascular disease and risk factors, may be harmful. This study also highlights the point that regression of proteinuria may not be an acceptable surrogate for improvement in renal function. It is important to take these results seriously and exercise caution in combining ACEI and ARB, but with the caveat that the results may not be generalisable to the chronic kidney disease population. Much of our rationale for use of either of these therapies in renal disease comes from studies of patients with low GFRs and greater degrees of proteinuria showing benefit.[8] The long-term value of combination therapy in such patients has not yet been clearly shown. Furthermore, in the current cohort, creatinines were measured prior to the study, at six weeks and then two years into the study. It is not known whether closer surveillance of renal function would have prevented some of the episodes of acute kidney injury seen in the combination group.

This study therefore highlights the need for caution and the monitoring of renal function in any patient receiving combination ACEI and ARB therapy. The findings suggest minimising the use of combination therapy in patients with low-grade proteinuria and preserved renal function in the presence of cardiovascular disease. However, further data are required to determine risk–benefit ratios in patients with overt renal dysfunction or higher-grade proteinuria. Unanswered questions remain as to whether higher doses of a single agent, either ACEI or ARB, would be better or worse than combination therapy, and whether different blood pressure targets may offset the potentially harmful effects of combination therapy while retaining some antiproteinuric activity.

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